13281 U.S. PTO
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062204

PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
U.S. Patent and Trademark Office
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Customer Window, **Mail Stop Patent Application**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: June 22, 2004

Prior Application No. 09/756,291
Prior Application Filing Date: January 9, 2001

Prior Group Art Unit: 1617
Prior Examiner: Hui, San Ming R.

CONTINUATION PATENT APPLICATION TRANSMITTAL UNDER 37 C.F.R. § 1.53(b)

This is a request for filing a patent application under 37 C.F.R. § 1.53(b).

1. This application is a Continuation patent application under 37 C.F.R. § 1.53(b), of copending prior application No. 09/756,291, filed January 9, 2001, of:

   Inventors: John R. EVANS and Rosalind U. GRUNDY
   For: FORMULATION

2. The papers enclosed are as follows:

   Application of 24 pages including:

19	Page(s) of specification	
3	Page(s) of claims	(23 numbered claims)
1	Page of abstract	
1	Pages of Drawings	(Figure 1)

3. Oath or Declaration

   ☒ A copy of an oath or declaration (1 page) filed in prior parent application No. 09/756,291 is enclosed under 37 C.F.R. § 1.63(d). The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied is considered as part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

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4. Relate Back - 35 U.S.C. § 120

☒ A Preliminary Amendment is being filed concurrently herewith amending the specification by inserting before the first line the sentence:

This is a Continuation of copending Application No. 09/756,291, filed January 9, 2001.

Each listed U.S. Patent and/or application is entirely incorporated herein by reference in its entirety.

5. Domestic/International priority is claimed under 35 USC 119(e)/120/365(c) based on the following provisional, nonprovisional and/or PCT international applications(s):

Application No.	Filing Date	Application No.	Filing Date
(1) 09/756,291	January 9, 2001	(2)	
(3)		(4)	

6. Priority - foreign applications under 35 U.S.C. § 119(a)-(d) or § 365(b) or PCT international applications under 35 U.S.C. § 365(a) designating at least one country other than the U.S.

☒ Priority of the following foreign application(s) is/are claimed:

Country	Application No.	Filed
Great Britain	0000313.7	January 10, 2000
Great Britain	0008837.7	April 12, 2000

Certified copy(ies):
☐ is/are attached.
☐ will follow.
☒ was/were filed in prior U.S. Application No. 09/756,291 filed January 9, 2001.

7. Assignment

☒ Prior application No. 09/756,291 is assigned of record to ASTRAZENECA AB on March 27, 2001, at Reel/Frame 011635/0063.

☐ An Assignment of the invention and Form 1595, Recordation Form Cover Sheet, is enclosed.

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8. Fee Calculation (37 C.F.R. § 1.16)

CLAIMS FOR FEE CALCULATION						
	Number Filed After Preliminary Amendment		Included in Filing Fee	Present Extra	at Rate of	Basic Fee Utility $770.00 Total Fees
Total Claims (37 C.F.R. §1.16(c))		minus	20		x $18.00 each=	$ 0.00
Independent Claims (37 C.F.R.§1.16(b))		minus	3		x $86 each=	$ 0.00
☐ First presentation of Multiple Dependent Claim(s)					290.00	$ 0.00
☐ Assignment Recording Fee						$ 0.00
TOTAL FEE =						$ 0.00

9. Power of Attorney

☒ The power of attorney in the prior application is to at least one of the registered practitioners of Morgan, Lewis & Bockius LLP included in the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and all correspondence shall be addressed to that Customer Number.

Please address all correspondence to Morgan, Lewis & Bockius LLP at **Customer Number: 09629**

☒ **PETITION FOR EXTENSION OF TIME.** If any extension of time is necessary for the filing of this application, including any extension in the prior application, application No. 09/756,291, filed January 9, 2001, for the purpose of maintaining copendency between the prior application and the present application, and such extension has not otherwise been requested, such an extension is hereby requested, and the Commissioner is authorized to charge necessary fees for such an extension to Deposit Account No. 50-0310.

InnoPharma Exhibit 1046.0003

10. Fee Payment

☒ No Fee is being paid at this time.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: June 22, 2004 By: _____

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InnoPharma Exhibit 1046.0004

FORMULATION

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

Oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means, and, in postmenopausal women, by the use of aromatase inhibitors.

An alternative approach to oestrogen withdrawal is to antagonise oestrogens with antioestrogens. These are drugs that bind to and compete for oestrogen receptors (ER) present in the nuclei of oestrogen-responsive tissue. Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of oestrogen-mediated activity (Furr and Jordan 1984, May and Westley 1987).

The potential for nonsteroidal antioestrogens to display agonistic properties prompted the search for novel compounds that would bind ER with high affinity without activating any of the normal transcriptional hormone responses and consequent manifestations of oestrogens. Such molecules would be "pure" antioestrogens, clearly distinguished from tamoxifen-like ligands and capable of eliciting complete ablation of the trophic effects of oestrogens. Such compounds are referred to as Estrogen Receptor-Downregulators (E.R.D.). The rationale for the design and testing of novel, pure antioestrogens has been described in: Bowler et al 1989, Wakeling 1990a, 1990b, 1990c. Wakeling and Bowler 1987, 1988.

Steroidal analogues of oestradiol, with an alkylsulphinyl side chain in the 7α position, provided the first examples of compounds devoid of oestrogenic activity (Bowler et al 1989). One of these, 7α-[9-(4,4,5,5,5-pentafluoropentyl sulphinyl)nonyl]oestra-1,3,5-(10)triene-3,17β-diol was selected for intensive study on the basis of its pure oestrogen antagonist activity and significantly increased antioestrogenic potency over other available

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antioestrogens. *In vitro* findings and early clinical experience with 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol have promoted interest in the development of the drug as a therapeutic agent for oestrogen-dependent indications such as breast cancer and certain benign gynaecological conditions.

7α-[9-(4,4,5,5,5-Pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol, or ICI 182,780, has been allocated the international non-proprietary name fulvestrant, which is used hereinafter. When referring to fulvestrant we include pharmaceutically-acceptable salts thereof and any possible solvates of either thereof.

Fulvestrant binds to ER with an affinity similar to that of oestradiol and completely blocks the growth stimulatory action of oestradiol on human breast cancer cells *in vitro*; it is more potent and more effective than tamoxifen in this respect. Fulvestrant blocks completely the uterotrophic action of oestradiol in rats, mice and monkeys, and also blocks the uterotrophic activity of tamoxifen.

Because fulvestrant has none of the oestrogen-like stimulatory activity that is characteristic of clinically available antioestrogens such as tamoxifen or toremifene, it may offer improved therapeutic activity characterised by more rapid, complete, or longer-lasting tumour regression; a lower incidence or rate of development of resistance to treatment; and a reduction of tumour invasiveness.

In intact adult rats, fulvestrant achieves maximum regression of the uterus at a dose which does not adversely affect bone density or lead to increased gonadotrophin secretion. If also true in humans, these findings could be of extreme importance clinically. Reduced bone density limits the duration of oestrogen-ablative treatment for endometriosis. Fulvestrant does not block hypothalamic ER. Oestrogen ablation also causes or exacerbates hot flushes and other menopausal symptoms; fulvestrant will not cause such effects because it does not cross the blood-brain barrier.

European Patent Application No. 0 138 504 discloses that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a

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pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration.

Fulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult. Fulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$ (this is an estimate from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute).

Currently there are a number of sustained release injectable steroidal formulations which have been commercialised. Commonly these formulations use oil as a solvent and wherein additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

In the formulations within Table 1 a number of different oils are used to solubilise the compound and additional excipients such as benzyl benzoate, benzyl alcohol and ethanol have been used. Volumes of oil needed to solubilise the steroid active ingredient are low. Extended release is achievable for periods from 1 to 8 weeks.

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Table 1 - OIL BASED LONG-ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMP'.	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	DOSING
SUSTANON 100	Testosterone proprionate Testosterone phenylproprionate Testosterone isocaproate Testosterone decanoate	30mg 60mg 60mg 100mg	Androgen	Organon	ABPI Data Sheet Comp.1999	Arachis		0.1ml		1ml	3 weeks
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250mgml^{-1}	Progestogen	Schering HC	ABPI Data Sheet Comp.1999	Castor	up to 46%			1 or 2ml	1 week
TOCOGESTAN	Hydroxy progesterone enantate Progesterone α-Tocopherol	200mg 50mg 250mg	Progestogen	Theramax	Dict. Vidal 1999	Ethyl oleate	*40%			2ml	< 1week
TROPHOBOLENE	Estrapronicate Nandrolone undecanoate Hydroxyprogesterone heptanoate	1.3mg 50mg 80mg	Mixed	Theramax	Dict. Vidal 1997	Olive	45%			1ml	15 to 30 days
NORISTERAT	Norethisterone oenanthoate	200mg	Contraceptive	Schering HC	ABPI Data Sheet Comp.1999	Castor	YES			1ml	8 weeks
BENZO-GYNOESTRYL	Estradiol hexahydrobenzoate	5mg	Estradiol	Roussel	Dict. Vidal 1998	Arachis				1ml	1 week
PROGESTERONE -RETARD	Hydroxy progesterone caproate	250mgml^{-1}	Progestogen	Pharlon	Dict. Vidal 1999	Castor	YES			1 or 2ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate Hydroxyprogesterone caproate	5mgml^{-1} 250mgml^{-1}	Mixed	Schering HC	Dict. Vidal 1995	Castor	YES			1 or 2ml	1 - 2 weeks

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PARABOLAN	Trenbolone	76mg	Androgen	Negma	Dict. Vidal 1997	Arachis		75mg	45mg	1.5ml	2 weeks
DELESTROGEN	Estradiol valerate	$20mgml^{-1}$ $40mgml^{-1}$	Estradiol	BMS	J.Pharm. Sci (1964) 53(8) 891	Castor	78% 58%	20% 40%	2% 2%		
DELALUTIN	17-Hydroxy progesterone	$250mgml^{-1}$	Progestrogen	DMS	J.Pharm. Sci.(1964) 53(8) 891	Castor	YES	YES	up to 2%		

BzBz = benzylbenzoate BzOH = benzylalcohol EtOH = ethanol Dict. Vidal = Dictionnaire Vidal

% are w/v and * approximate as measured directly from a single sample

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described which comprises 50mg of fulvestrant, 400mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. Manufacture at a commercial scale of a formulation as described in US 5,183,814 will be complicated by the high alcohol concentration. Therefore, there is a need to lower the alcohol concentration in fulvestrant formulations whilst preventing precipitation of fulvestrant from the formulation.

Table 2 shows the solubility of fulvestrant in a number of different solvents.

Table 2 - SOLUBILITY OF FULVESTRANT

SOLVENT	SOLUBILITY ($mgml^{-1}$ at 25°C)
Water	0.001
Arachis oil	0.45
Sesame oil	0.58
Castor oil	20
Miglyol 810	3.06
Miglyol 812	2.72
Ethyl oleate	1.25
Benzyl benzoate	6.15
Isopropyl myristate	0.80
Span 85 (surfactant)	3.79
Ethanol	>200
Benzyl Alcohol	>200

As can be seen fulvestrant is significantly more soluble in castor oil than any of the other oils tested. The greater solvating ability of castor oil for steroidal compounds is known and is attributed to the high number of hydroxy groups of ricinoleic acid, which is the major constituent of the fatty acids within the triglycerides present in castor oil - see (Riffkin et.al. J. Pharm. Sci., (1964), 53, 891).

However, even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically

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significant release rate. To achieve a therapeutically significant release rate the amount of fulvestrant needed would require the formulation volume to be large, at least 10 ml. This requires the doctor to inject an excessively large volume of formulation to administer a dose significantly high enough for human therapy.

Currently guidelines recommend that no more than 5mls of liquid is injected intramuscularly in a single injection. Pharmacologically active doses required for a 1 month long acting depot formulation of fulvestrant is around 250mg. Therefore, when dissolved in just castor oil, fulvestrant would need to be administered in at least 10ml of castor oil.

The addition of organic solvents in which fulvestrant is freely soluble, and which are miscible with castor oil, may be used, such as an alcohol. With the addition of high concentrations of an alcohol concentrations of >50mgml^{-1} of fulvestrant in a castor oil formulation is achievable, thereby giving an injection volumes of <5ml - see Table 3 below. We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 mgml^{-1} - see Table 3 below. The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil.

Therefore, we present as a feature of the invention a pharmaceutical formulation comprising fulvestrant (preferably fulvestrant is present at 3-10%w/v, 4-9%w/v, 4-8%w/v, 4-7%w/v, 4-6%w/v and most preferably at about 5%w/v) in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Another feature of the invention is a pharmaceutical formulation comprising fulvestrant in which the formulation is adapted for intra-muscular injection into a human and which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of

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formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant; 35% (preferably 30% and ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

For the avoidance of any doubt when using the term % weight per volume of formulation for the constituents of the formulation we mean that within a unit volume of the formulation a certain percentage of the constituent by weight will be present, for example a 1% weight per volume formulation will contain within a 100ml volume of formulation 1g of the constituent. By way of further illustration

% of x by weight per volume of formulation	weight of x in 1ml of formulation
30%	300mg
20%	200mg
10%	100mg
5%	50mg
1%	10mg

Preferred pharmaceutical formulations of the invention are as described above wherein:

1. The total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least 45mgml^{-1} .

2. The total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

3. The total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5-5.25ml.

It is appreciated that in the formulation an excess of formulation may be included to allow the attendant physician or care giver to be able to deliver the required dose. Therefore, when a 5ml dose is required it would be appreciated that an excess of up to 0.25ml, preferably up to 0.15ml will also be present in the formulation. Typically the formulation will be presented in a vial or a prefilled syringe, preferably a prefilled syringe, containing a unit dosage of the formulation as described herein, these being further features of the invention.

Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; at least 3%w/v, at least 5%w/v, at least 7%w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 14% w/v, at least 15% w/v and, preferably, at least 16% w/v. Preferred maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ;28% w/v or less, 22% w/v or less and 20% w/v or less.. Preferred ranges of pharmaceutically-acceptable alcohol present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 3-35%w/v, 4-35%w/v, 5-35%w/v, 5-32%w/v, 7-32%w/v, 10-30%w/v, 12-28%w/v, 15-25%w/v, 17-23%w/v, 18-22%w/v and ideally 19-21%w/v.

The pharmaceutically-acceptable alcohol may consist of one alcohol or a mixture of two or more alcohols, preferably a mixture of two alcohols. Preferred pharmaceutically-acceptable alcohols for parenteral administration are ethanol, benzyl alcohol or a mixture of both ethanol and benzyl alcohol, preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts. Preferably the formulation alcohol contains 10% w/v ethanol and 10% w/v benzyl alcohol.

The pharmaceutically-acceptable non-aqueous ester solvent may consist of one or a mixture of two or more pharmaceutically-acceptable non-aqueous ester solvents, preferably just one. A preferred pharmaceutically-acceptable non-aqueous ester solvent for parenteral administration is selected from benzyl benzoate, ethyl oleate, isopropyl myristate,isopropyl palmitate or a mixture of any thereof.

The ricinoleate vehicle should preferably be present in the formulation in a proportion of at least 30% weight per volume of the formulation, ideally at least 40% or at least 50% weight per volume of formulation.

It will be understood by the skilled person that the pharmaceutically-acceptable alcohol will be of a quality such that it will meet pharmacopoeial standards (such as are described in the US, British, European and Japanese pharmacopoeias) and as such will contain

some water and possibly other organic solvents, for example ethanol in the US Pharmacopeia contains not less than 94.9% by volume and not more than 96.0% by volume of ethanol when measured at 15.56°C. Dehydrated alcohol in the US Pharmacopeia contains not less than 99.5% ethanol by volume when measured at 15.56°C.

Preferred concentrations of the pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are; at least 5% w/v, at least 8% w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 15% w/v, at least 16% w/v, at least 17% w/v, at least 18% w/v, at least 19% w/v and at least 20% w/v. Preferred maximal concentrations of the pharmaceutically-acceptable non-aqueous ester solvent are; 60% w/v or less, 50%w/v or less, 45% w/v or less, 40% w/v or less, 35% w/v or less, 30% w/v or less and 25% w/v or less. A preferred concentration is 15% w/v. Preferred ranges of pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 5-60%w/v, 7-55%w/v, 8-50%w/v, 10-50%w/v, 10-45%w/v, 10-40%w/v, 10-35%w/v, 10-30%w/v, 10-25%w/v, 12-25%w/v, 12-22%w/v, 12-20%w/v, 12-18%w/v, 13-17%w/v and ideally 14-16%w/v. Preferably the ester solvent is benzyl benzoate, most preferably at about 15%w/v.

It will be understood by the skilled person that the pharmaceutically-acceptable non-aqueous ester solvent will be of a quality that it will meet pharmacopoeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

Preferred combinations of pharmaceutically-acceptable alcohol and pharmaceutically-acceptable non-aqueous ester solvent in the formulation are set out below:

Pharmaceutically-acceptable alcohol(%w/v)	**Pharmaceutically-acceptable non-aqueous ester (%w/v)**
10-30	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.

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17-23	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-	10-35
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-21.	12-18
ethanol and benzyl alcohol, most preferably each at about 10%	benzyl benzoate, most preferably at about 15%

By the use of the term ricinoleate vehicle we mean an oil which has as a proportion (at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. The ricinoleate vehicle may be a synthetic oil or conveniently is castor oil, ideally of pharmacopoeial standards, as described above.

We have surprisingly found that the above formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time.

This finding is indeed surprising for the following reasons.

1. Previously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the injection site as well as a poor release profile. It is believed that the tissue irritation/inflammation was due to the presence of fulvestrant in the form of solid particles. The release profile appeared to be determined by the extent of inflammation/irritation present at the injection site and this was variable and difficult to control. Also the fulvestrant release rate was not sufficiently high to be clinically significant.

2. Our findings from studies using ^{14}C labelled benzyl alcohol show that it dissipates rapidly from the injection site and is removed from the body within 24 hours of administration.

It would be expected that ethanol will dissipate at least as quickly, if not more rapidly, from the injection site.

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It is known that benzyl benzoate is metabolised by conjugation to glycine to form hippuric acid by the human liver and excreted into the urine - Martindale: The Extra Pharmacopoeia 32nd edition page 1103, and, therefore, it is unlikely that benzyl benzoate, when used, is present at the injection site during the whole of the extended release period.

We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and pharmaceutically-acceptable non-aqueous ester solvent, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period can still achieved by the formulation of the invention.

By use of the term "therapeutically significant levels" we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient. Preferably blood plasma levels should be less than 15 $ngml^{-1}$.

By use of the term "extended release" we mean at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved. In a preferred feature extended release is achieved for 36 days. Preferably extended release of fulvestrant is for at least 2- 5 weeks and more preferably for the following periods (weeks) 2.5-5, 2.5-4, 3-4, 3.5-4 and most preferably for at least about 4 weeks.

It will be understood that the attendant physician may wish to administer the intramuscular injection as a divided dose, i.e. a 5ml formulation is sequentially administered in two separate injections of 2.5ml, this is a further feature of the invention

Simply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site.

Table 3 shows the solubility of fulvestrant in a castor oil vehicle additionally containing alcohols ethanol and benzyl alcohol with or without benzyl benzoate. The results clearly show the positive effect of benzyl benzoate on fulvestrant solubility in castor oil, despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

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Table 3

Table 3 - EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25°C

				% w/v				
Ethanol (96%)	5	5	10	10	10	10	15	15
Benzyl Alcohol	5	5	5	5	10	10	15	15
Benzyl Benzoate		15		15		15		15
Castor Oil	to 100	to100	to 100	to 100	to 100	to 100	to 100	to 100
Fulvestrant Solubility [$mgml^{-1}$]	27	36	46	54	45	65	76	102

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The following Table 4 shows the solubility of fulvestrant in a range of oil based formulations which contain the same amounts of alcohol and benzyl benzoate but in which the oil is changed. The data also shows solubility of fulvestrant after removal of the alcohols.

Table 4

Solubility comparisons of fulvestrant in oil based formulations with and without alcohols

	Fulvestrant Solubility mg ml^{-1} @ 25°C	
Formulation [(a)]	Complete vehicle	Vehicle minus alcohols
Castor oil based	81.2	12.6
Miglyol 812-N based	86.8	1.7
Sesame seed/Castor oil (1:1) based	70.1	4.4
Sesame seed oil based	45.7	0.7
Arachis oil based	40.2	< 0.2

[(a)] **Complete Vehicle** Formulations comprised ethanol [96%](10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil. Excess fulvestrant was added to each solvent mixture and solubility determined.

Effect of formulation on precipitation of fulvestrant at the injection site

	Days						
Formulation [a]	2	3	4	7	10	30	51
Formulation F1 castor oil based	0	0	0	0	0	0	0
Formulation F2 Miglyol 812-N based	++ [b]	+++	+++	+++	+++	++	0
Formulation F3 sesame seed oil/castor oil based	+ [c]	++	++	+++	++	+	+

0, + , ++, +++ = Degree of precipitation (None detected, Mild, Moderate, Severe)

[a] Formulations comprised fulvestrant (5%), ethanol [96%] (10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil.

[b] Mainly large needle shaped crystals

[c] Small needles and/or sheafs of crystals

InnoPharma Exhibit 1046.0018

Precipitation of fulvestrant and the release profile was determined with the above formulations in an *in vivo* rabbit study.

Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits (data normalised to 50mg per 3kg; mean given; number of animals per timepoint = 8, plasma samples assayed for fulvestrant content using lc-ms/ms detection following solvent extraction). As can be seen the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site.

Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharmaceutically-acceptable excipients, so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

A further feature of the invention is a pharmaceutical formulation adapted for intramuscular injection, as defined above, for use in medical therapy.

A further feature of the invention is a method of treating a benign or malignant diseases of the breast or reproductive tract, preferably treating breast cancer, by administration to a human in need of such treatment by intramuscular injection an extended release ricinoleate vehicle based pharmaceutical formulation comprising at least $45mgml^{-1}$ of fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation.

Preferably 5ml of the intramuscular injection is administered.

A further feature of the invention is use of fulvestrant in the preparation of a pharmaceutical formulation as describe hereinabove, for the treatment of a benign or malignant disease of the breast or reproductive tract, preferably treating breast cancer.

InnoPharma Exhibit 1046.0019

Additional excipients commonly used in the formulation field including, for example, an antioxidant preservative, a colorant or a surfactant may be used. A preferred optional excipient is a surfactant.

As described above fulvestrant is useful in the treatment of oestrogen-dependent indications such as breast cancer and gynaecological conditions, such as endometriosis.

In addition to fulvestrant another similar type of molecule is currently under clinical investigation. SH-646 (11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol) is also putatively a compound with the same mode of action as fulvestrant and has a very similar chemical structure. It is believed that the compound will also share with fulvestrant similar physical properties and therefore the current invention will also have application with this compound.

A further feature of the invention is a pharmaceutical formulation adapted for intra-muscular injection comprising 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol; 35% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol.

Further features of the invention are those as described above but in which SH-646 is substituted for fulvestrant.

Formulation Example

Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid with Nitrogen. The solution is sterilised by filtration using one or two filters of 0.2μm porosity. The sterile filtrate is kept under a nitrogen overlay as it is filled under aseptic conditions into washed and depyrogenised, sterile primary containers, for example vials or pre-filled syringes. An overage is included in the primary

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pack to facilitate removal of the dose volume. The primary packs are overlaid with sterile nitrogen, before aseptically sealing.

See also process flow diagram below

Quantities of each component of the formulation is chosen according to the required formulation specification, examples are described above. For example quantities are added of each component to prepare a formulation which contains

10% weight per volume of benzyl alcohol

10% weight per volume of ethanol

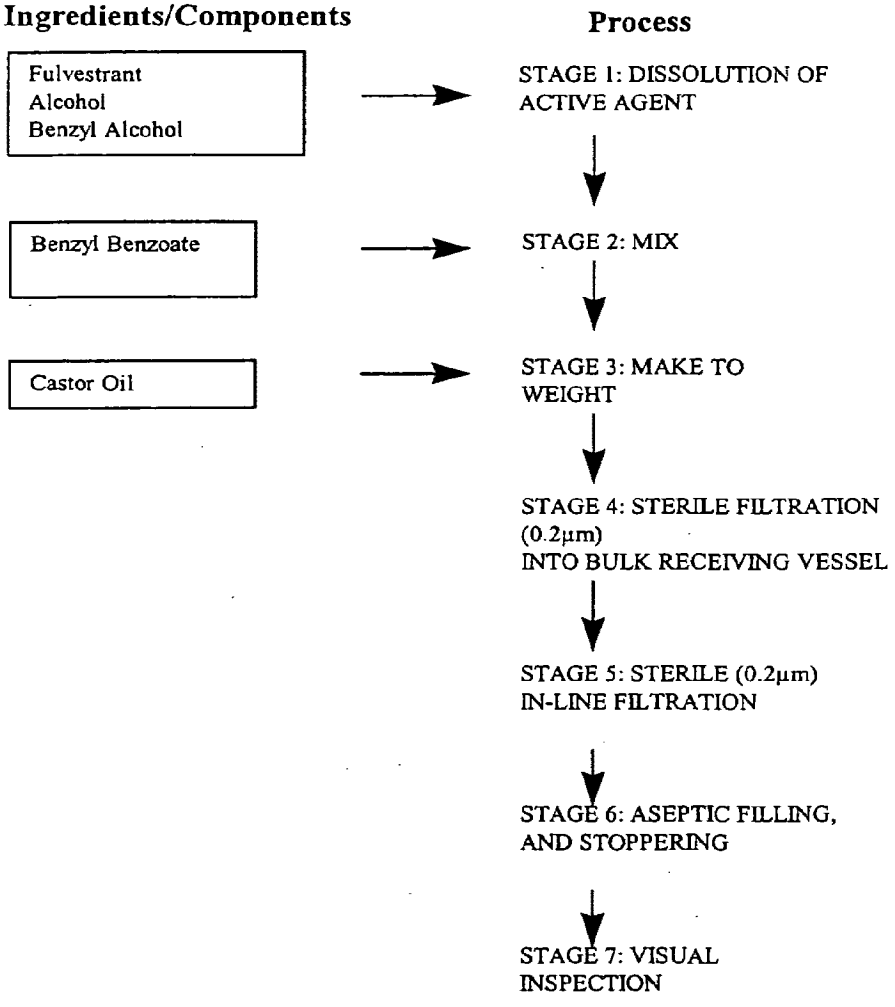
15% weight per volume of benzyl benzoate

250mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

InnoPharma Exhibit 1046.0021

FLOW DIAGRAM OF MANUFACTURING



InnoPharma Exhibit 1046.0022

References

1. Bowler J, Lilley TJ, Pittam JD, Wakeling AE. Novel steroidal pure antioestrogens. Steroids 989; 5471-99.

2. Wakeling AE. Novel pure antioestrogens: mode of action and therapeutic prospects. American New York Academy Science 1990a; 595: 348-56.

3. Wakeling AE. Steroidal pure antioestrogens. In Lippman M, Dickson R, editors. Regulatory mechanisms in breast cancer. Boston: Kluwer Academic, 1990b: 239-57.

4. Wakeling AE. Therapeutic potential of pure antioestrogens in the treatment of breast cancer. Journal Steroid Biochemistry 1990c; 37: 771-5.

5. Wakeling AE, Bowler J. Steroidal pure antioestrogens. Journal Endocrinology 1987; 112: R7-10.

6. Wakeling AE, Bowler J. Biology and mode of action of pure antioestrogens. Journal Steroid Biochemistry 1988; 3: 141-7.

InnoPharma Exhibit 1046.0023

Claims

1. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration of at least $2.5ngml^{-1}$ for at least 2 weeks.

2. A pharmaceutical formulation as claimed in claim 1 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks.

3. A pharmaceutical formulation as claimed in claim 1 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks.

4. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

5. A pharmaceutical formulation as claimed in claim 1 to 4 which contains 25% w/v or less of a pharmaceutically-acceptable alcohol.

6. A pharmaceutical formulation as claimed in claim 5 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

7. A pharmaceutical formulation as claimed in any claim from 1 to 6 which contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

8. A pharmaceutical formulation as claimed in claim 7 which contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent .

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9. A pharmaceutical formulation as claimed in claim 7 which contains 45% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

10. A pharmaceutical formulation as claimed in claim 7 which contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

11. A pharmaceutical formulation as claimed in claim 7 which contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

12. A pharmaceutical formulation as claimed in claim 7 which contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

13. A pharmaceutical formulation as claimed in claim 7 which contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

14. A pharmaceutical formulation as claimed in any claim from 1 to 13 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

15. A pharmaceutical formulation as claimed in any claim from 1 to 14 wherein the pharmaceutically-acceptable non-aqueous ester solvent is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmitate or a mixture of any thereof.

16. A pharmaceutical formulation as claimed in any claim from 1 to 15 wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

17. A pharmaceutical formulation as claimed in any claim from 1 to 16 wherein the total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.

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18. A pharmaceutical formulation as claimed in any claim from 1 to 13 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

19. A pharmaceutical formulation as claimed in claim 18 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5 to 5.25ml.

20. A pharmaceutical formulation as claimed in any of claims 1-19 wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

21. A method of treating a benign or malignant diseases of the breast or reproductive tract by administration to a human in need of such treatment by intramuscular a pharmaceutical formulation as claimed in claims 1 to 19.

22. A method as claimed in claim 21 for treating breast cancer.

23. A syringe or vial containing a pharmaceutical formulation as defined in claim 20.

InnoPharma Exhibit 1046.0026

ABSTRACT

TITLE: Formulation

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

InnoPharma Exhibit 1046.0027

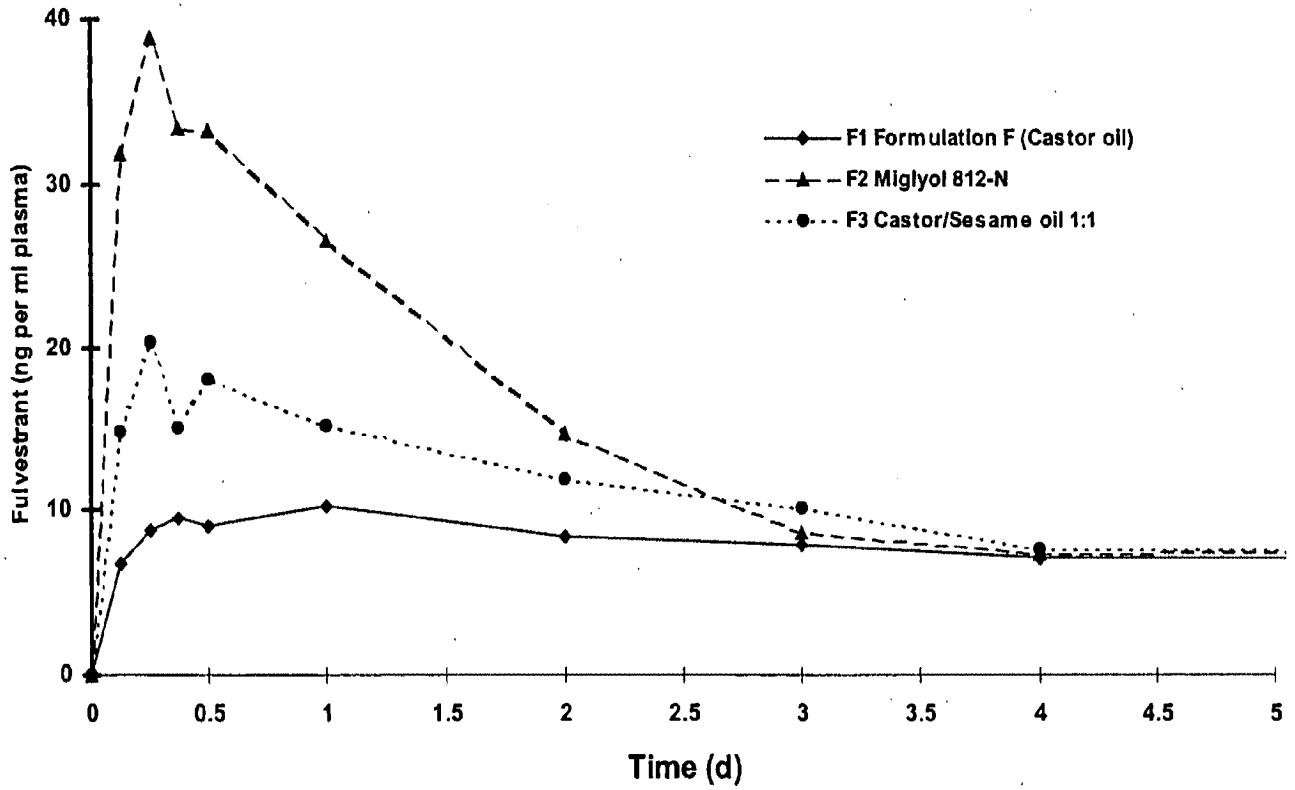
40
30
20
10
0
Fulvestrant (ng per ml plasma)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Time (d)
F1 Formulation F (Castor oil)
F2 Miglyol 812-N
F3 Castor/Sesame oil 1:1

Figure 1

Z70635/US

FOR UTILITY/DESIGN CIP/PCT NATIONAL/PLANT ORIGINAL/SUBSTITUTE/SUPPLEMENTAL DECLARATIONS

RULE 63 (37 C.F.R. 1.63) DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PM & S FORM

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED

FORMULATION

the specification of which (CHECK applicable BOX(ES))

X A. ☐ is attached hereto.

BOX(ES) → B. ☐ was filed on _____ as U.S. Application No. _____

→ → C. ☐ was filed as PCT International Application No. PCT/ _____ on _____

and (if applicable to U.S. or PCT application) was amended on _____

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. Except as noted below, I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International Application which designated at least one other country than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International Application, filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed, or (2) if no priority claimed, before the filing date of this application:

PRIOR FOREIGN APPLICATION(S) Number	Country	Day/MONTH/Year Filed	Date first Laid-open or Published	Date Patented or Granted	Priority NOT Claimed
0000313.7	GB	10 January 2000			
0008837.7	GB	12 April 2000			

If more prior foreign applications, X box *at bottom* and continue on attached page.

Except as noted below, I hereby claim domestic priority benefit under 35 U.S.C. 119(e) or 120 and/or 365(c) of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application:

PRIOR U.S. PROVISIONAL, NONPROVISIONAL AND/OR PCT APPLICATION(S) Application No. (series code/serial no.)	Day/MONTH/Year Filed	Status pending, abandoned, patented	Priority NOT Claimed

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

And I hereby appoint Pillsbury Madison & Sutro LLP, Intellectual Property Group, 1100 New York Avenue, N.W., Ninth Floor, East Tower, Washington, D.C. 20005-3918, telephone number (202) 861-3000 (to whom all communications are to be directed), and the below-named persons (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete names/numbers below of persons no longer with their firm and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/ organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct the above Firm and/or a below attorney in writing to the contrary.

Paul N. Kokulis	16773	Dale S. Lazar	28872	Mark G. Paulson	30793	Michael R. Dzwonczyk	36787
Raymond F. Lippitt	17519	Paul E. White, Jr.	32011	Stephen C. Glazier	31361	W. Patrick Bengtsson	32456
G. Lloyd Knight	17698	Glenn J. Perry	28458	Paul F. McQuade	31542	Jack S. Barufka	37087
Carl G. Love	18781	Kendrew H. Colton	30368	Ruth N. Morduch	31044	Adam R. Hess	41835
Kevin E. Joyce	20508	G. Paul Edgell	24238	Richard H. Zaitlen	27248		
George M. Sirilla	18221	Lynn E. Eccleston	35861	Roger R. Wise	31204		
Donald J. Bird	25323	Timothy J. Klima	34852	Jay M. Finkelstein	21082		
Peter W. Gowdey	25872	David A. Jakopin	32995	Anita M. Kirkpatrick	32617		

(1) INVENTOR'S SIGNATURE: John R Evans Date: 25th January 2001

	First	Middle Initial	Family Name
	John	R	EVANS
Residence	Macclesfield, Cheshire	United Kingdom	British
	City	State/Foreign Country	Country of Citizenship
Post Office Address (include Zip Code)	Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom (SK10 4TG)		

(2) INVENTOR'S SIGNATURE: Rosalind A Grundy Date: 25th January 2001

	First	Middle Initial	Family Name
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Residence	Macclesfield, Cheshire	United Kingdom	British
	City	State/Foreign Country	Country of Citizenship
Post Office Address (include Zip Code)	Charter Way, Macclesfield, Cheshire, SK10 2NA, United Kingdom (SK10 2NA)		

FOR ADDITIONAL INVENTORS, "X" box ☐ and proceed on the attached page to list each additional inventor.

☐ See additional foreign priorities on attached page (incorporated herein by reference).

Atty. Dkt. No. PM _____ (M#)

PAT-116 11/99C

InnoPharma Exhibit 1046.0029

PATENT
ATTORNEY DOCKET NO.: 056291-5004-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re CONTINUATION APPLICATION of:	)	
	)	
EVANS et al.	)	
	)	
Parent Application No.: 09/756,291	)	Prior Group Art Unit: 1617
	)	
Parent Application Filed: January 9, 2001	)	Prior Examiner: Hui, San Ming R.
	)	
For: FORMULATION	)	

Commissioner for Patents
U.S. Patent and Trademark Office
220 20th Street S
Customer Window, **Mail Stop Patent Application**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Dat e: June 22, 2004

Sir:

PRELIMINARY AMENDMENT

Prior to examination of the above-identified application on the merits, please amend the application as follows:

InnoPharma Exhibit 1046.0030

IN THE SPECIFICATION:

Please insert the following paragraph on page 1 of the specification between the title of the invention and the first paragraph of the specification:

-- This is a Continuation of copending Application No. 09/756,291, filed January 9, 2001.--.

InnoPharma Exhibit 1046.0031

REMARKS

Entry of these amendments is respectfully requested prior to considering this application and issuing a first Action on the merits.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: June 22, 2004 By: _____

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **009629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk

InnoPharma Exhibit 1046.0032

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2003

Application or Docket Number: 10872784

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	23	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	29 minus 20=	* 9
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	385.00	OR	BASIC FEE	770.00
XS 9=		OR	X$18=	162
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL		OR	TOTAL	932

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

InnoPharma Exhibit 1046.0033

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/872,784	06/22/2004	John R. Evans	056291-5004-01

CONFIRMATION NO. 2093

09629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

FORMALITIES LETTER

OC000000013539810

Date Mailed: 08/16/2004

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **770** *to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of **$452** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$1352** for a Large Entity

- **$770** Statutory basic filing fee.
- **$130** Late oath or declaration Surcharge.

- Total additional claim fee(s) for this application is **$452**

- **$162** for **9** total claims over 20.
- **$290** for multiple dependent claim surcharge.

Replies should be mailed to: Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

A copy of this notice MUST be returned with the reply.

B. To

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 3 - OFFICE COPY

InnoPharma Exhibit 1046.0035

PATENT
ATTORNEY DOCKET NO.: 056291-5004-01

OIPE JC177 OCT 18 2004 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	
	)	
EVANS et al.	)	
	)	
Application No.: 10/872,784	)	Prior Group Art Unit: 1617
	)	
Filed: June 22, 2004	)	Prior Examiner: Hui, Sang Ming R.
	)	
FOR: FORMULATION	)	

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop** ___
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: October 18, 2004
October 16 = Saturday

Sir:

RESPONSE TO NOTICE TO FILE MISSING PARTS

1. This replies to the Notice to File Missing Parts of Nonprovisional Application mailed August 16, 2004.

   A copy of the Notice To File Missing Parts Of Nonprovisional Application is enclosed.

2. Declaration Or Oath

   ☐ A copy of the original Combined Declaration and Power of Attorney was filed on June 22, 2004.

3. Extension of Time

   The proceedings herein are for a patent application and the provisions of 37 C.F.R. § 1.136(a) apply.

   ☒ Applicant believes that no extension of time is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

InnoPharma Exhibit 1046.0036

☒ If an additional extension of time is required, please consider this a Petition therefor.

4. Assignment

☒ An assignment of the invention to ASTRAZENECA AB and a PTO Form-1595, Recordation Form Cover Sheet, are enclosed.

5. Additional papers enclosed:

☒ Second Preliminary Amendment
☒ First Information Disclosure Statement with Form PTO-1449 (4 pages)
☒ Second Information Disclosure Statement
☒ Third First Information Disclosure Statement with Form PTO-1449 (1 page) and copies of cited references
☒ Terminal Disclaimer

6. Fee Calculation (37 C.F.R. §1.16) (Including Preliminary Amendment)

Application Filing Fee						$ 790.00
	Claims Remaining After Amendment		Claims Included in Filing Fee	Present Extra	at Rate of	
Total Claims (37 C.F.R. §1.16(c))	18	minus	20	0	x $18/$9 each=	$ 0.00
Independent Claims (37 C.F.R.§1.16(b))	2	minus	3	0	x $88/$44 each=	$ 0.00
First presentation of Multiple dependent claim(s)					$300/$150	$ 300.00
Late Filing Surcharge ($130.00)						$ 130.00
Fee for _0_ Month Extension of Time						$ 0.00
Assignment Recordal Fee						$ 40.00
Fee for Terminal Disclaimer ($110.00)						$ 110.00
TOTAL FEE =						$ **1,370.00**

7. Fee Payment

☒ The Commissioner is hereby authorized to charge **$1,370.00** to Deposit Account No. 50-0310 for Application Filing Fee ($790.00), Multiple Dependent Claims Fee ($300.00), Late Filing Surcharge ($130.00), Assignment Recordal Fee ($40.00) and Terminal Disclaimer Fee ($110.00).

InnoPharma Exhibit 1046.0037

☒ The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: October 18, 2004 By: _____

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
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DJB:mk

InnoPharma Exhibit 1046.0038

OIPE JC177 OCT 18 2004 PATENT & TRADEMARK OFFICE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/872,784	06/22/2004	John R. Evans	056291-5004-01

CONFIRMATION NO. 2093

09629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

FORMALITIES LETTER

OC0000000013539810

10/20/2004 SSESHE1 00000045 500310 10872784

01 FC:1001 790.00 DA
02 FC:1051 130.00 DA
03 FC:1203 300.00 DA

Date Mailed: 08/16/2004

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **770** *to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of $**452** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$1352** for a Large Entity

- **$770** Statutory basic filing fee.
- **$130** Late oath or declaration Surcharge.
- Total additional claim fee(s) for this application is **$452**

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AUG 1 ...
MORGAN, LEWIS & BOCKIUS LLP

- **$162** for **9** total claims over 20.
- **$290** for multiple dependent claim surcharge.

Replies should be mailed to: Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

A copy of this notice MUST be returned with the reply.

B. To

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

OIPE JC17
OCT 18 2004
PATENT & TRADEMARK OFFICE

PATENT
ATTORNEY DOCKET NO.: 056291-5004-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent Application of EVANS et al.	)	
	)	
Application No.: 10/872,784	)	Prior Group Art Unit: 1617
	)	
Filed June 22, 2004	)	Prior Examiner: Hui, San Ming R.
	)	
For: FORMULATION	)	

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop** _____
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: October 18, 2004

Sir:

SECOND PRELIMINARY AMENDMENT

Prior to examination of the above-identified application on the merits, please amend the application as follows:

InnoPharma Exhibit 1046.0041

IN THE CLAIMS:

Claims 1-23 (**cancelled**).

Claim 24 (**new**): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of from 8.5 to 11.5 % weight of ethanol per volume of formulation, from 8.5 to 11.5 % weight of benzyl alcohol per volume of formulation and 12 to 18 % weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle, whereby a therapeutically significant blood plasma fulvestrant concentration of at least $2.5ngml^{-1}$ is attained for at least 2 weeks after injection.

Claim 25 (**new**): The method of claim 24 wherein the amount of benzyl benzoate is 13 to 17 % weight per volume of formulation.

Claim 26 (**new**): The method as claimed in claim 24 or claim 25 wherein the benign or malignant disease is breast cancer.

Claim 27 (**new**): The method as claimed in claim 24 or claim 25 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks after injection.

Claim 28 (**new**): The method as claimed in claim 24 or claim 25 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks after injection.

Claim 29 (**new**): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of from 8.5 to 11.5 % weight of ethanol per volume of formulation, from 8.5 to 11.5 % weight of benzyl alcohol per volume of formulation and 12 to 18 % weight of benzyl

InnoPharma Exhibit 1046.0042

benzoate per volume of formulation and a sufficient amount of a castor oil vehicle, whereby the formulation comprises at least $45mgml^{-1}$ of fulvestrant.

Claim 30 (**new**): The method of claim 29 wherein the amount of benzyl benzoate is 13 to 17 % weight per volume of formulation.

Claim 31 (**new**): The method as claimed in claim 29 or claim 30 wherein the benign or malignant disease is breast cancer.

Claim 32 (**new**): The method as claimed in claim 24 or claim 29 wherein the total volume of the formulation administered to said human is 6ml or less, and the concentration of fulvestrant in said formulation is at least $45mgml^{-1}$.

Claim 33 (**new**): The method as claimed in claim 24 or claim 29 wherein the total volume of the formulation administered to said human is 6ml or less, and the total amount of fulvestrant in said volume of formulation is 250mg or more.

Claim 34 (**new**): The method as claimed in claim 33 wherein the total volume of the formulation is from 5 to 5.25ml, and the total amount of fulvestrant in said volume of formulation is 250mg.

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REMARKS

This application is a continuation of parent Application No. 09/756,291 (now US Patent No. 6,774,122; hereinafter "the '122 Patent"), wherein the quantity of the recited components in the formulation administered in the amended method claims is given as a relatively narrow range around the preferred quantities of these components recited in the formulation administered in the method claimed in the '122 Patent. Specification support for these amendments is discussed further below.

Entry of these amendments is respectfully requested prior to considering this application and issuing a first Action on the merits. Following entry of these amendments, claims 24 to 34 remain pending in this application.

Claim Amendments

Original claims 1-23 have been cancelled and replaced with new method of treatment claims 24-34. All claims are directed toward a method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by intra-muscular injection of a pharmaceutical formulation as recited in the various claims. Claims 26 and 31 are specifically directed toward the method wherein the hormonal dependent benign or malignant disease is breast cancer. For the Examiner's convenience, support for the particular ranges now claimed is found in the specification as follows:

- Support for the recitation in claims 24 and 29 of "from 8.5 to 11.5 % weight of ethanol per volume of formulation," and "from 8.5 to 11.5 % weight of benzyl alcohol per volume of formulation" is found in the specification, *inter alia*, at page 9, lines 12-15, wherein one of the preferred ranges of pharmaceutically-acceptable alcohol (total) is

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"17-23%w/v" at line 15. The immediately following paragraph at page 9, lines 16-20, discloses that the pharmaceutically-acceptable alcohol is "preferably a mixture of two alcohols," specifically noting a mixture of ethanol and benzyl alcohol, and that "preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts."

- Support for the recitation in claims 24 and 29 of "12 to 18 % weight of benzyl benzoate per volume of formulation" is found, *inter alia*, at page 10, lines 11-16, wherein one of the preferred ranges of pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations is 12-18%w/v (specifically at line 15), and in the statement that preferably the ester solvent is benzyl benzoate at line 16.
- Support in dependent claims 25 and 30 for the recitation that "the amount of benzyl benzoate is 13 to 17 % weight per volume of formulation" is found, *inter alia*, at page 10, lines 11-16, wherein one of the preferred ranges of pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations is 13-17%w/v (specifically at line 15).

Terminal Disclaimer

Inasmuch as the component ranges recited in the present claims encompass the preferred component amounts recited in the '122 Patent claims, a terminal disclaimer is being filed herein relative to the '122 Patent. This terminal disclaimer is being filed solely for the purpose of expediting prosecution of this continuing application. As provided in MPEP §804.02.II, this terminal disclaimer is not an acknowledgement, and does not raise any

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presumption, that any obviousness-type double patenting rejection, if raised, would have been appropriate in the present application relative to the claims of the '122 Patent.

Information Disclosure Statements

Submitted herewith are ***three*** information disclosure statements as follows, consideration of which by the Examiner is respectfully requested when taking up this continuing application for a first Action on the merits:

- A **First Information Disclosure Statement** comprising a form PTO-1449 on which is listed each patent and literature document cited by Applicants or by the Examiner during prosecution of the parent application. It is understood that copies of these previously cited and provided documents are in the file from the parent application, and that Applicants need not provide further copies in this continuing application. However, if the Examiner finds that any such document is missing from the file, it is requested that he telephone the undersigned, and a further copy will be quickly provided.
- A **Second Information Disclosure Statement** comprising a copy of the Second Information Disclosure Statement filed in the parent application on September 13, 2002, in which Applicants make of record the circumstances regarding the controlled, confidential and non-commercial testing of compositions falling within the scope of "pharmaceutical formulation," as used in the present method of treatment claims, which was carried out in the United States more than one year before the filing date of the parent application in preparation for and during the testing (IND) phase of the regulatory review of such formulation by the FDA.

InnoPharma Exhibit 1046.0046

- A **Third Information Disclosure Statement** comprising a further form PTO-1449 on which is recited several additional documents that were cited by the Japanese Examiner in a related Japanese application after close of prosecution of the parent application, and a copy of each additional document cited. None of these documents is believed to be more pertinent to the claims than documents already cited in the parent application, but since they were cited in a related international application, the Examiner's consideration thereof is thought to be appropriate.

It is respectfully requested that the Examiner consider each of the above-noted items of information disclosure when this application is taken up for a first Action on the merits. Moreover, to insure that each document is listed on the face of the patent issuing from this application, it is respectfully requested that the Examiner acknowledge consideration of each cited document by initialing each form PTO-1449 in the spaces provided, and return an initialed copy to the undersigned.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit

InnoPharma Exhibit 1046.0047

Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: October 18, 2004 By: _____

Morgan Lewis & Bockius LLP
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Fax No.: (202) 739-3001

InnoPharma Exhibit 1046.0048

OIPE JC17
OCT 18 2004
PATENT & TRADEMARK OFFICE

PATENT
ATTORNEY DOCKET NO.: 056291-5004-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	
	)	
EVANS et al.	)	
	)	
Application. No.: 10/872,784	)	Prior Group Art Unit: 1617
	)	
Filed: June 22, 2004	)	Prior Examiner: Hui, Sang Ming R.
	)	

FOR: FORMULATION

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop** _____
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: October 18, 2004

Sir:

FIRST INFORMATION DISCLOSURE STATEMENT

Attached is a Form PTO-1449 listing the cited references.

Copies of the listed documents were previously submitted or cited by the Examiner in parent Application No. 09/756,291. Accordingly, no copies of the listed documents are provided herewith. Applicants respectfully request that the Examiner consider the listed documents and evidence that consideration by making appropriate notations on the attached form.

The present Information Disclosure Statement is being filed before the mailing date of a first Office Action, and therefore no certification under 37 CFR §1.97(e) or fee under 37 CFR §1.17(p) is required.

This Information Disclosure Statement is intended to be in full compliance with the rules, but should the Examiner find any part of its required content to have been omitted,

InnoPharma Exhibit 1046.0049

prompt notice to that effect is earnestly solicited, along with additional time under Rule 97(f), to enable Applicant to fully comply.

Consideration of the foregoing and enclosures plus the return of a copy of the herewith filed Form PTO-1449 with the Examiner's initials in the left column per MPEP 609 along with an early action on the merits of this application are earnestly solicited.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

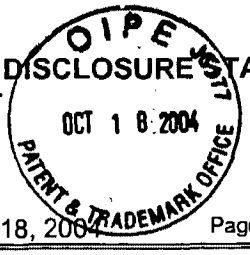
Date: October 18, 2004 By: _____
Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk

InnoPharma Exhibit 1046.0050

FORM PTO-1449 (modified)
To: U.S. Department of Commerce
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT BY APPLICANT



Date: October 18, 2004 Page 1 of 4

Atty. Dkt. No.	M#	Client Ref.
	056291-5004-01	

Applicant: Evans et al.

Appln. No.: 10/872,784

Filing Date: June 22, 2004

Prior Examiner: Hui, Sang Ming R. | Prior Group Art Unit: 1617

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR	2,822,316	02/1958	Richter et al.			
	BR	2,983,649	05/1961	Ercoli et al.			
	CR	3,541,209	11/1970	Neumann et al.			
	DR	4,048,309	09/1977	Chen et al.			
	ER	4,048,310	09/1977	Chen et al.			
	FR	4,659,516	04/1987	Bowler et al.			
	GR	4,888,331	12/1989	Elger et al.			
	HR	5,095,129	03/1992	Ottow et al.			
	IR	5,183,814	02/1993	Dukes			

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	JR	0 138 504	04/1985	EPA	Bowler et al.					
	KR	0 346 014	12/1989	EPA	Dukes					
	LR	6241	09/1968	France	Schering AK		X			
	MR	817,241	07/1959	GB	Francecso Vismara, S.p.A.					
	NR	1 569 286	06/1980	GB	Schering AK					
	OR	1 207 571	10/1970	GB	Takeda Chemical Industries, Ltd.					
	PR	1 126 892	09/68	GB	Schering AK					
	QR	681014	02/1968	South Africa	Kimbel					
	RR	682530	04/1968	South Africa	Ufer et al.					

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

	SR	Anschel, "Lösungsmittel und Lösungsvermittler in Injektionen", Pharm, Ind., 1965, Vol. 27 (11a), pp. 781-787			X	
	TR	Davis et al., "17-Alpha-Hydroxyprogesterone-Caproate:...with Chemically Pure Progesterone", J. Clin. Endocrinol. And Metabolism, 1955, Vol. 15, pp. 923-930				
	UR	Dukes et al., "Antiuterotrophic effects of the pure antioestrogen ICI 182, 780 ...quantitative magnetic resonance imaging"; J. Endocrinology, 1992, Vol. 138, pp. 203-209				
	VR	Dukes et al., "Antiuterotrophic effects of pure antioestrogen. ICI 182,780, ...the uterus in ovariectomized monkeys", J. Endocrinology, 1992, Vol. 135, pp. 239-247				

Examiner | Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

InnoPharma Exhibit 1046.0051

FORM PTO-1449 (modified) To: U.S. Department of Commerce Patent and Trademark Office	Atty. Dkt. No.	M#	Client Ref.
		056291-5004-01	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Applicant: Evans et al.		
	Appln. No.: 10/872,784		
	Filing Date: June 22, 2004		
Date: October 18, 2004 Page 2 of 4	Prior Examiner: Hui, Sang Ming R.	Prior Group Art Unit: 1617	

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR	5,484,801	01/1996	Al-Razzak et al.			
	BR	5,733,902	03/1998	Schneider			
	CR	5,929,030	07/1999	Hamied et al.			
	DR	Re. 28,690	01/1976	Lehmann et al.			
	ER						
	FR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	GR	549118	03/1977	Soviet Union	Prokofeva		X			
	HR	676284	07/1979	Soviet Union	Bikkulov et al.		X			
	IR	WO 95/12383	05/1995	WIPO	Fang et al.		X			
	JR	WO 96/19997	07/1996	WIPO	Chwalisz et al.		X			
	KR	WO 97/21440	06/1997	WIPO	Ferdinando et al.					
	LR	WO 97/37653	10/1997	WIPO	Grosse-Bley et al.		X			
	MR	WO 97/40823	11/1997	WIPO	Perry et al.					
	NR	WO 98/11902	03/1998	WIPO	Grosse-Bley et al.		X			

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)						
	OR	Howell et al., "Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer", British Journal of Cancer, 1996, Vol. 74, pp. 300-308				
	PR	Martindale, 32nd Ed., "Alcohol", Pharmaceutical Press, 1999, pp. 1099-1101				
	QR	Martindale, 32nd Ed., "Benzoates" and "Benzyl Alcohol"; Pharmaceutical Press, 1999, pp. 1102-1104				
	RR	Martindale, 32nd Ed., "Caster Oil"; 32nd Ed., Pharmaceutical Press, 1999, p. 1560				
	SR	Migally, "Effect of Castor Oil and Benzyl Benzoate Used as a Vehicle for Antiandrogens on the Adrenal Cortex", Archives of Andrology 2, 1979 pp. 365-369				
	TR	Pellegrino, "Use of 17 α Hydroxyprogesterone Caproate in Threatened Abortion", Current Therapeutic Research, Vol. 4, No. 6, June, 1962, pp. 301-305				
	UR	Piver et al., "Medroxyprogesterone Acetate (Depo-Provera) vs. . . . Women with Metastatic Endometrial Adenocarcinoma", Cancer, Vol. 45, American Cancer Society, 1980, pp. 268-272				

Examiner	Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

InnoPharma Exhibit 1046.0052

FORM PTO-1449 (modified) To: U.S. Department of Commerce Patent and Trademark Office	Atty. Dkt. No.	M#	Client Ref.
		056291-5004-01	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Applicant: Evans et al.		
	Appln. No.: 10/872,784		
	Filing Date: June 22, 2004		
Date: October 18, 2004 Page 3 of 4	Prior Examiner: Hui, Sang Ming R.	Prior Group Art Unit: 1617	

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR						
	BR						
	CR						
	DR						
	ER						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	FR									
	GR									
	HR									
	IR									
	JR									
	KR									

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

	LR	Riffkin et al., "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones", Journal of Pharmaceutical Sciences, Vol. 53, No. 8, August 1964, pp. 891-895
	MR	Sawada et al., "Estrogen Receptor Antagonist ICI182,780 Exacerbates Ischemic Injury in Female Mouse", Journal of Cerebral Blood Flow and Metabolism, Vol. 20. No. 1, 2000, pp. 112-118.
	NR	Vidal, Le Dictionnaire, "Benzo-Gynoestryl Retard", 1998 pg. 201
	OR	Vidal, Le Dictionnaire, "Gravibinan", 1995, pp 660-661
	PR	Vidal, Le Dictionnaire, "Parabolan", 1997, pg. 1245
	QR	Vidal, Le Dictionnaire, "Trophobolene", 1997, pp. 1706-1707
	RR	Wakeling et al., "A Potent Specific Pure Antiestrogen with Clinical Potential", Cancer Research, 1991, Vol. 51, pp. 3867-3873
	SR	Waterton et al., "A Case of Adenomyosis in a Pigtailed Monkey...Treated with the Novel Pure Antiestrogen, ICI 182,780"; Laboratory Animal Science, 1993, Vol. 43, No. 3, 1993, pp. 247-251
	TR	Mackey et al, "Tolerability of intramuscular injections of testosterone ester in oil vehicle", Human Reproduction, vol. 10, no. 4, pp, 869-865, 1995

Examiner	Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

InnoPharma Exhibit 1046.0053

FORM PTO-1449 (modified)
To: U.S. Department of Commerce
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date: October 18, 2004 Page 4 of 4

Atty. Dkt. No.	M#	Client Ref.
	056291-5004-01	

Applicant: Evans et al.

Appln. No.: 10/872,784

Filing Date: June 22, 2004

Prior Examiner: Hui, Sang Ming R. | Prior Group Art Unit: 1617

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR						
	BR						
	CR						
	DR						
	ER						
	FR						
	GR						
	HR						
	IR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	JR									
	KR									
	LR									
	MR									
	NR									
	OR									
	PR									

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

	QR	Howell et al., "Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer", The Lancet, Jan. 7, 1995, pp. 29-30
	RR	Osborne et al., "Comparison of the Effects of a Pure Steroidal Antiestrogen With Those of Tamoxifen in a Model of Human Breast Cancer", Journal of the National Cancer, May 1995, Vol. 87, No. 10, pp. 746-750
	SR	Robertson et al., "A PARTIALLY-BLIND, RANDOMISED, MULTICENTRE STUDY COMPARING THE ANTI-TUMOR EFFECTS OF SINGLE DOSES (50, 125 AND 250MG) OF LONG-ACTING (LA) 'FASLODEX' (ICI 182,780 WITH TAMOXIFIN IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER PRIOR TO SURGERY"; Abstract 28, 22nd Annual San Antonio Breast Cancer Symposium: Dec. 8-11, 1999, San Antonio, Breast Cancer Research and Treatment 1999; 57 (1; special issue); p. 31
	TR	Remington's Pharmaceutical Sciences, 18th ed., 1990, p. 219

Examiner | Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

InnoPharma Exhibit 1046.0054

OIPE JC17
OCT 18 2004
PATENT & TRADEMARK OFFICE

PATENT
ATTORNEY DOCKET NO.: 056291-5004-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent Application of EVANS et al.)
)
Application. No.: 10/872,784) Prior Group Art Unit: 1617
)
Filed: June 22, 2004) Prior Examiner: Hui, San Ming R.
)
FOR: FORMULATION

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop** _____
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: October 18, 2004

Sir:

SECOND INFORMATION DISCLOSURE STATEMENT

Applicants wish to specifically call to the Examiner's attention in this continuing application the same circumstances as detailed in the Second Information Disclosure Statement filed September 13, 2002 in the parent application, a copy of this is attached hereto for convenience. Specifically, the attached Second Information Disclosure Statement details circumstances regarding the controlled, confidential and non-commercial testing of compositions falling within the scope of the definition of "pharmaceutical formulation", as used in the present method of treatment claims, which was carried out in the United States more than one year before the filing date of the parent application in preparation for and during the testing (IND) phase of the regulatory review of such formulation by the FDA.

The present Information Disclosure Statement is being filed before the mailing date of a first Office Action, and therefore no certification under 37 CFR §1.97(e) or fee under 37 CFR §1.17(p) is required.

InnoPharma Exhibit 1046.0055

This Information Disclosure Statement is intended to be in full compliance with the rules, but should the Examiner find any part of its required content to have been omitted, prompt notice to that effect is earnestly solicited, along with additional time under Rule 97(f), to enable Applicant to fully comply.

Consideration by the Examiner of the circumstances detailed in the attached document is respectfully requested when taking up this continuing application for a first Action on the merits.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: October 18, 2004 By: _____
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InnoPharma Exhibit 1046.0056

OIPE JC177
OCT 18 2004
PATENT & TRADEMARK OFFICE

PATENT
ATTORNEY DOCKET NO.: 056291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

EVANS et al.

Appln. No.: 09/756,291

Filed: January 9, 2001

FOR: FORMULATION

Group Art Unit: 1617

Examiner: Hui, San-ming

September 13, 2002

Commissioner of Patents
Washington, D.C. 20231

Sir:

SECOND INFORMATION DISCLOSURE STATEMENT

Applicant wishes to make of record the following circumstances regarding the controlled, confidential and non-commercial testing of compositions meeting the definition of "pharmaceutical formulation", as used in the present method of treatment claims, which was carried out in the United States more than one year before the filing date of the present application in preparation for and during the testing (IND) phase of the regulatory review of such formulation by the FDA.

1. The elected invention as presently claimed is directed toward a method for treating a benign or malignant disease of the breast or reproductive tract of a human by intra-muscular injection of a particular pharmaceutical formulation comprising the active drug fulvestrant in a vehicle comprising ricinoleate, a pharmaceutically-acceptable alcohol, and a pharmaceutically-acceptable non-aqueous ester solvent miscible in ricinoleate, as detailed in the claims.

InnoPharma Exhibit 1046.0057

2. Fulvestrant is the international non-proprietary (generic) name for the compound 7-alpha-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]estra-1,3-5(10)-triene-3,17-beta-diol, which compound is encompassed by claims of U.S. Patent No. 4,659,516 issued to Bowler *et al.* in 1987 (hereinafter the "Bowler '516 patent").

3. The present specification acknowledges that fulvestrant is included among the steroid derivatives disclosed in European Patent Application No. 0 138 504 (corresponding to the Bowler '516 patent) as being effective antioestrogenic agents. The Bowler '516 patent notes at the bottom of column 7 that compositions of the disclosed steroid derivatives may be in a form suitable for oral or parenteral administration, and that compounds having antioestrogenic effect may have value in the treatment of, *e.g.*, anovulatory infertility, breast tumors and menstrual disorders.

4. However, certain characteristics of fulvestrant make it very difficult to formulate a pharmaceutically acceptable and effective composition for administration to humans. In particular, fulvestrant is an extremely lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low, placing severe limitations on the manner and mechanism by which it can be administered.

5. Subsequent to grant of the Bowler '516 patent, applicants developed an injectable extended release formulation of fulvestrant by which it became feasible to effectively utilize the known pharmacological properties of fulvestrant in the treatment of benign or malignant diseases of the breast or reproductive tract in humans, as presently claimed. This injectable extended release formulation of fulvestrant was subjected to extensive *in*

vitro and *in vivo* testing in animals, and eventually in clinical trials as detailed below, leading up to the first FDA approval of this formulation in April 2002.

6. In brief chronology, fulvestrant was initially put into development by Imperial Chemical Industries PLC (hereinafter "ICI"), under the product designation ICI 182,780. Development of fulvestrant was continued by Zeneca Limited (formed from ICI in 1993) under the product designation ZD9238. By December 6, 1996, preliminary testing of an injectable formulation containing fulvestrant as active ingredient had progressed to the point that an IND (Investigational New Drug) application was filed with the FDA for FASLODEX® (fulvestrant) Injection. As of the January 5, 1997 effective date of the IND application, clinical testing could, for the first time, commence in human subjects in the United States.

7. Clinical testing under the IND continued on behalf of AstraZeneca (formed by merger in 1999) until it was believed that sufficient evidence of safety and efficacy of the formulation had been obtained, and on March 28, 2001 an NDA (New Drug Application) was submitted to the FDA. Meanwhile, the subject application for patent, Application No. 09/756,291, was filed in the United States on January 9, 2001, claiming priority from GB Application 0000313.7, filed January 10, 2000, and GB Application 0008837.7, filed April 12, 2000. Thereafter, on April 25, 2002, the NDA for the Faslodex (injectable fulvestrant formulation) was approved by the FDA, whereupon Faslodex was approved for commercial marketing for the treatment of certain breast cancers.

8. The injectable fulvestrant formulation constituting Faslodex comes within the definition of "pharmaceutical formulation" as used in the method of treatment claims presently

pending in this application. The April 25, 2002 approval date constitutes the earliest possible date for commercial marketing in the United States of a formulation for use in accordance with the present claims.

9. This FDA approval came after the present application was filed, and was the culmination of many years of testing and gathering of data on the injectable formulation of fulvestrant (ICI 182,780 or ZD9238), both in the United States and abroad, in animals and eventually in human clinical trials. As will be evident below, all such testing in the United States more than one year before this application was filed was carried out under agreements which imposed obligations of confidentiality on the involved institutions and/or investigators, gave AstraZeneca strict control over the permitted use and disposition of the test samples of formulation, and provided that AstraZeneca was entitled to all information or data derived from the testing.[1] Moreover, all persons enrolled in the clinical trials were advised of the experimental nature of the formulation, and acknowledged this in signed informed consent forms as a precondition to their enrollment. AstraZeneca received no payment for the samples, and was not otherwise compensated for the use of these samples in the clinical trials. Under these conditions and the applicable case law discussed later below, these tests of the fulvestrant formulation in the United States did not constitute a "public use" under 35 U.S.C. § 102(b) of the present invention because the tests were carried out under strict obligations of confidentiality, and the tests and the use and disposition of the formulation, remained

[1] Reference to AstraZeneca hereinafter should be understood to refer to AstraZeneca and/or its predecessors in interest, ICI and Zeneca, unless the context indicates otherwise.

InnoPharma Exhibit 1046.0060

under the control of AstraZeneca throughout the entire period. These tests did not place the formulation in the public domain or cause the public to believe that the formulation of the invention was freely available, and certainly did not constitute a commercial exploitation of the invention more than one year before this application was filed.

10. Prior to the January 5, 1997 effective date of the IND application, all testing of fulvestrant formulation in the United States was necessarily carried out *in vitro* or in animals, and therefore cannot come within the scope of the present method of treatment claims. Nevertheless, it should be noted that all such testing was carried out under strict conditions of confidentiality and limitations of use imposed by a Statement of Proposed Investigation (SOPI) form that each investigator was required to sign as a condition to receiving samples of fulvestrant formulation.

11. The SOPI forms used by ICI in the early 1990s required a statement of proposed use of the material (necessarily not including any use in humans) that had to be approved by ICI, and stated just above the required signature of the investigator:

"If samples are supplied, I undertake:-

1. to make available all results to ICI;
2. that the results will not be submitted for publication or disclosed in any other way prior to disclosure to ICI;
3. to use the samples only for the purposes described above and not to pass the samples or any portion thereof to any investigators for any other purpose;
4. not to use the samples for any commercial purpose or for any study requested by a commercial organization."

12. The SOPI forms used by Zeneca and AstraZeneca (even after the effective date of the IND, for any samples provided to investigators outside of formal protocols for clinical or compassionate use trials discussed below) similarly required a statement of proposed use of the material that had to be approved by Zeneca or AstraZeneca, and explicitly stated, "Laboratory studies/tests on animals only. (Not for human use)." Again, just above the signature of the investigator, the following undertaking was printed on each form:

"1. All results acquired as a direct result of the use of the sample(s) will be promptly furnished to AstraZeneca.

2. The results will not be submitted for publication or disclosed in any other way without prior consent from AstraZeneca, which will not be unreasonably withheld.

3. The sample(s) will only be used for the purpose described above and shall not be passed to a third party. Any unused material will be returned to AstraZeneca.

4. The sample(s) will not be used to support the development of any commercial product containing the compound(s) supplied by AstraZeneca.

5. AstraZeneca shall be granted first option of a license to all rights in any discoveries or inventions made as a direct result of the investigations described above (whether patentable or not). In particular, the option will include an option for a license under any patents and patent applications relating to the use of the sample(s).

6. AstraZeneca requires assurance from all external investigators that all studies carried out on behalf of AstraZeneca and/or involving AstraZeneca compounds are carried out in compliance with all animal welfare legislation, regulations and policies applicable in that country/state. Please let us have your confirmation in writing that this is the case. We would also like to receive any additional

information on your in-house animal welfare arrangements which you are able to provide."

13. It is understood that no investigator receiving fulvestrant formulation pursuant to a SOPI, at least in the United States and prior to the filing of the present application for patent, was informed of the components and/or proportions thereof constituting the injectable vehicle in which the fulvestrant was carried, and that no investigator publication of results approved by AstraZeneca included such a disclosure.

14. Two clinical studies involving Faslodex were carried out at least in part in the United States prior to the filing date of the present application for patent.

- Clinical Study 9238IL/0021 began, in the United States, in April 1997 and extended to June 2000; was carried out in 69 centers involving 414 patients; and had the objective of comparing the effect, in terms of time to progression, of two doses of Faslodex (125 and 250 mg) with one dose of Arimidex (1 mg) in postmenopausal women with advanced breast cancer.

- Clinical Study 9238IL/0025 began, in the United States, in November 1998 and extended to July 2001; was carried out in 32 centers involving 51 patients; and had the objective of comparing the effect, in terms of time to progression, of Faslodex (250 mg) with Nolvadex (20 mg) as first-line therapy in postmenopausal women with advanced breast cancer.

15. Each clinical study was carried out under a Clinical Study Agreement entered into by each Institution and Investigator taking part in the study.

InnoPharma Exhibit 1046.0063

16. A representative Clinical Study Agreement for Clinical Study 9238IL/0021 provided in relevant part:

> "The clinical Study to be performed pursuant to this Agreement shall be that set forth in the Protocol entitled "A Double-blind, Randomized, Multicenter Trial comparing the Efficacy and Tolerability of 125 and 250 mg of FASLODEX™ (Long-acting ICI 182,780) With 1 mg ARIMIDEX™ (Anastrozole) in Postmenopausal Women With Advanced Breast Cancer" (hereinafter referred to as "Protocol"). Institution shall use its best efforts to ensure that the work required under the Protocol is properly performed in accordance therewith."
>
> * * * * *
>
> "ZENECA reserves the right to terminate this Agreement and Study at any time in its sole discretion upon thirty (30) days prior written notice. However, ZENECA may terminate this agreement upon five (5) days written notice for safety, regulatory or ethical reasons. In the event of termination, all unused Study materials shall be returned to ZENECA and ZENECA shall reimburse Institution for all actual costs reasonably incurred up until the effective termination date."
>
> * * * * *
>
> "All rights to all data, inventions or discoveries Institution may make or conceive in the course of their work for ZENECA in their performance under this Agreement and using product in accordance with the detailed protocol provided by ZENECA will be the property of ZENECA and will be assigned to ZENECA, and Institution will assist ZENECA, at ZENECA's expense, by executing rightful papers for obtaining proper patent protection in such inventions or discoveries in any country which ZENECA at ZENECA's option, desires to obtain patent protection. All control of and decisions regarding such patent filings and prosecution, whether U.S. or foreign, and all costs and fees associated therewith, shall be exercised and/or borne by ZENECA."

* * * * *

"It may be necessary for Zeneca to disclose to Institution certain information considered proprietary or confidential (hereinafter 'Confidential Information') to aid Institution in effecting or completing their performance under this Agreement. Institution agrees to maintain in confidence all Confidential Information Institution obtains from ZENECA relating to this Agreement and not to disclose any of said Confidential Information to a third party for a period of three (3) years after the termination of this Agreement without the prior written consent of ZENECA. Notwithstanding the foregoing, it is understood that Confidential Information shall not include the following: (i) information that is now publicly available, (ii) information that later becomes publicly available, after it has become publicly available, (iii) information which Institution obtain from some third party not under any obligation to ZENECA with respect to such information, or (iv) information which Institution already have in their possession, prior to any disclosure by ZENECA, as evidenced by written records, (v) is independently developed by Institution or (vi) is required by law or regulation to be disclosed, provided, however, that Institution notifies and consults with Zeneca prior to such disclosure.

"Subject to the provisions of confidentiality set forth in Section 6(d) above, ZENECA agrees to grant Institution the right to publish its findings in the scientific literature, provided that ZENECA shall have the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored or co-authored by Institution or by anyone in their research group and which are based in whole or in part on research conducted under this Agreement. Upon request by ZENECA, in order to protect intellectual property rights, Institution agrees to delay submission of such final draft manuscripts for publication for a period not exceeding six (6) months from the date on which ZENECA receives such final draft manuscripts. Institution agrees to implement any reasonable suggestions made to preserve ZENECA's

right in its Confidential Information before any disclosure for publication or presentation; Investigator and Institution agrees to take appropriate cognizance of any other suggestions by ZENECA before any disclosure for publication or presentation."

17. A representative Clinical Study Agreement for Clinical Study 9238IL/0025 similarly provided in relevant part:

"The clinical Study to be performed pursuant to this Agreement shall be that set forth in the Protocol which is attached hereto as Exhibit A and incorporated herein by reference. Institution and Investigator shall use their best efforts to ensure that the work required under the Protocol is properly performed in accordance therewith."

* * * * *

"Zeneca reserves the right to terminate this Agreement and Study at any time in its sole discretion upon five (5) days prior written notice. In the event of termination, all unused Study materials shall be returned to Zeneca and Zeneca shall reimburse Institution and Investigator for all actual costs reasonably incurred up until the effective termination date."

* * * * *

"All rights to all data, inventions or discoveries Institution and Investigator may make or conceive in the course of their work for Zeneca in their performance under this Agreement will be the property of Zeneca and will be assigned to Zeneca, and Institution and Investigator will assist Zeneca, at Zeneca's expense, by executing rightful papers for obtaining proper patent protection in such inventions or discoveries."

* * * * *

"It may be necessary for Zeneca to disclose to Investigator and Institution certain information considered proprietary or confidential (hereinafter "Confidential

Information") to aid Investigator and Institution in effecting or completing their performance under this Agreement. Confidential Information shall also include Study data; however, Investigator's and Institution's right to publish pursuant to Section (d) below* shall not be affected by this provision. Investigator and Institution agree to maintain in confidence all Confidential Information Investigator and Institution obtain from Zeneca relating to this Agreement and not to disclose any of said Confidential Information to a third party without the prior written consent of Zeneca. Notwithstanding the foregoing, it is understood that Confidential Information shall not include the following: (i) information that is now publicly available, (ii) information that later becomes publicly available, after it has become publicly available, (iii) information which Investigator and Institution obtain from some third party not under any obligation to Zeneca with respect to such information, or (iv) information which Investigator and Institution already have in their possession, prior to any disclosure by Zeneca, as evidenced by written records.

"Nothing herein shall prevent Investigator and Institution from complying with the legal obligation to disclose Confidential Information so long as Investigator and Institution (i) provide Zeneca prompt notice of its intent to disclose (or to resist disclosure) (ii) take reasonable steps to require the recipient to preserve the confidential nature of the information once disclosed and (iii) afford Zeneca the opportunity to attempt to prevent the disclosure (whether or not Investigator and Institution have sought to resist disclosure) or obtain protection for the information disclosed."

* * * * *

*[(d)] "Subject to the provisions of confidentiality set forth in Section 6(c) above, Zeneca agrees to grant Investigator and Institution the right to publish their findings in the scientific literature, provided that Zeneca shall have the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored or co-authored by Investigator and

InnoPharma Exhibit 1046.0067

Institution or by anyone in their research group and which are based in whole or in part on research conducted under this Agreement. In the event it is necessary for Zeneca to prepare a patent application(s) and other documentation, and upon request by Zeneca, Investigator and Institution agree to delay submission of such final draft manuscripts for publication for a period not exceeding six (6) months from the date on which Zeneca receives such final draft manuscripts. Investigator and Institution agree to implement any reasonable suggestions made to preserve Zeneca's right in its Confidential Information before any disclosure for publication or presentation; Investigator and Institution agree to take appropriate cognizance of any other suggestions by Zeneca before any disclosure for publication or presentation."

* * * * *

"Zeneca shall be entitled to make copies, at Zeneca's expense, of any and all documents and data generated from the Study. In addition, Institution and Investigator agree to allow Zeneca to audit the Study records (including administrative files and source documents such as hospital charts, office records and written results of laboratory and diagnostic tests) of Institution and Investigator at mutually convenient times.

18. An additional clinical study involving Faslodex was commenced in the United States more than one year prior to the filing date of the present application for patent, being Clinical Study 9238IL/0037, a compassionate-use trial under a protocol initially entitled "An Open-label, Treatment-use Protocol of 250 mg of FASLODEX™ (Long-acting ICI 182,780) in Postmenopausal Women With Advanced Breast Cancer." It is understood that as of one year prior to the filing date of this application, seven subjects had been enrolled in Clinical Study 9238IL/0037.

19. A "Confidentiality and Proprietary Rights Agreement" was entered into by each Investigator prior to his involvement in Clinical Study 9238IL/0037, in which the Investigator acknowledged that "he will have access to and obtain knowledge of certain proprietary and confidential Information of Zeneca and that as a condition of receiving such information" the parties agreed, in part as here relevant:

"1. 'Confidential Information' shall mean all information (a) disclosed by Zeneca to Investigator, either orally or in writing or (b) obtained by the Investigator from a third party or any other source, regarding the protocol entitled 'An Open-label, Treatment-use Protocol of 250 mg of FASLODEX™ (Long-acting ICI 182,780) in Postmenopausal Women With Advanced Breast Cancer, Study No. 9238IL/0037' ('Study')

"Confidential Information shall not include information that: (i) was already in the possession of Investigator before disclosure thereof by Zeneca to Investigator as evidenced by Investigator's written records (ii) is independently developed by Investigator as evidenced by Investigator's written records, (iii) is or becomes publicly available through no fault of Investigator, or (iv) is obtained by Investigator from a third party under no obligation not to disclose same.

"Nothing herein shall prevent Investigator from complying with a legal obligation to disclose Confidential Information so long as Investigator (i) provides Zeneca prompt notice of its intent to disclose (or to resist disclosure) (ii) takes reasonable steps to require the recipient to preserve the confidential nature of the information once disclosed and (iii) affords Zeneca the opportunity to attempt to prevent the disclosure (whether or not Investigator has sought to resist disclosure) or obtain protection for the Information disclosed.

"2. The purpose of the disclosure of Confidential Information is to allow Investigator to participate in the Treatment-use Protocol.

"3. Investigator agrees to maintain in strictest confidence and to take all reasonable steps to maintain the confidentiality of the Confidential Information. Investigator also agrees not to disclose Confidential Information to any third party, and to use Confidential Information only for the purposes stated in paragraph 2 of this Agreement.

"4. Investigator recognizes that all documents and records received by Investigator from Zeneca and all copies of such records and documents shall be Zeneca's property exclusively. The Investigator shall at all times keep all such documents, records and copies of documents and records in Investigator's custody and subject to Investigator's control and shall surrender the same upon request by Zeneca.

"5. Investigator shall not disclose any Confidential Information to any of its employees, except employees of Investigator who have a need to know the Confidential Information for the purposes stated in paragraph 2 of this Agreement and who have assumed an obligation to maintain Zeneca's Confidential Information in confidence at least to the extent that Investigator is bound hereunder. Investigator shall advise each such employee of the confidential nature of the Confidential Information received from Zeneca and the existence and importance of the confidentiality provisions of this Agreement and shall be responsible for ensuring that such employees maintain the Confidential Information in confidence in accordance with the terms of this Agreement.

"6. Because of the unique nature of the Confidential Information, Investigator understands and agrees that Zeneca will suffer irreparable harm in the event that Investigator fails to comply with any of its obligations contained hereinabove and that monetary damages will be inadequate to compensate Zeneca for such breach. Accordingly, Investigator agrees that Zeneca shall have the right to seek immediate injunctive relief to enforce the confidentiality obligations contained herein.

"7. All rights to all data, inventions or discoveries Investigator may make or conceive in the course of Investigator participation in the Study will be the property of Zeneca and will be assigned to Zeneca, and Investigator will assist Zeneca, at Zeneca's expense, by executing rightful papers for obtaining proper patent protection in such inventions or discoveries. Investigator agrees to make no claim which will restrict the rights of Zeneca to use and disclose to others any information, knowledge, and ideas which are disclosed to Zeneca by Investigator in the course of performance of the Study.

"8. Subject to the provisions of confidentiality set forth herein, Zeneca agrees to grant Investigator the right to publish his findings in the scientific literature, provided that Zeneca shall have the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored by Investigator or by anyone in his research group and which are based in whole or in part on research conducted pursuant to this Study. In the event it is necessary for Zeneca to prepare a patent application(s) and other documentation, and upon request by Zeneca, Investigator agrees to delay submission of such final draft manuscripts for publication for a period not exceeding six (6) months from the date on which Zeneca receives such final draft manuscripts. Investigator agrees to implement any reasonable suggestions made to preserve Zeneca's right in its Confidential Information before any disclosure for publication or presentation; Investigator agrees to take appropriate cognizance of any other suggestions by Zeneca before any disclosure for publication or presentation."

20. The Protocols referenced with respect to the above-noted Studies No. 9238IL/0021, No. 9238IL/0025 and No. 9238IL/0037 provided details of, *inter alia*, the:

- criteria for the selection and screening for eligibility of subjects for entry into the trial, as well as exclusion criteria;

- route, dose and regimen for administration of the respective drugs to individual subjects;
- procedures for drug accountability, including maintenance of accurate records on receipt and disposition of investigational materials, and return or destruction of any unused drug;
- frequency and procedures for clinical and laboratory evaluations;
- regular recordation of data on case report forms, record retention and submission of records to AstraZeneca; and
- trial monitoring and data verification by representatives of AstraZeneca.

21. These Protocols furthermore required that each subject be given appropriate information on the treatment prior to its commencement, including the experimental aspects of the treatment and the risks involved, and sign an informed consent form approved by AstraZeneca, and conforming to the requirements of 21 C.F.R. 50.20 *et seq.* , which requires as a basic element of informed consent, that each subject be provided with, *inter alia*, a "statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental." 21 C.F.R. 50.25(a)(1).

In evaluating the above circumstances in context of 35 U.S.C. § 102(b), the Examiner's attention is called to MPEP ¶ 2133.03 "Rejections Based on 'Public Use' or 'On Sale', and particularly MPEP ¶ 2133.03(a) "Public Use", section *B.* headed "*Use by Third*

Parties Deriving the Invention from Applicant." It is respectfully submitted that the above circumstances *do not* constitute a "public use" of the presently claimed invention under the criteria set forth in the MPEP, and as established by decisions of the Federal Circuit, because of the strict confidentiality and control imposed and maintained by AstraZeneca throughout the relevant trial periods. MPEP ¶ 2133.03(a)*B*. provides:

> **An Invention Is in Public Use If the Inventor Allows Another To Use the Invention Without Restriction or Obligation of Secrecy**
>
> "Public use" of a claimed invention under 35 U.S.C. 102(b) occurs when the inventor allows another person to use the invention without limitation, restriction or obligation of secrecy to the inventor." *In re Smith*, 714 F.2d 1127, 1134, 218 USPQ 976, 983 (Fed. Cir. 1983). The presence or absence of a confidentiality agreement is not itself determinative of the public use issue, but is one factor to be considered along with the time, place, and circumstances of the use which show the amount of control the inventor retained over the invention. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1265, 229 USPQ 805, 809 (Fed. Cir. 1986). See *Ex parte C*, 27 USPQ2d 1492, 1499 (Bd. Pat. App. & Inter. 1992) (Inventor sold inventive soybean seeds to growers who contracted and were paid to plant the seeds to increase stock for later sale. The commercial nature of the use of the seed coupled with the "on-sale" aspects of the contract and apparent lack of confidentiality requirements rose to the level of a "public use" bar.); *Egbert v. Lippmann*, 104 U.S. 333, 336 (1881) (Public use found where inventor allowed another to use inventive corset insert, though hidden from view during use, because he did not impose an obligation of secrecy or restrictions on its use.).

The samples of fulvestrant formulation provided under the SOPI forms was not for human use, and therefore outside of the scope of the present method of use claims. Nevertheless, the tests conducted on these samples by the third party Investigators did not constitute a "public use". Through the SOPI forms, AstraZeneca maintained strict confidentiality over the samples and tests conducted therewith, maintained control over the use and disposition of the samples, and was entitled to all data developed in the course of the

tests. (¶¶ 10-13, *supra*). Moreover, AstraZeneca received no payment or other commercial benefit from providing these samples

Similarly, the three clinical trials or studies conducted in human subjects did not constitute a "public use" under the definition thereof set out in the MPEP as developed by the courts. Prior to the release of any materials or formulations on which to carry out these studies, the institutions and/or investigators involved were required to sign an agreement whereunder strict confidentiality was required, and all information provided to or developed by the institution/investigator during the course of such studies remained or became the property of AstraZeneca. (¶¶ 16, 17 and 19, *supra*). Through the Clinical Study Agreements, and the Protocols under which all three studies were conducted, AstraZeneca maintained full control over the use and disposition of the study materials or formulation that it provided to the institutions/investigators throughout the course of these studies, and the right to receive the data and records that were produced. (¶¶ 16, 17 and 20, *supra*). Moreover, each subject of these studies was fully informed of the experimental nature of the formulation and its use, as acknowledged in signed informed consent forms, and clearly did not have any basis to believe that the formulation or its use in the treatments was in the public domain or otherwise freely available. (¶ 21, *supra*). Again, AstraZeneca received no payment for the formulation used in these studies, and these studies did not constitute a commercial exploitation of the formulation.

Therefore, under the case law as developed by the courts, and its application by the Patent and Trademark Office as set out in the above-quoted paragraph from the MPEP, it is

respectfully submitted that the foregoing circumstances do not constitute a "public use" under 35 U.S.C. § 102(b).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

September 13, 2002 By: _____

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OIPE JC177
OCT 18 2004
PATENT & TRADEMARK OFFICE

PATENT
ATTORNEY DOCKET NO.: 056291-5004-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	
	)	
EVANS et al.	)	
	)	
Application No.: 10/872,784	)	Prior Group Art Unit: 1617
	)	
Filed: June 22, 2004	)	Prior Examiner: Hui, Sang Ming R.
	)	
FOR: FORMULATION	)	

Commissioner for Patents
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Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: October 18, 2004

Sir:

THIRD INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), Applicant brings to the attention of the Examiner the documents listed on the attached PTO-1449. This Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits for the above-referenced application.

A copy of each listed document is attached.

Applicant respectfully requests that the Examiner consider the listed document and evidence that consideration by making appropriate notations on the attached form.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that the listed document is material or constitutes "prior art." If it should be determined that the listed document does not constitute "prior art" under United States law, Applicant reserve the right to present to the Office the relevant facts and law regarding the appropriate status of such document. Applicant further reserve the

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right to take appropriate action to establish the patentability of the disclosed invention over the listed document, should the document be applied against the claims of the present application.

For the Examiner's assistance, the following correlation of English language documents to the Japanese documents is noted:

1. US 2001/0006963 A1 (English equivalent of JP-11-501649-A)
2. GB 1 270571 (English equivalent of JP-43-27327-B)
3. English Abstract of JP09-208496 and translation of paragraph [00056] thereof
4. English Abstract of JP10-152438 and translation of paragraph [0038] thereof
5. EP 819 431 A1 (English equivalent of JP-10-203982)
6. EP 905-143 A2 (English equivalent of JP 11-158200)

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: October 18, 2004 By: _____

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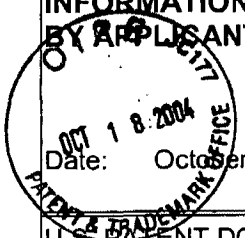
FORM PTO-1449 (modified)
To: U.S. Department of Commerce
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT BY APPLICANT



Date: October 18, 2004 Page 1 of 1

Atty. Dkt. No.	M#	Client Ref.
	056291-5004-01	

Applicant: Evans et al.

Appln. No.: 10/872,784

Filing Date: June 22, 2004

Prior Examiner: Hui, Sang Ming R.

Prior Group Art Unit: 1617

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR	2001/0006963 A1	07/2001	Lachnit-Fixson et al. *English equivalent of JP 11-501649			
	BR						
	CR						
	DR						
	ER						
	FR						
	GR						
	HR						
	IR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name	English Abstract		Translation Readily Available	
						Enclosed	No	Enclose	No
	JR	11-501649	02/1999	Japan					
	KR	43-27327		Japan					
	LR	1207571	10/1970	GB	Takeda Chemical Industries English equivalent of JP-43-27327-B				
	MR	09-208496	12/1997	Japan	Toshihiro et al.	X			
	NR	10-152438	06/1998	Japan	Koji et al.	X			
	OR	10/203982	04/1998	Japan					
	PR	0819431 A1	03/1999	EP	Yamagata et al. English equivalent of JP Pub. 10-203892				
	QR	11-158200	06/1999	JP					
	RR	0905143 A2	03/1999	EP	Yamagata et al. English equivalent of JP Pub. 11-158200				
	SR								

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

	TR	
	UR	
	VR	
	WR	

Examiner | Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

InnoPharma Exhibit 1046.0078

30 C 411
(30 C 4)

特許庁

特許公報

特許出願公告
昭43-27327
公告 昭 43.11.25

(全1頁)

油性注射液の製造法

特願 昭 42—2484
出願日 昭 42. 1. 13
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代表者 小西新兵衛
代理人 弁理士 松居祥二

発明の詳細な説明

本発明は取扱容易なホルモン作用物質含有油性注射液の製造法に関する。

一般にホルモン作用物質は水にきわめて難溶であつて、注射液としては良質の植物油に溶解して油性注射液とされる場合が多い。併し、油性注射液は一般に粘度が高過ぎて、製造時の溶解、濾過作業、製品容器や注射筒への充填作業も容易でなく、その取り扱いがはなはだ不便である。

本発明者らは、このような欠点を除くため、種種研究の結果その目的を達成し、本発明を完成するに至つた。

すなわち、本発明はベンジルベンゾエート10～50%、クロロブタノール0．5～5%を配合することを特徴とするホルモン作用物質の油性注射液の製造法である。

本発明にいうホルモン作用物質とは、ステロイド、非ステロイドを含めて全ての油溶性のホルモン作用を有する物質をいい、たとえばエストラジオールバレレート、エストラジオールシクロペンチルプロピオネート、テストステロンプロピオネート、ヘキセストロールジカプリレート、ジエチルスチルベストロールジプロピオネート等が挙げられる。

そして、これらを溶解する植物油としては、高純度のゴマ油、綿実油、ピーナツ油、オリーブ油等が用いられる。

本発明は、これら植物油にベンジルベンゾエートとクロロブタノールとを含有させることによつて低粘度で取り扱い容易な油性注射液の調製を可能ならしめたものであつて、ここに使用されるベンジルベンゾエートは全量の10～50%程度、クロロブタノールは全量の0．5～5%程度とするのが最も好ましい。

実施例 1

4—ヒドロキシ—19—ノル—テストステロン—17—シクロペンチルプロピオネート2．5%、クロロブタノール2%をベンジルベンゾエート20%に混ぜ、これを滅菌した精製ゴマ油に溶解させて全量100%とし、無菌濾過しアンプルに充填する。

対照として、4—ヒドロキシ—19—ノル—テストステロン—17—シクロペンチルプロピオネート2．5%、ベンジルアルコール10%を含有するゴマ油注射液をつくり、この両者を比較して前者が粘度も低く、その製造、使用時の取り扱いが格段に容易で優れていることを認めた。

	粘度	取扱の難易
実施例 1	50～60	易
対照	80～70	難

実施例 2

ヘキセストロールジカプリレート2%、クロロブタノール3%をベンジルベンゾエート30%と混合し、これを滅菌した精製ゴマ油に溶解して全量100%とし、無菌濾過してアンプルに充填する。

対照としてヘキセストロールジカプリレート2%、ベンジルアルコール3%を含有するゴマ油注射液をつくり、この両者を比較するに、前者は後者に比し粘度も低く、その製造・使用時の取り扱いとも格段に容易ですぐれていることを認めた。

	粘度	取扱の難易
実施例 2	40～50	易
対照	70～90	難

特許請求の範囲

1 ホルモン作用物質をベンジルベンゾエート10～50%、クロロブタノール0．5～5%を含有する植物油に溶解することを特徴とするホルモン作用物質注射液の製造法。

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PATENT SPECIFICATION (11) 1 207 571

NO DRAWINGS

1 207 571

(21) Application No. 1415/68 (22) Filed 10 Jan. 1968
(31) Convention Application No. 2 484 (32) Filed 13 Jan. 1967 in
(33) Japan (JA)
(45) Complete Specification published 7 Oct. 1970
(51) International Classification A 61 k 9/00 17/00
(52) Index at acceptance
A5B 240 244 248 24Y 30X 30Y 38Y 396 39X 400 402 40Y 421 42Y 481 48Y 586 58Y 644 64Y 763

(54) INJECTABLE COMPOSITION

(71) We, TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA (TAKEDA CHEMICAL INDUSTRIES, LTD.), of 27, Doshomachi 2-chome, Higashi-ku, Osaka, Japan, a corporate body organised under the laws of Japan, do hereby declare the invention, for which pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to an oily injectable composition and to the production thereof.

It is well known that such hormones as estradiol divalerate, estradiol cyclopentylpropionate, testosterone propionate, hexestrol dicaprylate and diethylstilbestrol dipropionate have their specific actions on humans and animals. In order to produce the specific effects of the hormones effectively, it is necessary to prepare such hormones in the form of injectable preparations. For the purpose of preparing injections of such hormones, attempts were made, for example, to dissolve such hormones in vegetable oils such as sesame oil, cotton-seed oil, peanut oil and olive oil. However, these vegetable oil solutions of the hormones have so high a viscosity that they cannot be administered parenterally without giving local pain or necrosis to the host. Attempts were made to reduce the local pain by adding benzyl alcohol to the vegetable oil solution of the hormones, but the high viscosity was not reduced to a sufficient degree.

The concentration of the lipophilic hormones in the injectable preparations is usually higher than about 0.5 weight per cent, and is desirably often as high as 5 weight per cent or even up to 10 weight per cent.

Therefore, the solvent, i.e. the injectable vehicle for the lipophilic hormones, is also required to have the capacity to keep the hormones dissolved therein at a desired concentration, at a number of temperatures, e.g. −20° C. to 40°C.

Under such circumstances, attempts have been made to find a suitable vehicle composition for making the hormones satisfactorily injectable.

The present invention provides an oily vehicle composition for injection of the hormones, an oily injectable solution of the hormones which can be satisfactorily administered and methods of preparing the oily vehicle and the oily injectable solution.

The oily vehicle of the present invention is prepared by admixing benzyl benzoate, chlorobutanol and vegetable oil.

The benzyl benzoate is used in an amount of from 10 to 50 weight per cent, especially from 15 to 30 weight per cent, relative to the total weight of the vehicle composition.

The chlorobutanol is used in a proportion of from 0.5 to 5 weight per cent, especially from about 1 to about 3 weight per cent, relative to the vehicle composition.

When the amount of the benzyl benzoate of the present invention is less than 10 weight per cent, the viscosity of the oily vehicle is not sufficiently low to make the resulting solution injectable without harm. When the amount of the chlorobutanol of the present invention is less than about 0.5 weight per cent, the antiseptic effect of the oily vehicle is remarkably reduced. The upper limits of the benzyl benzoate and chlorobutanol of the present invention are provided for practical purpose. On preparing the oily vehicle of the present invention, the respective ingredients may be admixed in any order. The vegetable oil of the present invention is exemplified, by sesame oil, cottonseed oil, peanut oil and olive

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oil.

The oily vehicle thus prepared is employed for preparing an injectable solution of the hormones of the present invention. The injectable solution of the present invention is prepared by incorporating the hormones into the oily vehicle produced in the manner mentioned above. The respective ingredients constituting the injectable solution of the present invention may be admixed in any order. Of course, the injection solution of the present invention should be prepared under sterile conditions.

The injectable solution of the present invention thus prepared preferably has a viscosity which is such that it is satisfactorily injected without any undesirable effects. Furthermore, the injectable solution of the present invention gives only slight pain upon injection due to the incorporation of chlorobutanol in the solution.

An example of the present invention is now given. Throughout the description and claims, part is on a weight basis unless otherwise stated.

EXAMPLE

2.5 Parts of 4-hydroxy-19-nor-testosterone 17 - cyclopentylpropionate and 2 parts of chlorobutanol are admixed with 20 parts of benzyl benzoate. The resulting mixture is dissolved in a sufficient amount of sterilised pure sesame oil to make the total up to 100 parts. The resulting oil solution is filtered under sterile condition and then filled up into ampules.

As the control, an oily solution is similarly prepared employing 2.5 parts of the same steroid compound as the above and 10 parts of benzyl alcohol.

The viscosity of each of the two kinds of oily solution thus prepared is examined to give the following result when measured by rotary viscometer at 20°C..

Oily solution	Viscosity (centipoises)
The present invention	50
Control	80

An oily injectable vehicle (solvent) is prepared according to the following formulae, and the viscosity of each of the oily solutions is similarly examined to give the results shown below.

Formula:

Chlorobutanol	3 parts
Benzyl benzoate	30 parts
Sterilised pure sesame oil	67 parts

This vehicle is suitable for dissolving 2 parts of hexestrol dicaprylate to give a satisfactorily injectable solution.

The viscosity of the injectable preparation containing 2 parts of hexestrol dicaprylate dissolved in the vehicle composition prepared as above is compared with that of a hitherto-employed preparation which has the following formula:

Hexestrol dicaprylate	2 parts
Benzyl alcohol	3 parts
Sterilised sesame oil	Added to make 100° parts in total.

Oily solution	Viscosity
Oily solution of the formula	40
Control solution of the formula	90

WHAT WE CLAIM IS:—

1. An oily injection vehicle for lipophilic hormone injections, which consists substantially of (a) from 10 to 50 weight per cent of benzyl benzoate, (b) from 0.5 to 5 weight per cent of chlorobutanol and (c) remainder vegetable oil.

2. An injection vehicle according to claim 1, wherein the amount of benzyl benzoate is from 15 to 30 weight per cent.

3. An injection vehicle according to claim 1 or 2, wherein the amount of chlorobutanol is from 1 to 3 weight per cent.

4. An injectable solution which consists substantially of (a) from 10 to 50 weight per cent of benzyl benzoate, (b) from 0.5 to 5 weight per cent of chlorobutanol, (c) lipophilic hormone and (d) remainder vegetable oil, wherein percentages are based on the total weight of the injection vehicle comprising (a), (b) and (d).

5. An injectable solution according to claim 4, wherein the amount of the hormone is from 0.5 to 10 weight per cent, based on the total weight of the injectable solution.

6. An injectable solution according to claim 4 or 5, wherein the hormone is 4-hydroxy-19-nor - testosterone-17 - cyclopentyl propionate.

7. An injectable solution according to claim 4 or 5, wherein the hormone is hexestrol dicaprylate.

8. A method of preparing an oily injection vehicle for lipophilic hormones which comprises admixing (a) from 10 to 50 weight per cent of benzyl benzoate, (b) from 0.5 to 5 weight per cent of chlorobutanol and (c) remainder vegetable oil.

9. A method of preparing an oily injection solution which comprises admixing a lipophilic hormone with the oily injection vehicle claimed in claim 1.

10. A method according to claim 8 or 9, wherein the amount of the benzyl benzoate is from 15 to 30 weight per cent.

11. A method according to any of

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claims 8 to 10, wherein the amount of the chlorobutanol is from 1 to 3 weight per cent.

12. A method according to any of claims 8 to 11 wherein the vegetable oil is sesame oil, cotton-seed oil, peanut oil or olive oil.

13. A method according to any of claims 8 to 12, wherein the lipophilic hormone is hexestrol dicaprylate.

14. A method according to any of claims 8 to 12 wherein the lipophilic hormone is 4-hydroxy-19-nor-testosterone-17-cyclopentylpropionate.

15. A method according to any of claims 8 to 14, wherein the amount of the lipophilic hormone is from 0.5 to 10 weight per cent, based on the total weight of the injectable solution.

16. An oily injection vehicle as claimed in claim 1 substantially as herein described with reference to the specific example.

17. An injectable solution as claimed in claim 4 substantially as herein described with reference to the specific example.

18. A method as claimed in claim 8 or 9 substantially as herein described with reference to the specific example.

ELKINGTON AND FIFE,

Chartered Patent Agents,
High Holborn House,
52-54 High Holborn,
London W.C.1.
Agents for the Applicants.

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(19)日本国特許庁（ＪＰ）　(12) 公開特許公報（Ａ）　(11)特許出願公開番号

特開平9－208496

(43)公開日　平成９年(1997)８月12日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ		技術表示箇所
Ａ６１Ｋ　47/40			Ａ６１Ｋ　47/40	Ｅ	
				Ｇ	
				Ｊ	
31/435	ＡＤＵ		31/435	ＡＤＵ	
	ＡＥＤ			ＡＥＤ	

審査請求　未請求　請求項の数12　ＯＬ　（全 26 頁）　最終頁に続く

(21)出願番号　特願平8－14322

(22)出願日　平成８年(1996)１月30日

(71)出願人　000002934
武田薬品工業株式会社
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(72)発明者　石黒　敏弘
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(74)代理人　弁理士　朝日奈　忠夫　（外１名）

(54)【発明の名称】　ＬＨ－ＲＨ拮抗物質含有組成物

(57)【要約】
【課題】非ペプチド系ＬＨ－ＲＨ拮抗薬の水に対する溶解性向上、経口吸収性および薬剤の安定性向上。
【解決手段】非ペプチド系ＬＨ－ＲＨ拮抗物質と分岐シクロデキストリン－カルボン酸とを含有してなる組成物。
【効果】分岐シクロデキストリン－カルボン酸を用いることにより、非ペプチド性ＬＨ－ＲＨ拮抗物質の水に対する溶解性、経口吸収性および薬剤の安定性が該化合物単独の場合よりも著しく向上する。

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PATENT ABSTRACTS OF JAPAN

(11)Publication number : 09-208496

(43)Date of publication of application : 12.08.1997

(51)Int.CI. A61K 47/40
A61K 31/435
A61K 31/435
A61K 31/505
A61K 45/06
// C07D495/04

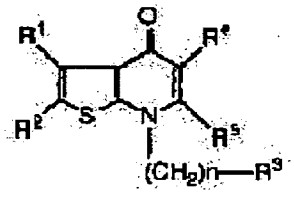
(21)Application number : 08-014322

(22)Date of filing : 30.01.1996

(71)Applicant : TAKEDA CHEM IND LTD

(72)Inventor : ISHIGURO TOSHIHIRO
FURUYA SHUICHI
SUZUKI NOBUHIRO

(54) COMPOSITION CONTAINING LH-RH ANTAGONIST



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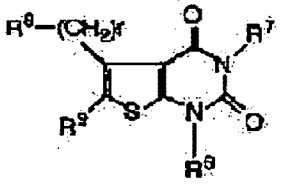

II

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a medicine having heightened solubility in water, cutaneous absorption and drug stability, particularly a composition containing a luteinizing hormone releasing hormone (LH-RH) antagonist useful as a LH-RH antagonist.

SOLUTION: This composition contains a nonpeptide-based LH-RH antagonist of formula I (R1 and R2 are each H or a group through C, N, O or S; R3 is a homocyclic or a heterocyclic ring; R4 is H, formyl, carbonyl, etc.; R5 is H or a group through C; (n) is 0-3) or formula II (R6 is H, an alkyl, etc.; R7 is H, an alkyl, an aryl, etc.; R8 is an amino; R9 is an aryl, (r) is 0-3) and a branched cyclodextrin-carbonic acid. For 1 mole of the LH-RH antagonist, 0.1-20 moles of the branched cyclodextrin-carbonic acid are included. This composition suppresses secretion of a gonadotropic hormone, controls concentration of a sex hormone in blood and is useful for prostato-tumor, gynecological tumor, leukemia, large intestine tumor, gastiritis, Hodgkin's disease, malignant melanoma, peptic ulcer, etc., and oestrous control of an animal, flesh improvement for an edible meat, growth promotion, etc., in a field of stockbreeding.

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(10)

D

English translation of paragraph [0056] of Citation D

[0056] As suitable examples of the aforesaid excipient, lactose, white soft sugar, D-mannitol, starch, crystalline cellulose, light anhydrous silicic acid, etc. are mentioned. As suitable examples of the aforesaid lubricant, magnesium stearate, calcium stearate, talc, a colloidal silica, etc. are mentioned, for example. As suitable examples of the aforesaid binder, white soft sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, etc. are mentioned. As suitable examples of the aforesaid disintegrator, starch, carboxymethyl cellulose, carboxymethyl-cellulose calcium, cross carmellose sodium, carboxy-methyl-starch sodium, etc. are mentioned. As suitable examples of the aforesaid solvent, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, etc. are mentioned. Aas suitable examples of the aforesaid solubilizing agent, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc. are mentioned. As suitable examples of the aforesaid suspending agent, a surface active agent such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride and benzethonium chloride ; and a hydrophilic polymer such as polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethyl-cellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, are mentioned. As suitable examples of the aforesaid isotonizing agent, sodium chloride, glycerine, D-mannitol, etc. are mentioned. As suitable examples of the aforesaid buffer, phosphates, acetates, carbonates, citrates, etc. are mentioned. As suitable examples of a soothing agent, benzyl alcohol, etc. are mentioned. As suitable examples of the aforesaid antiseptic, p-hydroxybenzoic esters, chlorobutanol, benzylalcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc. are mentioned. As suitable examples of the aforesaid antioxidant, sulfite salts, ascorbic acid, etc. are mentoined.

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(19)日本国特許庁（ＪＰ）　(12)公開特許公報（Ａ）　(11)特許出願公開番号

特開平10－152438

(43)公開日　平成10年(1998)６月９日

(51)Int.Cl.[6]	識別記号	ＦＩ	
Ａ６１Ｋ　31/435	ＡＢＬ	Ａ６１Ｋ　31/435	ＡＢＬ
9/08		9/08	Ｖ
47/10		47/10	Ｊ
47/12		47/12	Ｊ
// Ｃ０７Ｄ 491/052		Ｃ０７Ｄ 491/052	

審査請求　未請求　請求項の数37　ＯＬ　（全 14 頁）

(21)出願番号　特願平8－312437

(22)出願日　平成８年(1996)11月22日

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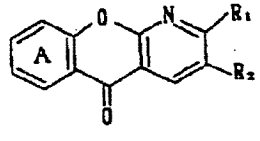
(54)【発明の名称】　１－アザキサントン誘導体またはその塩の安定化方法および１－アザキサントン誘導体含有組成物

(57)【要約】

【解決手段】　フェノール性水酸基含有化合物を、一般式

【化１】



〔式中、Ａ環は置換されていてもよく、R_1 は水素または保護されていてもよいアミノ基を、R_2 はプロトンを放出し得る基を示す〕で表される１－アザキサントン誘導体またはその塩の水溶液に添加することを特徴とする１－アザキサントン誘導体またはその塩の安定化方法、および１－アザキサントン誘導体〔Ｉ〕またはその塩およびフェノール性水酸基含有化合物を含有する組成物。

【効果】　１－アザキサントン誘導体〔Ｉ〕またはその塩の水溶液を安定化することができ、該水溶液の長期保存を可能にする。また低刺激性で臨床上の使用感のよい安定な１－アザキサントン誘導体含有組成物を得ることができる。

InnoPharma Exhibit 1046.0086

(12)

PATENT ABSTRACTS OF JAPAN

E

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SENJU PHARMACEUT CO LTD

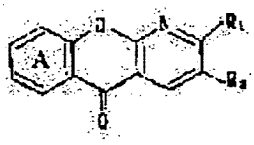
(72)Inventor : DOI KOJI
KIMOTO AKIHIRO

(54) STABILIZATION OF 1-AZAXANTHONE DERIVATIVE OR ITS SALT AND 1-AZAXANTHONE DERIVATIVE-CONTAINING COMPOSITION

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a clinically advantageous pharmaceutical composition by adding a phenolic hydroxyl group-containing compound to the subject specific derivative or its salt.

SOLUTION: This composition is obtained by adding 0.001-1(W/V)% compound selected from p-hydroxybenzoic acid, phenol, cresol and dibutylhydroxytoluene to 0.01-2.0(W/V)% compound of the formula (A ring may be substituted; R1 is H or an amino group; R2 is a group capable of releasing proton) or its salt. The composition is stabilized in the compound of the formula and excellent in feeling to user and useful as a pharmaceutical preparation for administration for local part of an eye. When the composition is administered as an eye drop to adult, the composition is administered in a daily dose of one or several drops one to several times per day according to the symptom as an aqueous eye drop containing about 0.01-2.0% compound of the formula or its salt.



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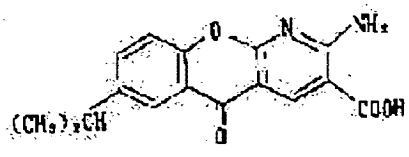

II

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English translation of paragraph [0038] of Citation E

[0038] As a suitable example of a solvent, water for injection, alcohols (an example, ethanol, propylene glycol, macro gall, glycerol, etc.), and fats and oils (an example, olive oil, sesame oil, peanut oil, cotton seed oil, castor oil, corn oil, etc.) are mentioned, for example. As a suitable example of a solubilizing agent, a polyvinyl pyrrolidone, cyclodextrin, caffeine, a polyethylene glycol, propylene glycol, a mannitol, benzyl benzoate, ethanol, tris aminomethane, cholesterol, triethanolamine, a sodium carbonate, a sodium citrate, etc. are mentioned, for example. As a suitable example of a suspending agent, hydrophilic macromolecules, such as surface active agents, for example, polyvinyl alcohol, such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, glyceryl monostearate, and polysorbate 80, a polyvinyl pyrrolidone, carboxymethylcellulose sodium, methyl cellulose, a hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, gum arabic, gelatin, and albumin, etc. are mentioned, for example. As a suitable example of a thickener, yolk lecithin, gelatin, gum arabic, tragacanth gum, methyl cellulose, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropylcellulose, polyvinyl alcohol, sodium polyacrylate, sodium alginate, pectin, etc. are mentioned, for example. As a suitable example of an isotonizing agent, a sorbitol, a glycerol, a polyethylene glycol, propylene glycol, a glucose, a sodium chloride, etc. are mentioned, for example. As a suitable example of a buffer, a phosphoric-acid buffer, a boric-acid buffer, a citric-acid buffer, a tartaric-acid buffer, an acetic-acid buffer, etc. are mentioned, for example. As a suitable example of an aponia-ized agent, benzyl alcohol etc. is mentioned, for example.

InnoPharma Exhibit 1046.0088

(19)日本国特許庁（ＪＰ）　(12)公開特許公報（A）　(11)特許出願公開番号

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Ａ６１Ｋ　31/435	ＡＢＬ	Ａ６１Ｋ　31/435	ＡＢＬ
9/08		9/08	Ｖ
47/32		47/32	Ｇ
Ｃ０７Ｄ 491/052		Ｃ０７Ｄ 491/052	

審査請求　未請求　請求項の数19　ＯＬ　（全 14 頁）

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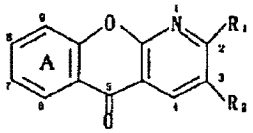
最終頁に続く

(54)【発明の名称】　視機能障害の予防・治療剤

(57)【要約】
【解決手段】　一般式
【化１】



〔Ｉ〕

〔式中、Ａ環は置換されていてもよく、R_1 は水素または保護されていてもよいアミノ基を、R_2 はプロトンを放出し得る基を示す〕で表される化合物またはその塩を含有してなる視機能障害の予防・治療剤。
【効果】　本発明の視機能障害の予防・治療剤は、臨床的に優れた眼精疲労予防・治療効果、眼軸長の伸長抑制作用、網膜機能の低下抑制作用、および網膜機能回復作用を有するため、臨床応用可能な視機能障害の予防・治療剤として有利に用いることができる。

InnoPharma Exhibit 1046.0089

(19) Europäisches Patentamt
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(11) EP 0 819 431 A1

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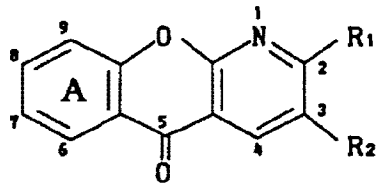
(54) Agent for prophylaxis and treatment of disturbance of visual function

(57) An agent for the prophylaxis and treatment of disturbance of visual function, which comprises a compound of the formula [I]



[I]

wherein

A ring is optionally substituted;
R_1 is a hydrogen or an optionally protected amino; and
R_2 is a group capable of releasing a proton,

or a salt thereof.

The agent for the prophylaxis and treatment of disturbance of visual function of the present invention has superior preventive and therapeutic effect on asthenopia, and shows suppression of axial elongation, suppression of degradation of retinal functions and retinal function-recovery action. Hence, the agent can be advantageously used as a clinically applicable agent for the prophylaxis and treatment of disturbance of visual function.

EP 0 819 431 A1

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Description

TECHNICAL FIELD OF THE INVENTION

The present invention relates to an agent for the prophylaxis and treatment of disturbance of visual function. By disturbance of visual function is meant a condition where normal vision cannot be obtained, which condition inclusive of myopia, hypermetropia, strabismus, disorders of retina which is a receptor of light, the condition where normal vision of an object is temporarily prevented by systemic or local fatigue of eyes, and other conditions.

BACKGROUND OF THE INVENTION

Of the disturbances of visual function, myopia and hypermetropia refer to the condition wherein the light that passed through cornea cannot form an image on the retina, and thus cannot grasp the image clearly. Of these, myopia is divided into axial myopia and refractive myopia according to the cause of the condition. The refractive myopia is caused by an increased refraction of cornea and lens, while axial myopia is caused by an elongation of the eyeball in the direction of optic axis, i.e. axial direction. It is nevertheless not easy to simply divide these two. The etiology of myopia has not been fully elucidated and a pharmaceutical agent to completely cure myopia has not been found yet.

In most cases, myopia is treated by a means utilizing correction of optical refraction. Correction of optical refraction by wearing glasses is not an ideal means as far as the quality of life and convenience for studying etc. are concerned. Correction of optical refraction using contact lenses often causes complications, and corneal ulcer may occur, which could possibly lead to the loss of sight in severe cases. In addition, recent application of corneal surgery to cure myopia is sometimes associated with failure to achieve expected levels of refraction, as well as occurrence of pain during operation and postoperative corneal opacity. In view of the fact that the correction of optical refraction and surgical operation such as the above-mentioned cannot be a perfect cure of myopia, treatment of myopia by the use of a drug is desired.

As the pharmaceutical agent to suppress axial elongation, the usefulness of muscarine I receptor antagonist and dopamine receptor agonist has been documented. However, a pharmaceutical agent which can be clinically applied has not been created so far.

Meanwhile, the retina consists of photoreceptor cells, bipolar cells, ganglion cells, horizontal cells, amacrine cells and the like, which transmit optical information to the central nerves. The functions of these cells contribute to the fulfillment of retinal function to organize the received optical information and transmit same to the central nerves.

When the retina is damaged, visual loss, disturbance of light sense and disturbance of visual field are induced, thereby causing central retinal artery and vein occlusions, congenital stationary night blindness, diabetic retinopathy, pigmentary retinal degeneration, retinal detachment, uveitis and the like.

While the therapeutics of retinal diseases and convalescence thereof vary depending on the kind and degree of the diseases, in particular, central retinal artery occlusion, diabetic retinopathy and retinal detachment scarcely allow complete recovery of retinal functions. It may happen that visual acuity does not improve after all and even an operation does not result in full recovery of visual acuity. What is more, no effective cure is currently available for pigmentary retinal degeneration but a symptomatic therapy such as use of sun glasses to avoid direct sun light.

In the internal treatment currently applied to cure retinal diseases, a pharmaceutical agent capable of suppressing degradation of retinal functions and achieving remarkable recovery of retinal function has not been found.

The asthenopia refers to a condition involving a kind of accommodation disorder of ciliary muscle due to systemic or local fatigue of the eye. Fatigue of eyes results in progressively growing distance of near point, which proceeds to the point that the eyes cannot recognize an object temporarily. However, recovery from fatigue can restore the original condition.

The treatment of asthenopia has heretofore included administration of medicaments such as vitamins (e.g., vitamin B_1 and vitamin B_{12}), ATP and the like, though sufficient therapeutic effects against asthenopia have not been attained.

As mentioned supra, no medicament that purportedly is useful for the prophylaxis and treatment of disturbance of visual function is satisfactory, and the development of an agent for the prophylaxis and treatment of disturbance of visual function has been desired by both doctors and patients.

SUMMARY OF THE INVENTION

According to the present invention, there has now been provided an agent for the prophylaxis and treatment of disturbance of visual function. Thus, the present invention provides:

(1) an agent for the prophylaxis and treatment of disturbance of visual function, which comprises a compound of the formula [I]

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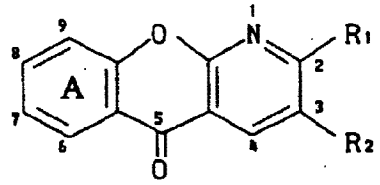


[I]

wherein

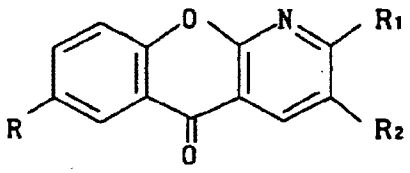
A ring is optionally substituted;
R_1 is a hydrogen or an optionally protected amino; and
R_2 is a group capable of releasing a proton,

or a salt thereof;

(2) the agent for the prophylaxis and treatment of disturbance of visual function according to (1) above, wherein the A ring is optionally substituted by halogen atom, nitro, alkyl, alkoxy or butadienylene (-CH=CH-CH=CH-) which forms a benzene ring with two adjacent carbon atoms at two of the 6, 7, 8 and 9 positions;

(3) the agent for the prophylaxis and treatment of disturbance of visual function according to (1) above, wherein the group capable of releasing a proton is carboxyl or tetrazolyl;

(4) the agent for the prophylaxis and treatment of disturbance of visual function according to (1) above, wherein the compound is represented by the formula [II]



[II]

wherein

R is an alkyl;
R_1 is a hydrogen or an optionally protected amino; and
R_2 is a group capable of releasing a proton;

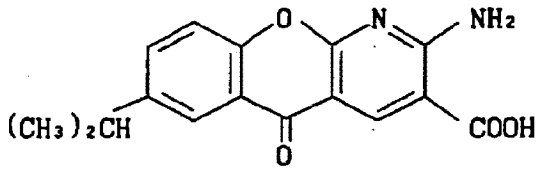
(5) the agent for the prophylaxis and treatment of disturbance of visual function according to (4) above, wherein the alkyl has 1 to 6 carbon atoms;

(6) the agent for the prophylaxis and treatment of disturbance of visual function according to (4) above, wherein the alkyl is isopropyl;

(7) the agent for the prophylaxis and treatment of disturbance of visual function according to (1) or (4) above, wherein R_1 is an amino;

(8) the agent for the prophylaxis and treatment of disturbance of visual function according to (1) or (4) above, wherein R_2 is a carboxyl;

(9) the agent for the prophylaxis and treatment of disturbance of visual function according to (1) above, wherein the compound is represented by the formula [III]



[III]

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(10) the agent for the prophylaxis and treatment of disturbance of visual function according to (1) above, which is used for local administration to the eye;
(11) the agent for the prophylaxis and treatment of disturbance of visual function according to (1) above, which is in the form of a liquid preparation;
(12) the agent for the prophylaxis and treatment of disturbance of visual function according to (10) or (11) above, which is in the form of an ophthalmic solution;
(13) the agent for the prophylaxis and treatment of disturbance of visual function according to (12) above, which is in the form of an aqueous ophthalmic solution;
(14) the agent for the prophylaxis and treatment of disturbance of visual function according to (11) above, which is in the form of an injection;
(15) the agent for the prophylaxis and treatment of disturbance of visual function according to (13) or (14) above, which further comprises a solubilizer;
(16) the agent for the prophylaxis and treatment of disturbance of visual function according to (15) above, wherein the solubilizer is polyvinylpyrrolidone;
(17) the agent for the prophylaxis and treatment of disturbance of visual function according to (16) above, wherein the polyvinylpyrrolidone is contained in a concentration of 0.2 - 20 (W/V)%;
(18) the agent for the prophylaxis and treatment of disturbance of visual function according to any one of (13) to (17) above, which comprises the compound of the formula [I] or a salt thereof in a concentration of 0.01 - 2.0 (W/V)%;
(19) the agent for the prophylaxis and treatment of disturbance of visual function according to any one of (1) to (18) above, wherein the disturbance of visual function is asthenopia, axial myopia or a retinal disease; and the like.

The compound to be the active ingredient in the present invention is disclosed to have potent antiallergic action and antiinflammatory action in, for example, Japanese Patent Unexamined Publication No. 10587/1986. Japanese Patent Unexamined Publication No. 258083/1995 discloses that the compound to be used in the present invention has prophylactic and therapeutic effects on myopia caused by relaxation of ciliary muscle. It is not until the present invention has been made that the compound to be used in the present invention has been found to have superior prophylactic and therapeutic effects on asthenopia, suppressive action on axial elongation, and therefore, superior prophylactic and therapeutic effects on axial myopia, and suppressive action on degradation of retinal functions and retinal function-recovery action, and therefore, superior prophylactic and therapeutic effects on retinal diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing CV(T)/CV(O) as determined in Experimental Example 1 with regard to coefficient of variation (CV) of 6 patients A to F before administration of test drug (Day 0), 7 days and 14 days after administration thereof, wherein the average coefficient of variation before administration (Day 0) is CV(O) and the average coefficient of variation at 7 days and 14 days after administration is CV(T) wherein T is 7 or 14. In the Figure, the horizontal axis shows the period of drug administration (7 days and 14 days) and the vertical axis shows CV(T)/CV(O).

Fig. 2 shows amplitude of a wave of ERG at 2 days after eyelid suture, wherein each column shows mean±standard error.

Fig. 3 shows amplitude of b wave of ERG at 2 days after eyelid suture, wherein each column shows mean±standard error.

Fig. 4 shows amplitude of oscillatory potential of ERG at 2 days after eyelid suture, wherein each column shows mean±standard error.

DETAILED DESCRIPTION OF THE INVENTION

In the formula [I], the substituents on the A ring may be, for example, halogen atom, nitro, alkyl, alkoxy, butadienylene (-CH=CH-CH=CH-) which forms a benzene ring with two adjacent carbon atoms at two of the 6, 7, 8 and 9 positions, and the like.

The halogen atom is exemplified by chlorine, bromine, fluorine and the like.

The alkyl is preferably linear or branched alkyl having 1 to 6 carbon atoms. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl and the like. More preferred is linear or branched alkyl having 1 to 3 carbon atoms.

The alkoxy preferably has 1 to 4 carbon atoms. Examples of said alkoxy include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

One or more than one, the same or different substituent(s) may be substituted at optional position(s) of the A ring.

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In the formulas [I] and [II], the protecting group at R_1 of optionally protected amino group is, for example, (1) alkanoyl having 2 to 7 carbon atoms which may have 1 to 3 substituents selected from (a) halogen atom (e.g., chlorine, bromine and fluorine), (b) alkanoyl having 1 to 7 carbon atoms (e.g., formyl, acetyl, propionyl, isopropionyl, n-butyryl, isobutyryl, n-valeryl, isovaleryl, pivaloyl and n-hexanoyl) and (c) nitro, which alkanoyl is exemplified by acetyl, propionyl, isopropionyl, n-butyryl, isobutyryl, n-valeryl, isovaleryl, pivaloyl and n-hexanoyl; (2) arylcarbonyl having 7 to 11 carbon atoms which may have 1 to 3 substituents selected from the above-mentioned (a), (b) and (c), which arylcarbonyl is exemplified by benzoyl, p-toluoyl, 1-naphthoyl and 2-naphthoyl; (3) alkoxycarbonyl having 2 to 7 carbon atoms which may have 1 to 3 substituents selected from the above-mentioned (a), (b) and (c), which alkoxycarbonyl is exemplified by methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and tert-butoxycarbonyl; (4) aryloxycarbonyl having 7 to 11 carbon atoms which may have 1 to 3 substituents selected from the above-mentioned (a), (b) and (c), which aryloxycarbonyl is exemplified by phenoxycarbonyl; (5) aralkylcarbonyl having 8 to 13 carbon atoms which may have 1 to 3 substituents selected from the above-mentioned (a), (b) and (c), which aralkylcarbonyl is exemplified by benzylcarbonyl and phenethylcarbonyl; (6) aralkyloxycarbonyl having 8 to 13 carbon atoms which may have 1 to 3 substituents selected from the above-mentioned (a), (b) and (c), which aralkyloxycarbonyl is exemplified by benzyloxycarbonyl and phenethyloxycarbonyl; (7) phthaloyl optionally having 1 to 3 substituents selected from the above-mentioned (a), (b) and (c), (8) arylsulfonyl having 6 to 10 carbon atoms which may have 1 to 3 substituents selected from the above-mentioned (a), (b) and (c), which arylsulfonyl is exemplified by phenylsulfonyl and tosyl; (9) alkylsulfonyl having 1 to 6 carbon atoms which may have 1 to 3 substituents selected from the above-mentioned (a), (b) and (c), which alkylsulfonyl is exemplified by methylsulfonyl, ethylsulfonyl and n-propylsulfonyl; (10) alkyl having 1 to 6 carbon atoms which may have 1 to 3 substituents selected from the above-mentioned (a), (b) and (c) and amino, which alkyl is exemplified by methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl; (11) aralkyl having 7 to 19 carbon atoms which may have 1 to 3 substituents selected from the above-mentioned (a), (b) and (c), which aralkyl is exemplified by benzyl, phenethyl, benzhydryl and trityl; and the like.

The protecting group at amino includes, for example, alkanoyl having 2 to 7 carbon atoms, arylcarbonyl having 7 to 11 carbon atoms, alkoxycarbonyl having 2 to 7 carbon atoms, aryloxycarbonyl having 7 to 11 carbon atoms, aralkylcarbonyl having 8 to 13 carbon atoms and aralkyloxycarbonyl having 8 to 13 carbon atoms, all of which may have 1 to 3 substituents selected from the above-mentioned (a) halogen atom, (b) alkanoyl having 1 to 7 carbon atoms and (c) nitro.

As R_1, preferred is an unsubstituted amino.

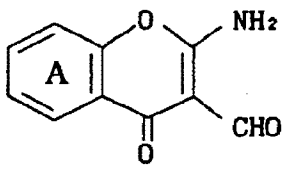
In the formulas [I] and [II], the group capable of releasing proton and represented by R_2 is exemplified by a group which easily releases H^+ and becomes an anion, such as carboxyl, tetrazolyl, trifluoromethanesulfonylamino ($-NHSO_2CF_3$), phosphono and sulfo, which may be any as long as it can release proton under biological or physiological conditions (e.g., reactions in the body such as oxidation, reduction and hydrolysis by biological enzymes) or chemically, or a group capable of converting to such group, and which may be protected by alkyl optionally substituted by a suitable substituent (e.g., alkyl having 1 to 4 carbon atoms such as methyl and n-butyl), optionally substituted acyl (e.g., alkanoyl having 2 to 4 carbon atoms such as acetyl and propionyl which are optionally substituted by halogen atom, and benzoyl optionally substituted by halogen atom or amino) and the like.

The group capable of releasing proton is, for example, preferably carboxyl and tetrazolyl, with particular preference given to carboxyl.

In the formula [II], the alkyl represented by R is preferably linear or branched alkyl having 1 to 6 carbon atoms. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl and n-hexyl. Preferred is linear or branched alkyl having 1 to 3 carbon atoms. R is particularly preferably isopropyl.

The compound of the formula [I] is preferably a compound of the formula [II], and more preferably a compound of the formula [III].

The compound of the formula [I] can be produced by, for example, reacting a compound of the formula [IV]



[IV]

wherein each symbol is as defined above, and an active methylene compound or acetylenecarboxylic acid derivative, followed by hydrolysis.

Examples of active methylene compound include methyl acetoacetate, ethyl acetoacetate, methyl cyanoacetate, ethyl cyanoacetate, cyanoacetamide, malononitrile, ethyl oxalacetate, diethyl malonate, dimethyl malonate, ethyl ben-

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zoylacetate, methyl 3-oxo-n-caproate and the like. These active methylene compounds are used in amounts practically corresponding to about 1 to 10-fold moles per mole of starting compound [IV] or a salt thereof.

Examples of acetylenecarboxylic acid derivative include dimethyl acetylenedicarboxylate, diethyl acetylenedicarboxylate, methyl propiolate, ethyl propiolate and the like. When propiolic acid ester is used, an intermediate aminoacrylate derivative can be isolated. Alternatively, it can be subjected to ring-closing reaction without isolation. These acetylenecarboxylic acid derivatives are used in amounts practically corresponding to about 1 to 10-fold moles per mole of starting compound [IV] or a salt thereof.

In generality, the reaction preferably proceeds in the presence of a base which is exemplified by organic amines such as primary amine (e.g., n-butylamine, benzylamine and aniline), secondary amine (e.g., diethylamine, dipropylamine, dibutylamine, piperidine, pyrrolidine and morpholine), tertiary amine (e.g., 1,8-diazabicyclo[5,4,0]-7-undecene and triethylamine), and heterocyclic base (e.g., imidazole and 2-methylimidazole). These organic bases are used in amounts corresponding to about catalytic amount to 5-fold moles per mole of starting compound [IV] or a salt thereof.

The reaction preferably proceeds in an organic solvent which is exemplified by alcohols such as methanol, ethanol, propanol and butanol, aromatic hydrocarbons such as benzene and toluene, dimethylformamide, and the like. The reaction temperature, reaction time and other conditions for the reaction are not particularly limited. The reaction is generally carried out at a temperature of from room temperature to near boiling point of the solvent used, for about 1 to 24 hours. When desired, amino group of cyanoacetamide, which is an active methylene compound, may be protected in the instant production step. Said protection can be carried out according to a conventional method in the pertinent field.

The conditions of hydrolysis are those for conventional acid hydrolysis. For example, sulfuric acid, hydrochloric acid, phosphoric acid and the like are used in excess and hydrolysis is performed by the action of said acids alone, or in an organic solvent such as organic acids (e.g., formic acid and acetic acid) or alcohols such as methanol, ethanol, propanol and butanol, after which the mixture is generally heated to about 50-150°C. While the reaction time varies depending on the kind of compound to be used, it is generally about 1 hour to several days.

The compound [I] can be also used after being converted to a pharmacologically acceptable salt. Examples of such salt include salts with a base such as inorganic base and organic base and acid addition salts with inorganic acid, organic acid, basic or acidic amino acid and the like.

The inorganic base is exemplified by alkali metals such as sodium and potassium; alkaline earth metals such as calcium and magnesium; aluminum; ammonium and the like.

The organic base is exemplified by primary amine (e.g., ethanolamine), secondary amine (e.g., diethylamine, diethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine), tertiary amine (e.g., trimethylamine, triethylamine, pyridine, picoline and triethanolamine), and the like.

The inorganic acid is exemplified by hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like.

The organic acid is exemplified by formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like.

The basic amino acid is exemplified by arginine, lysine and ornithine, and acidic amino acid is exemplified by aspartic acid and glutamic acid.

The salt of compound [I] can be produced according to the method described in, for example, Japanese Patent Unexamined Publication Nos. 10587/1986, 10588/1986 and 88298/1979, US-A-4267332 or a method analogous to these methods.

The compound [I] and a salt thereof have, as is evident from Experimental Examples to be mentioned later, superior therapeutic effect on asthenopia, suppressive action on axial elongation, suppressive action on degradation of retinal functions, and retinal function-recovery action. Therefore, they are useful as agents for the prophylaxis and treatment of disturbance of visual functions.

The agents for the prophylaxis and treatment of disturbance of visual function of the present invention have low toxicity and can be administered safely to mammals such as human, rabbit, dog, cat, cow, horse, monkey and the like by an oral or parenteral route.

The agents for the prophylaxis and treatment of disturbance of visual function of the present invention can be produced by, for example, admixing the compound [I] or a salt thereof with a pharmaceutically acceptable carrier.

The pharmaceutically acceptable carrier includes, for example, various organic and inorganic carriers commonly used as materials for preparations, such as, for solid preparations, excipients, lubricants, binders, disintegrators and the like, and, for liquid preparations, solvents, solubilizers, suspending agents, tackifiers, isotonizing agents, buffers, analgesic agents and the like, which can be used as appropriate. Where necessary, preservatives, chelating agents, antioxidants, colorings, sweeteners, flavors, aromatics, and other additives for preparations may be added by a conventional method.

Examples of suitable excipients include lactose, sucrose, mannitol, starch, crystalline cellulose, light anhydrous sil-

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icic acid and the like.

Examples of suitable lubricants include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

Examples of suitable binders include sucrose, mannitol, maltitol, starch, gelatin, gum arabic, tragacanth, crystalline cellulose, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, sodium arginate, chitin, chitosan and the like.

Examples of suitable disintegrators include starch, carboxymethylcellulose, calcium carboxymethylcellulose, croscarmellose sodium, sodium carboxymethyl starch, chitin, chitosan and the like.

Examples of suitable solvents include water for injection, alcohols (e.g., ethanol, propylene glycol, macrogol, glycerine and the like), fats and oils (e.g., olive oil, sesame oil, peanut oil, cotton seed oil, castor oil, corn oil and the like), and the like.

Examples of suitable solubilizers include polyvinylpyrrolidone, cyclodextrin, caffeine, polyethylene glycol, propylene glycol, mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like.

Examples of suitable suspending agents include surfactants (e.g., stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithine, glyceryl monostearate and Polysorbate 80), hydrophilic polymers (e.g., polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, gum arabic, gelatin, albumin, and the like) and the like.

Examples of suitable tackifiers include egg yolk lecithine, gelatin, gum arabic, tragacanth, methylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, polyvinyl alcohol, sodium polyacrylate, sodium alginate, pectin and the like.

Examples of suitable isotonizing agents include sorbitol, glycerol, polyethylene glycol, propylene glycol, glucose, sodium chloride and the like.

Examples of suitable buffers include phosphate buffer, borate buffer, citrate buffer, tartrate buffer, acetate buffer and the like.

Examples of suitable analgesic agents include benzyl alcohol and the like.

Examples of suitable preservatives include p-hydroxybenzoate, benzalkonium chloride, benzethonium chloride, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and salt thereof, p-chlorometaxylenol, chlorocresol, thimerosal and the like.

Examples of suitable chelating agents include disodium edetate, sodium citrate, condensed sodium phosphate and the like.

Examples of suitable antioxidants include sulfite, ascorbic acid, α-tocopherol, cysteine and the like.

Examples of suitable colorants include tar pigment, glycyrrhiza extract, riboflavin, zinc oxide and the like.

Examples of suitable sweeteners include glucose, sucrose, fructose, honey, saccharic acid, glycyrrhiza and the like.

Examples of suitable flavors include vanillin, menthol, rose oil and the like.

Examples of suitable aromatics include fennel oil, borneol, menthol and the like.

Besides the above-mentioned, agar, casein, collagen and the like are pharmaceutically acceptable carriers.

Other agents for the prophylaxis and treatment of asthenopia such as a drug containing, as an active ingredient, vitamins (e.g., vitamin B_1, vitamin B_{12} and the like), ATP and the like; agents for the prophylaxis and treatment of myopia such as neostigmine methylsulfate, tropicamide and a drug containing these as an active ingredient; other drugs having retinal function-improving action such as tocopherol nicotinate [Juvela N (trademark, manufacture by EISAI CO., LTD.)]; and other ingredients having different efficacy, may be added to the preparation as appropriate.

When the agent for the prophylaxis and treatment of disturbance of visual function of the present invention is used in the form of an aqueous liquid, its pH is 4 to 9 in view of the stability of the compound [I] and a salt thereof.

The oral preparations may be, for example, solid preparations (e.g., powders, granule, tablets and capsules) or liquid preparations (e.g., emulsions, syrups and suspensions).

For example, tablets can be produced by adding the above-mentioned excipients, disintegrators, binders, lubricants and the like as appropriate to compound [I] or a salt thereof and compression formulating the mixture. In so doing, the above-mentioned sweetners, flavors, aromatics and the like may be further added on demand after compression formulation, or coating may be applied by a method known *per se* for enteric use or controlled release of the preparation. The coating agent used for this end includes, for example, hydroxypropylcellulose, hydroxypropylmethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, ethylcellulose and the like.

A suspending agent can be produced by, for example, suspending the compound [I] or a salt thereof in the aforementioned solvent. When desired, the above-mentioned suspending agents may be used as appropriate.

Parenteral preparation includes, for example, injections, preparations for local administration to the eye, and the like. The injection includes subcutaneous injection, intravenous injection, intramuscular injection and the like. Injections may be aqueous or non-aqueous, and a solution or suspension.

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The preparations for local administration to the eye include ophthalmic solution, ophthalmic ointment, gel and the like, with particular preference given to ophthalmic solution which may be aqueous or non-aqueous, and a solution or suspension.

The agent for the prophylaxis and treatment of disturbance of visual function of the present invention is preferably used as a preparation for local administration to the eye. More preferably, it is used as an ophthalmic solution, particularly an aqueous ophthalmic solution.

An aqueous injection can be prepared by, for example, dissolving compound [I] or a salt thereof in water for injection together with the above-mentioned preservatives, isotonizing agents, solubilizers and the like. An oily injection can be prepared by dissolving or suspending compound [I] or a salt thereof in propylene glycol, olive oil, sesame oil, cotton seed oil and the like.

An aqueous ophthalmic solution can be prepared by, for example, heating distilled water, dissolving a preservative therein, adding a solubilizer, and adding and completely dissolving compound [I] or a salt thereof. Where necessary, buffers, isotonizing agents, chelating agents, tackifiers and the like may be also added.

The solubilizer is preferably polyvinylpyrrolidone, cyclodextrin, caffeine and the like, with particular preference given to polyvinylpyrrolidone. When polyvinylpyrrolidone is used, compound [I] and a salt thereof are noticeably improved in solubility and come to have greater stability [see Japanese Patent Unexamined Publication No. 123116/1987, i.e., Japanese Patent Examined Publication No. 78614/1992].

For example, polyvinylpyrrolidone to be used has an average molecular weight of about 25,000 to about 120,000, preferably about 40,000 (e.g., polyvinylpyrrolidone K30). Polyvinylpyrrolidone is generally added in a concentration of 0.2 to 20 (W/V)%, preferably 0.5 to 15 (W/V)%, particularly preferably 1 to 10 (W/V)%.

The buffer is particularly preferably a borate buffer. When borate buffer is used, a less irritant liquid as compared to other buffers, such as phosphate buffer, can be obtained. In this case, boric acid is added in a concentration of 0.2 to 4 (W/V)%, preferably 0.5 to 2 (W/V)%.

The aqueous ophthalmic suspension can be prepared by adding, besides the above-mentioned additives used for aqueous ophthalmic solutions, the aforementioned suspending agents as appropriate.

The pH of the above-mentioned aqueous ophthalmic solution and aqueous ophthalmic suspension is preferably 4 to 9, particularly preferably 5 to 8.

A non-aqueous ophthalmic solution can be prepared by dissolving or suspending compound [I] or a salt thereof in an aqueous solvent such as alcohols (e.g., ethanol, ethylene glycol, macrogol, propylene glycol, glycerol and the like) and an oily solvent such as fats and oils (e.g., olive oil, sesame oil, peanut oil, cotton seed oil, castor oil, corn oil and the like).

An ophthalmic ointment can be prepared by appropriately using, for example, petrolatum, plastibase, liquid paraffin and the like as a base.

An ophthalmic gel can be prepared by appropriately using, for example, carboxyvinyl polymer, polymer of ethylene maleic anhydride, polyoxyethylene-polyoxypropylene block copolymer, gellan gum and the like as a base.

While the dose of the agent for the prophylaxis and treatment of disturbance of visual function of the present invention varies depending on the administration route, kind of diseases, symptoms, age and body weight of patients, and the like, for example, it is preferably administered to an adult patient with asthenopia, axial myopia or retinal disease as an aqueous ophthalmic solution comprising compound [I] or a salt thereof, which is an active ingredient, in a concentration of 0.01 to 2.0 (W/V)%, preferably 0.1 to 1.0 (W/V)%, in a single dose of one to several drops thereof according to symptoms, once to several times a day, preferably 2 to 5 times a day, to one eye of a patient.

The present invention is described in more detail in the following by way of Examples, and the effects of the invention are clarified by way of Experimental Examples, which should not be construed as limiting the invention.

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Example 1

aqueous ophthalmic solution

(Formulation)

compound [III]	5 g
boric acid	9 g
sodium tetraborate	16 g
polyvinylpyrrolidone K30	20 g
methyl p-hydroxybenzoate	0.26 g
propyl p-hydroxybenzoate	0.14 g
hydrochloric acid	suitable amount
sterile purified water	amount to make the total 1,000 ml
	(pH 6.0)

(Preparation method)

Sterile purified water (800 ml) was heated and methyl p-hydroxybenzoate and propyl p-hydroxybenzoate were dissolved therein. Then, boric acid, sodium tetraborate, polyvinylpyrrolidone K30 and compound [III] were successively added and dissolved. After cooling, hydrochloric acid was added to adjust the pH to 6.0 and sterile purified water was added to make the total amount 1,000 ml. The mixture was sterilized by filtration through a 0.22 μm membrane filter and filled in a predetermined container to give an aqueous ophthalmic solution.

Example 2

aqueous ophthalmic solution

(Formulation)

compound [III]	5 g
boric acid	16 g
sodium tetraborate	10 g
polyvinylpyrrolidone K30	20 g
caffeine	2 g
polyethylene glycol (average molecular weight 4,000)	5 g
methyl p-hydroxybenzoate	0.26 g
propyl p-hydroxybenzoate	0.14 g
hydrochloric acid	suitable amount
sterile purified water	amount to make the total 1,000 ml
	(pH 6.0)

(Preparation method)

Sterile purified water (800 ml) was heated and methyl p-hydroxybenzoate and propyl p-hydroxybenzoate were dissolved therein. Then, boric acid, sodium tetraborate, polyvinylpyrrolidone K30, caffeine, polyethylene glycol and compound [III] were successively added and dissolved. After cooling, hydrochloric acid was added to adjust the pH to 6.0

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and sterile purified water was added to make the total amount 1,000 ml. The mixture was sterilized by filtration through a 0.22 μm membrane filter and filled in a predetermined container to give an aqueous ophthalmic solution.

Example 3

aqueous ophthalmic solution

(Formulation)

compound [III]	2.5 g
boric acid	16 g
sodium tetraborate	7 g
polyvinylpyrrolidone K30	20 g
methyl p-hydroxybenzoate	0.26 g
propyl p-hydroxybenzoate	0.14 g
sodium hydroxide	suitable amount
sterile purified water	amount to make the total 1,000 ml (pH 7.5)

(Preparation method)

Sterile purified water (800 ml) was heated, and methyl p-hydroxybenzoate and propyl p-hydroxybenzoate were dissolved therein by heating and the solution was cooled to room temperature. Then, boric acid, sodium tetraborate and polyvinylpyrrolidone K30 were successively added and dissolved. Compound [III] was added and dissolved therein. Sodium hydroxide was added to adjust the pH to 7.5 and sterile purified water was added to make the total amount 1,000 ml. The mixture was sterilized by filtration through a 0.22 μm membrane filter and filled in a predetermined container to give an aqueous ophthalmic solution.

Example 4

aqueous ophthalmic solution

(Formulation)

compound [III]	5 g
boric acid	16 g
sodium tetraborate	7 g
polyvinylpyrrolidone K30	20 g
methyl p-hydroxybenzoate	0.26 g
propyl p-hydroxybenzoate	0.14 g
sodium hydroxide	suitable amount
sterile purified water	amount to make the total 1,000 ml (pH 8.0)

(Preparation method)

Sterile purified water (800 ml) was heated, and methyl p-hydroxybenzoate and propyl p-hydroxybenzoate were dissolved therein by heating and the solution was cooled to room temperature. Then, boric acid, sodium tetraborate and

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polyvinylpyrrolidone K30 were successively added and dissolved. Compound [III] was added and dissolved therein. Sodium hydroxide was added to adjust the pH to 8.0 and sterile purified water was added to make the total amount 1,000 ml. The mixture was sterilized by filtration through a 0.22 μm membrane filter and filled in a predetermined container to give an aqueous ophthalmic solution.

Example 5

aqueous ophthalmic solution

(Formulation)

compound [III]	10 g
boric acid	16 g
sodium tetraborate	7 g
polyvinylpyrrolidone K30	20 g
methyl p-hydroxybenzoate	0.26 g
propyl p-hydroxybenzoate	0.14 g
sodium hydroxide	suitable amount
sterile purified water	amount to make the total 1,000 ml (pH 8.0)

(Preparation method)

Sterile purified water (800 ml) was heated, and methyl p-hydroxybenzoate and propyl p-hydroxybenzoate were dissolved therein by heating and the solution was cooled to room temperature. Then, boric acid, sodium tetraborate and polyvinylpyrrolidone K30 were successively added and dissolved. Compound [III] was added and dissolved therein. Sodium hydroxide was added to adjust the pH to 8.0 and sterile purified water was added to make the total amount 1,000 ml. The mixture was sterilized by filtration through a 0.22 μm membrane filter and filled in a predetermined container to give an aqueous ophthalmic solution.

Example 6

aqueous ophthalmic suspension

(Formulation)

compound [III]	10 g
sodium dihydrogenphosphate	50 g
sodium chloride	9 g
polysorbate 80	20 g
chlorobutanol	3 g
sodium hydroxide	suitable amount
sterile purified water	amount to make the total 1,000 ml (pH 5.0)

(Preparation method)

Sterile purified water (800 ml) was heated, and chlorobutanol was dissolved therein. Then, sodium dihydrogen-

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phosphate, sodium chloride and polysorbate 80 were successively added and dissolved. The solution was cooled to room temperature. Sodium hydroxide was added to adjust the pH to 5.0 and sterile purified water was added to make the total amount 1,000 ml. The mixture was sterilized by filtration through a 0.22 µm membrane filter, thereby to uniformly disperse compound [III] sterilized in advance, whereby an aqueous ophthalmic suspension was prepared.

Example 7

oily ophthalmic solution

(Formulation)

compound [III]	20 g
cotton seed oil	amount to make the total 1,000 ml

(Preparation method)

Compound [III] was added to cotton seed oil sterilized in advance to give an oily ophthalmic solution.

Example 8

ophthalmic ointment

(Formulation)

compound [III]	10 g
liquid paraffin	100 g
white petrolatum	amount to make the total 1,000 g

(Preparation method)

Liquid paraffin and white petrolatum were sterilized by heating in advance. Then, compound [III] was thoroughly admixed with liquid paraffin and then sufficiently admixed with white petrolatum to give an ophthalmic ointment.

Example 9

ophthalmic gel

(Formulation)

compound [III]	5 g
carboxyvinyl polymer	10 g
phenethyl alcohol	5 g
sodium hydroxide	suitable amount
sterile purified water	amount to make the total 1,000 g
	(pH 7.0)

(Preparation method)

Phenethyl alcohol was dissolved in sterile purified water (800 ml) and sterilized by filtration through a 0.22 µm mem-

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brane filter. Compound [III] sterilized in advance was suspended in this solution and the suspension was vigorously stirred, during which sterilized carboxyvinyl polymer was added and dissolved. The obtained solution was adjusted to pH 7.0 with sodium hydroxide, and sterile purified water was added to make the total amount 1,000 g to give an ophthalmic gel.

Example 10

tablet

(Formulation)

compound [III]	10 mg
lactose	35 mg
corn starch	150 mg
microcrystalline cellulose	30 mg
magnesium stearate	5 mg
per tablet	230 mg

(Preparation method)

Compound [III], lactose, corn starch, 2/3 amount of microcrystalline cellulose and 1/2 amount of magnesium stearate were admixed and granulated. The rest of microcrystalline cellulose and magnesium stearate was added and the mixture was compression formed to give tablets.

Example 11

capsule

(Formulation)

compound [III]	10 mg
lactose	90 mg
microcrystalline cellulose	70 mg
magnesium stearate	10 mg
per capsule	180 mg

(Preparation method)

Compound [III], lactose, microcrystalline cellulose and 1/2 amount of magnesium stearate were admixed and granulated. The rest of magnesium stearate was added and the mixture was concealed in gelatin capsules to give capsules.

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Example 12

injection

(Formulation)

compound [III]	10 mg
inositol	100 mg
benzyl alcohol	20 mg
per ampoule	130 mg

(Preparation method)

Compound [III], inositol and benzyl alcohol were dissolved in distilled water for injection to the total amount of 2 ml and the solution was concealed in an ampoule. The entire procedure was carried out under sterile conditions.

Experimental Example 1

Therapeutic effect on asthenopia by administration of the agent of the invention to patients with asthenopia

According to the near point determination method proposed by Taturo Himi [Drug Effect on Asthenopia-Analysis of Drug Effect by Age, *Atarashii Ganka* (Journal of the Eye), vol. 3, No. 9, pp. 1247-1253 (1986)], therapeutic effect of the preparation of the present invention on asthenopia was investigated.

Six patients A-F (age 20-26) who visited hospital for asthenopia underwent instillation of the preparation of the present invention (aqueous ophthalmic solution obtained in Example 1) into one eye and placebo (aqueous ophthalmic solution prepared by removing the main drug, compound [III], from the preparation of the present invention) into the other eye by 2 drops per time and four times a day (9 o'clock, 13 o'clock, 17 o'clock and 21 o'clock), which was continued for 14 days. The patients A to F underwent 10 repeats of near point determination using an accommodopolyrecorder HS-9E equipped with continuous near pointometer (manufactured by Kowa Corp.) before instillation, and 7 and 14 days after instillation. Note that the values used for the evaluation this time were near point disappearance values, and the distance to the point(position) at which a near point table (index) drawing near blurred was recorded as the determination values. This is somewhat different from the measurement method generally employed. The reason this method was employed was that, from experience, this method is known to give stable and most fine responses when test subjects have different age, educational and environmental backgrounds (see publication supra, pp. 1248 and 1252).

Then, mean (M) and standard error (SD) of the near point as determined 10 times in the above with respect to the preparation of the present invention and placebo were calculated, and based on the obtained results, coefficient of variation CV (SD/M) was calculated. It is known that the progression of asthenopia leads to greater CV values. The average coefficients of variation (CV) of the six patients A-F was calculated with respect to the results obtained before instillation (day 0), 7 days after instillation and 14 days after instillation, and CV (T)/CV (O) (where T is 7 or 14) of the preparation of the present invention and placebo was calculated using the average of coefficient of variation before instillation (day 0) as CV (O), and that of 7 days after instillation and 14 days after instillation as CV (T) where T is 7 or 14. The results are shown in Table 1 and Fig. 1.

Table 1

CV (T)/CV (O) at 7 days and 14 days after instillation of test drug		
test drug	7 days after instillation CV (7)/CV (O)	14 days after instillation CV (14)/CV (O)
preparation of invention	0.78	0.87
placebo	1.02	1.12

As is evident from Table 1 and Fig. 1, the eyes instilled with the preparation of the present invention showed lower

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CV values (smaller than 1) at 7 days and 14 days after instillation, as compared to that before instillation. In contrast, the eyes instilled with placebo did not show decrease in CV values (greater than 1). Thus, the preparation of the present invention showed superior therapeutic effect on asthenopia in clinical tests, and was found to be clinically useful for the treatment of asthenopia.

Experimental Example 2

Therapeutic effect on axial myopia by administration of the agent of the invention

(Method)

As test animals, 7 days old male white leghorn chicks were used. The chicks were raised under 12 hour (8:00-20:00) lighting of 600 lux illumination. A mixture of ketamine hydrochloride [Ketalar (trademark, Sankyo Company, Limited)] and xylazine hydrochloride [Celactal (trademark, Bayer, Ltd.)] was intramuscularly injected to the chicks for general anesthesia. The upper and lower eyelids of one eye were sutured at the edge (hereinafter the eye sutured in this way may be referred to as sutured eye). At 4 days post-suture, the eyelids were opened and anterior chamber depth, lens thickness and vitreous chamber depth of both eyes were measured using A scan mode ultrasound (Z-1000, General). As a test drug, an aqueous ophthalmic solution containing compound [III] (content 0.5% and 1%) obtained in Examples 4 and 5 was subconjunctivally administered by 10 µl under ether anesthesia to the sutured eye twice on the day of suture and measurement day, and 4 times a day from day 1 to day 3. In the same manner, physiological saline was subconjunctivally administered to the sutured eye of the control group. The other eye of the chicks of both groups was untreated to suture and administration of the test drug (hereinafter the other eye may be referred to as non-sutured eye).

(Results)

The difference in vitreous chamber depth of sutured eye and non-sutured eye at 4 days post-suture is shown in Table 2.

Table 2

group	vitreous chamber depth (mm)	
	sutured eye - non-sutured eye	n
physiological saline	0.46±0.03	25
aqueous ophthalmic solution of Ex. 4 (0.5% compound [III])	0.37±0.03*	25
aqueous ophthalmic solution of Ex. 5 (1% compound [III])	0.34±0.03*	25

* : significance level less than 5% by Student's t-test

The vitreous chamber depth of control group at 4 days after eyelid suture was 0.46 mm significantly longer than that of non-sutured eye. The difference between sutured eye and non-sutured eye of the group administered with 0.5% and 1% compound [III] was 0.37 and 0.34 mm, respectively. Thus, compound [III] significantly suppressed elongation of vitreous chamber depth. As regards anterior chamber depth and lens thickness, no difference was observed between sutured eye and non-sutured eye of the control group and the group administered with compound [III].

From the above results, it is evident that compound [III] suppressed elongation of vitreous chamber depth due to eyelid suture in chick eyes.

The pharmaceutical preparation of the present invention significantly suppressed elongation of vitreous chamber depth due to eyelid suture in chick eyes. The involvement of retinal neurotransmitter is speculated in the onset mechanism of myopia induced by eyelid suture, though not yet fully elucidated. Most of the changes seen in model with axial myopia, such as elongation of vitreous chamber depth, extension of sclera, and thinning of choroid and retinal pigment epithelial layer, resembles the changes found in myopia of human. Inasmuch as compound [III] suppressed elongation of vitreous chamber depth in the instant models, the pharmaceutical preparation of the present invention is considered to be effective for the prevention and treatment of axial myopia in human.

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Experimental Example 3

Suppression of decrease of retinal function by administration of the agent of the invention

(Method)

ERG (electroretinogram) which is one of the methods to examine retinal functions can detect action potential of retina in response to light, from the surface of an eyeball. When a retinal disorder occurs, extension of peak latency and reduced amplitude are found. Inasmuch as ERG changes in central retinal artery and vein occlusions, congenital stationary night blindness, diabetic retinopathy, pigmentary retinal degeneration, retinal detachment, uveitis and the like, it has been used as useful objective auxiliary diagnostic of these diseases. Meanwhile, a report has documented that eye-occluded chicks showed the reduction of amplitude of oscillatory potential in ERG and thinning of retina (Takashi Fujikado, *Nihon Ganka Kiyo*, 42:1189-1194, 1991).

In this Experimental Example, white leghorn chicks were used as test animals, and action potential of retina was induced and recorded by ERG to evaluate retinal functions. The method therefor are described in the following.

The chicks were raised under 12 hour (8:00-20:00) lighting of 600 lux illumination at temperature 31±3°C, humidity 50±10%. Six days old chicks were accommodated in a complete dark room for 30 minutes, and a 1:1 mixture of ketamine hydrochloride [Ketalar (trademark, Sankyo Company, Limited)] and xylazine hydrochloride [Celactal (trademark, Bayer, Ltd.)] was intramuscularly injected to the chicks by 10 µl per 10 g body weight for general anesthesia. The head was fixed in a brain stereotaxis apparatus, and different and indifferent electrodes were respectively connected to the center of cornea and bulbar conjunctiva of the left eye by the use of a 0.5 mm diameter platinum wire, with grounding electrode led from under the skin of the head. After acclimation in the dark for one minute, 3 joule xenon light was irradiated 8 times from 20 cm before the cornea at 10-second intervals, and the averaged consecutive responses were evaluated using a potential recorder. The ERG obtained here is taken as the initial value.

A mixed solution of ketamine hydrochloride and xylazine hydrochloride was intramuscularly injected to the chicks for general anesthesia. The upper and lower eyelids were cut off under a stereoscopic microscope, and the left eye was sutured 5 stitches using 8-0 silk suture thread with needle (hereinafter the eye sutured in this way may be referred to as sutured eye).

As the test drug, compound [III] was dissolved in 0.1 M NaH_2PO_4 (pH 10) solution to a concentration of 0.5% (pH 7.8 after adjustment) and intraperitoneally administered 3 times a day on the day and the next day of suture, and once a day at two days after suture. The dose was 50 mg/kg. In the same manner, physiological saline was administered to the control group.

At 2 days post-suture, ERG was taken in the same manner as above after administration of the drug, and the averaged consecutive responses were evaluated using a potential recorder.

The a wave amplitude of ERG as determined at 2 days post-suture is shown in Fig. 2; b wave amplitude is shown in Fig. 3; and amplitude of oscillatory potential is shown in Fig. 4. The amplitude of a wave decreased to 6% of the initial value as a result of eyelid suture. In contrast, the group administered with compound [III] showed decrease to 42% of the initial value, thus showing significant suppression of amplitude decrease as compared to the control group. The amplitude of b wave decreased to 8% of the initial value as a result of eyelid suture. In contrast, the group administered with compound [III] showed decrease to 37% of the initial value, thus showing significant suppression of amplitude decrease as compared to the control group. The amplitude of oscillatory potential decreased to 10% of the initial value as a result of eyelid suture. In contrast, the group administered with compound [III] showed decrease to 37% of the initial value, thus showing significant suppression of amplitude decrease as compared to the control group.

From these results, it is appreciated that compound [III] significantly suppressed decrease of the amplitude of a wave, b wave and oscillatory potential of ERG caused by eyelid suture of chick eyes. Therefrom it is clear that compound [III] suppresses lowering of retinal functions, and therefore, the pharmaceutical agent of the present invention is useful as an agent for the prophylaxis and treatment of retinal diseases.

The agent for the prophylaxis and treatment of disturbance of visual function of the present invention has superior preventive and therapeutic effect on asthenopia, and shows suppression of axial elongation, suppression of degradation of retinal functions and retinal function-recovery action. Hence, the agent can be advantageously used as a clinically applicable agent for the prophylaxis and treatment of disturbance of visual function.

This application is based on application Nos. 176933/1996, 213941/1996 and 314033/1996 filed in Japan, the contents of which are incorporated hereinto by reference.

Claims

1. Use of a compound of the formula [I]

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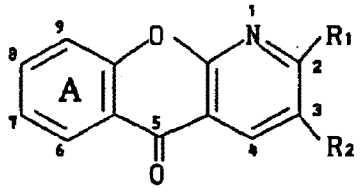


[I]

wherein

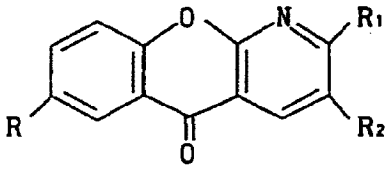
A ring is optionally substituted;
R_1 is a hydrogen or an optionally protected amino; and
R_2 is a group capable of releasing a proton,

or a salt thereof for the manufacture of a pharmaceutical agent for the prophylaxis and treatment of disturbance of visual function.

2. The use of claim 1, wherein the A ring is optionally substituted by halogen atom, nitro, alkyl, alkoxy or butadienylene (-CH=CH-CH=CH-) which forms a benzene ring with two adjacent carbon atoms at two of the 6, 7, 8 and 9 positions.

3. The use of claim 1, wherein the group capable of releasing a proton is carboxyl or tetrazolyl.

4. The use of claim 1, wherein the compound is represented by the formula [II]



[II]

wherein

R is an alkyl;
R_1 is a hydrogen or an optionally protected amino; and
R_2 is a group capable of releasing a proton.

5. The use of claim 4, wherein the alkyl has 1 to 6 carbon atoms.

6. The use of claim 4, wherein the alkyl is isopropyl.

7. The use of claim 1 or claim 4, wherein R_1 is an amino.

8. The use of claim 1 or claim 4, wherein R_2 is a carboxyl.

9. The use of claim 1, wherein the compound is represented by the formula [III]

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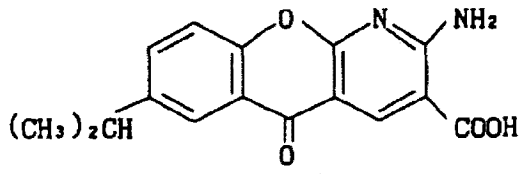

[III]

10. The use of claim 1 wherein the pharmaceutical agent is for local administration to the eye.

11. The use of claim 1 wherein the pharmaceutical agent is in the form of a liquid preparation.

12. The use of claim 10 wherein the pharmaceutical agent is in the form of an ophthalmic solution.

13. The use of claim 12, wherein the ophthalmic solution is an aqueous ophthalmic solution.

14. The use of claim 11 wherein the pharmaceutical agent is in the form of an injection.

15. The use of claim 13 or claim 14, wherein the pharmaceutical agent further comprises a solubilizer.

16. The use of claim 15, wherein the solubilizer is polyvinylpyrrolidone.

17. The use of claim 16, wherein the pharmaceutical agent comprises the polyvinylpyrrolidone in a concentration of 0.2 - 20 (W/V)%.

18. The use of claim 13 or claim 14, wherein the pharmaceutical agent comprises the compound of the formula [I] or a salt thereof in a concentration of 0.01 - 2.0 (W/V)%.

19. The use of claim 1, wherein the disturbance of visual function is asthenopia, axial myopia or a retinal disease.

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FIG. 1

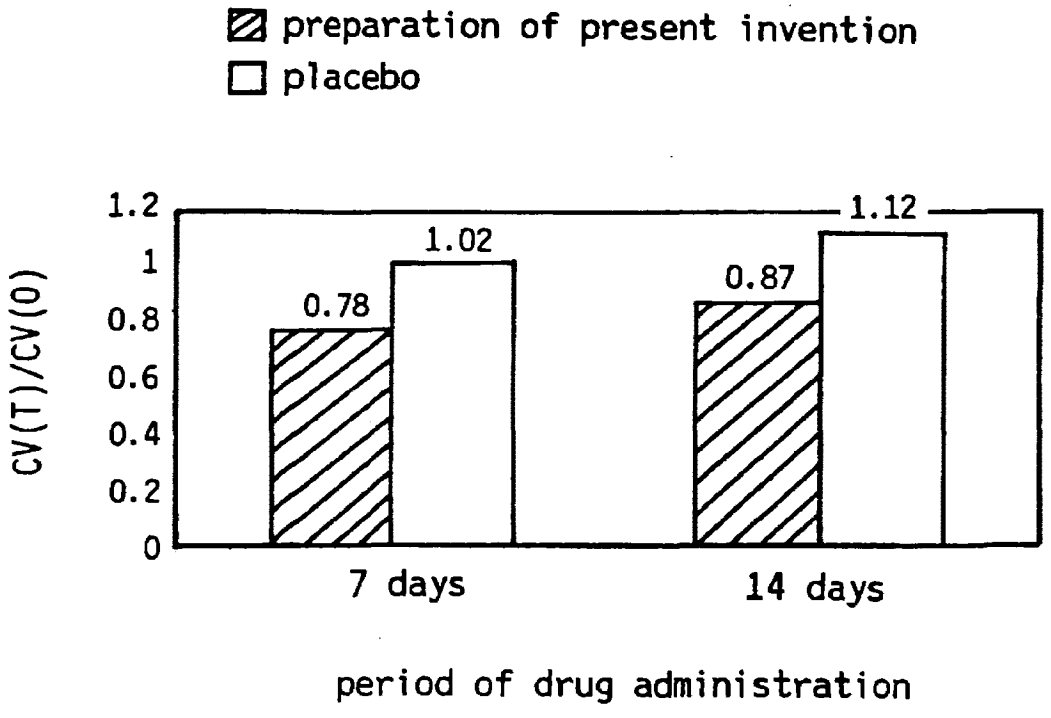

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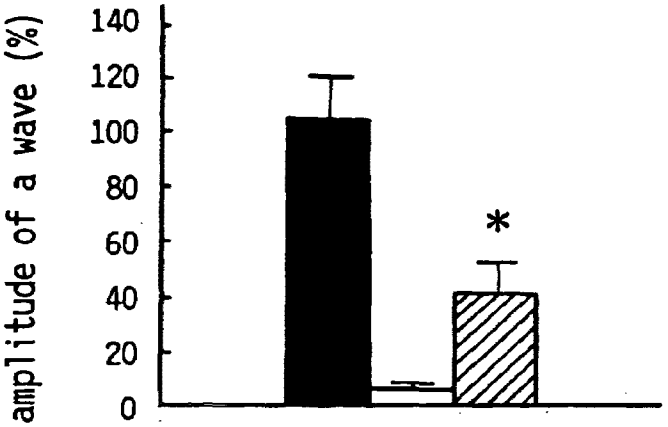
FIG. 2

■ normal group (n=9)
□ control group (n=8)
▨ group administered with compound [III] (n=9)



* $p < 0.001$ (Dunnet's test)

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FIG. 3

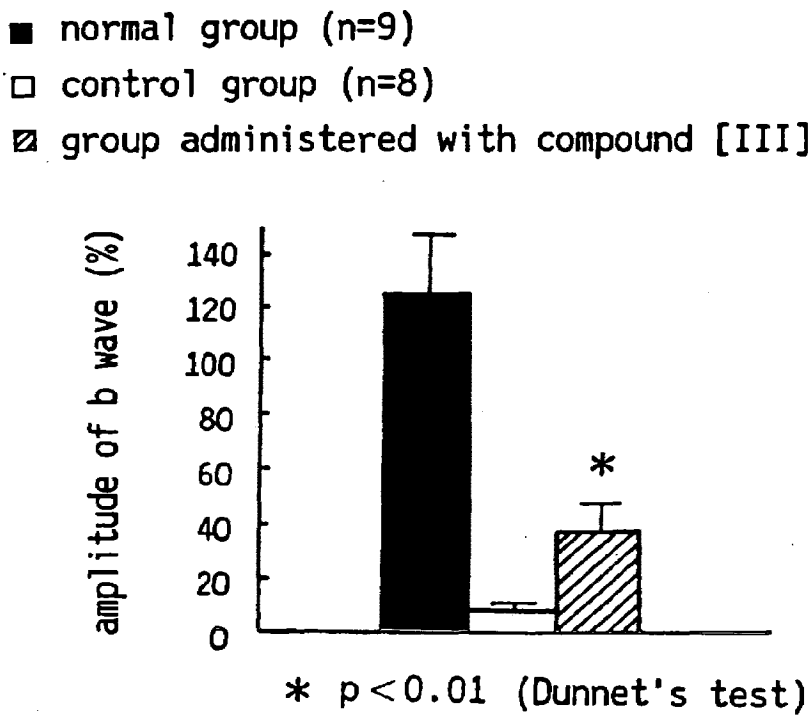

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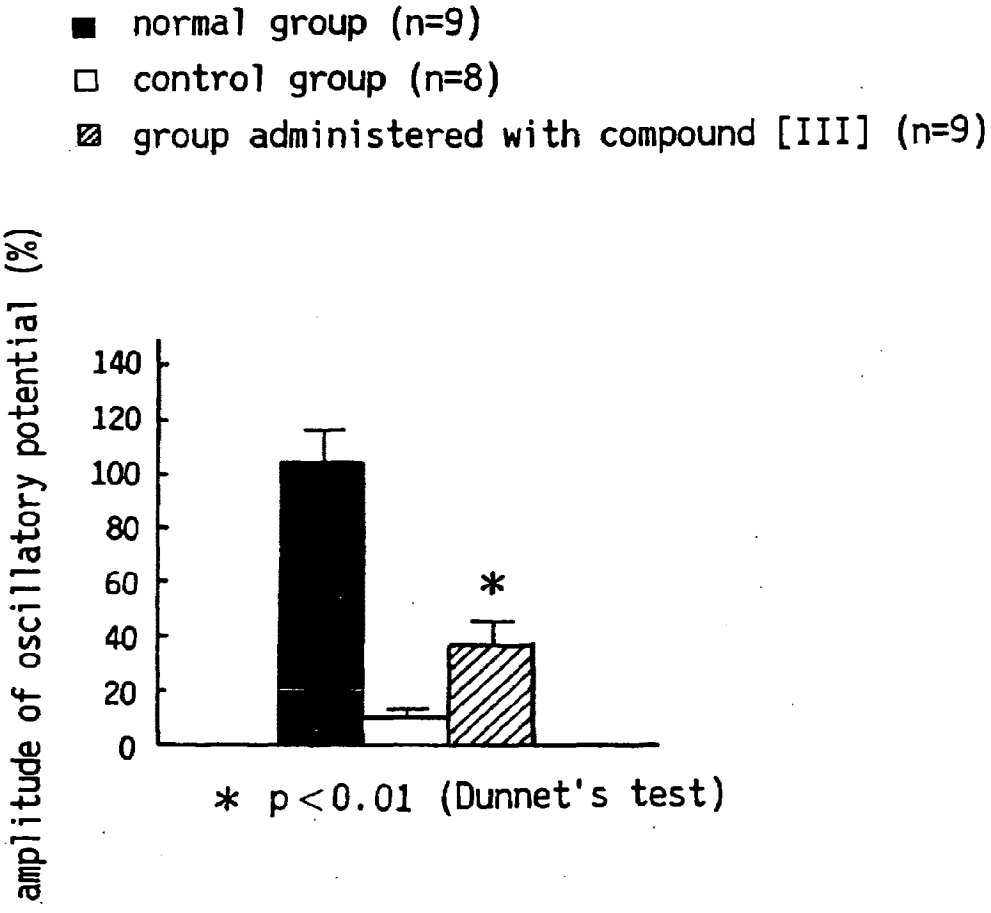
FIG. 4



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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 11 0899

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X,D Y	EP 0 647 445 A (SENJU PHARMA CO) * page 2, line 9 - line 37; claims 1-11 * * page 4, line 52 - line 54 * ---	1-18 19	A61K31/44
Y	DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US Dialog Acc. Nr. 13172014, March 1996 T. OGAWA ET AL.: "Effects of amlexanox on myopia induced by instillation of carbachol in monkeys" XP002047556 * abstract * & 69th Annual Meeting of the Japanese Pharmacological Soc., Nagasaki, Japan March 20-23, 1996 ---	19	
Y	DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US Dialog Acc. Nr. 12157704, April 1996 N. WATANABE ET AL.: "Effect of amlexanox on myopic change induced by topical carbachol in monkeys" XP002047557 * abstract * & 1996 Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida, USA, April 21-26 1996 ---	19	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
A	GB 1 577 304 A (ABBOTT LAB) * page 1, line 46 * ---	1-19	
D,A	US 4 728 509 A (SHIMIZU HISAYOSHI ET AL) * the whole document * -----	1-19	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	20 November 1997	Foerster, W

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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(54)【発明の名称】　ヒト成長ホルモン・亜鉛複合体及びその用途

(57)【要約】
【課題】封入率を高め、初期放出の抑制されたヒト成長ホルモン含有徐放性製剤の提供。
【解決手段】ヒト成長ホルモンと亜鉛とを約１：１.６から約１：２.４のモル比で含有するヒト成長ホルモン・亜鉛複合体及び生体内分解性ポリマーを含有してなる徐放性製剤。
【効果】本発明によれば、製剤操作が容易で、ヒト成長ホルモンの封入率を高め、初期放出の抑制された安定した持続性を示すヒト成長ホルモン含有徐放性製剤が得られる。

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(54) Complex of human growth hormone and zinc and use

(57) The present invention provides a complex of human growth hormone and zinc containing human growth hormone and zinc at a molar ratio of about 1:1.6 to about 1:2.4, and a sustained-release preparation which comprises the complex of human growth hormone and zinc and a biodegradable polymer and which has a high entrapment ratio of human growth hormone and exhibits a stable sustained-release suppressing the initial burst.

EP 0 905 143 A2

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Description

[0001] The present invention relates to a complex of human growth hormone and zinc containing human growth hormone and zinc at a molar ratio of about 1:1.6 to about 1:2.4, a sustained-release preparation which comprises the complex of human growth hormone and zinc and a biodegradable polymer, and so on.

Background Art

[0002] In recent years, human growth hormone (hereinafter abbreviated as GH) has been produced on a large scale by utilizing genetic engineering technology, and is used widely, for example, being clinically applied to Turner's syndrome, infantile chronic renal diseases, achondroplasia and adult GH hyposecretion as well as pituitary dwarfism. Further, applications for osteoporosis in an aging society and static heart diseases are expected.

[0003] Since GH is usually administered by intramuscular or subcutaneous injection repeatedly and over a long term, due to consideration of stability in the body, a significant physical burden on patients is a problem. For instance, in the case of pituitary dwarfism, a daily subcutaneous administration to infants or young patients over a long period of time ranging from a few months to at least 10 years is practised. On the one hand, development of a sustained release preparation containing GH, which is medicinally effective with an administration ranging from once every few weeks to few months, has been reported (S.T.P. Pharma.Sci., 4(6), pages 437-441, 1994; Nature Med., 2(7), pages 795-799, 1996; J.Pharm.Exp.Ther., 281, pages 1431-1439, 1997,; WO 94/12158; WO 95/29664; WO 97/01331).

Brief Explanation of Drawings

[0004] Figure 1 shows the changes in particle size distribution according to the changes in the composition ratio of GH and zinc in a complex of GH and zinc.

[0005] Figure 2 shows the changes in solubility of a complex according to the changes of the composition ratio of GH and zinc in a complex of GH and zinc.

Detailed Description of Invention

[0006] Current sustained-release preparations containing GH have been produced by a method which comprises making GH in water (in water phase) and dispersing the water phase in organic solvent (in oil phase) containing a biodegradable polymer to make a water-in-oil emulsion. But, in this method, GH is remarkably denaturalized in the production process or on the shelves and a sufficient entrapment ratio and release is not obtained. On the one hand, a method which comprises dispersing GH powder into organic solvent (in oil phase) containing a biodegradable polymer to make a solid-in-oil dispersion is not appropriate for producing a sustained-release preparation on a large scale, since it is necessary to maintain stability by spraying the solid-in-oil dispersion into liquid nitrogen. Furthermore, since GH is not in the form of fine particles and is usually used after atomizing, the activity of GH is remarkably lowered by atomization of GH and it is difficult to make a solid-in-oil dispersion containing GH having a high content.

[0007] Thus, it is very difficult to maintain stability of GH and micronize GH in the process for producing preparations. Further, it is very difficult to produce quality sustained-release preparations containing a high content of GH on a large-scale, without lowering the activity of GH but at the same time maintaining quality and stability.

[0008] Therefore, a clinically useful preparation comprising GH which overcomes the above problems and has constant release over a long period of time, and a method for producing the sustained-release preparation on a large scale at high yield, are desired.

[0009] The present inventors made extensive and intensive studies and as a result, made a complex of GH and zinc containing GH and zinc at a molar ratio of about 1:1.6 to about 1:2.4 for the first time. Further, they found that the complex is substantially water-soluble and the micronization of the complex is easier than GH itself, without lowering the activity of GH, and when the obtained complex of GH and zinc having a small particle diameter is used to produce a sustained-release preparation, the sustained-release preparation can be produced on a large scale with assured stability and without denaturalizing GH in the process, having also an enhanced entrapment of GH and an improvement in release properties.

[0010] Namely, the present invention provides

(1) a complex of human growth hormone and zinc containing human growth hormone and zinc at a molar ratio of about 1:1.6 to about 1:2.4,
(2) a complex of the above (1), which is water-soluble,
(3) a complex of the above (1), wherein the mean particle diameter of the complex is less than about 10 μm,
(4) a sustained-release preparation, which comprises the complex of the above (1) and a biodegradable polymer,

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(5) a preparation of the above (4), wherein the biodegradable polymer is an aliphatic polyester,
(6) a preparation of the above (5), wherein the aliphatic polyester is a polymer of lactic acid and glycolic acid,
(7) a preparation of the above (6), wherein the content ratio of a polymer of lactic acid and glycolic acid is 100/0 to 40/60 (mole %),
(8) a preparation of the above (5), wherein the weight-average molecular weight of the aliphatic polyester is about 3,000 to about 20,000,
(9) a preparation of the above (5), wherein the aliphatic polyester is a salt of polyvalent metal,
(10) a preparation of the above (9), wherein the polyvalent metal is zinc,
(11) a preparation of the above (4), wherein the preparation is a microcapsule,
(12) a preparation of the above (11), wherein the microcapsule is for injection,
(13) a preparation of the above (4), wherein the initial burst ratio of GH is less than about 50%,
(14) a method for producing a complex of human growth hormone and zinc, which comprises mixing human growth hormone and zinc salt at a molar ratio of about 1:1.6 to about 1:2.4,
(15) a method for producing micronized human growth hormone, which comprises forming a complex of human growth hormone and zinc containing human growth hormone and zinc at a molar ratio of about 1:1.6 to about 1:2.4 and atomizing them,
(16) use of a complex of human growth hormone and zinc containing human growth hormone and zinc at a molar ratio of about 1:1.6 to about 1:2.4 for producing a sustained-release preparation containing human growth hormone,
(17) a method for producing a sustained-release preparation containing human growth hormone, which comprises dispersing a complex of human growth hormone and zinc containing human growth hormone and zinc at a molar ratio of about 1:1.6 to about 1:2.4 in an oil phase containing a biodegradable polymer to make a solid-in-oil emulsion, adding the solid-in-oil emulsion to water phase to make a solid-in-oil-in-water emulsion, and then in-water drying the solid-in-oil-in-water emulsion,
(18) a pharmaceutical composition which comprises the complex of the above (1), and
(19) a pharmaceutical composition for treating or preventing pituitary drawfism, which comprises the complex of the above (1).

[0011] GH used in the present invention may be any type, for example, natural type (extracted products, etc.) or genetic recombinant type GH (Nature Vol.281, page 544 (1979), Vol.293, page 408 (1981), Proc. Natl. Acad. Sci. USA, Vol. 80, page 397 (1983), Biotechnol. , Vol. 5, page 161 (1981), etc.), and genetic recombinant type GH is preferred in terms of its safety and quality. Further, in the present invention, muteins, derivatives, analogous and active fragments of GH may be used as GH (J.Biol.Chem., Vol.253, page 2679 (1978), B.B.R.C., Vol.92, page 511 (1980), Endocrinol., Vol.109, page 1301 (1981), Protein Eng. Vol.3, page 49 (1989),etc.).

[0012] Complexes of GH and zinc according to the present invention may be produced by any method, for example, methods generally used in the production of complexes, suitable for a molar ratio of GH and zinc in the range of from about 1:1.6 to about 1:2.4. The said complex of GH and zinc is usually produced by bringing GH into contact with a water-soluble zinc salt. This contact reaction is preferably employed in a solvent, for example, aqueous-solvent. The reaction time ranges from 1 minute to 1 hour. The reaction temperature ranges from 4°C to 37°C. Water-soluble zinc salts used in this method, include salts of zinc and inorganic acids, salts of zinc and organic acids and so on. Inorganic acids include hydrochloric acid, sulfuric acid, nitric acid, thiocyanic acid and so on and organic acids include aliphatic carboxylic acids, aromatic acids and so on.

[0013] Examples of aliphatic carboxylic acids used as organic acids, are aliphatic monocarboxylic acids, aliphatic dicarboxylic acids, and aliphatic tricarboxylic acids. These aliphatic carboxylic acids may be saturated or unsaturated. The aliphatic carboxylic acid is preferably an aliphatic carboxylic acid having 2 to 9 carbon atoms.

[0014] Examples of aliphatic monocarboxylic acids are saturated aliphatic monocarboxylic acids having 2 to 9 carbon atoms (e.g., acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, enanthic acid, caprylic acid, pelargonic acid, caprynic acid etc.) and unsaturated aliphatic monocarboxylic acids having 2 to 9 carbon atoms (e.g., acrylic acid, propiolic acid, methacrylic acid, crotonic acid, isocrotonic acid etc.).

[0015] Examples of aliphatic dicarboxylic acids are saturated aliphatic dicarboxylic acids having 2 to 9 carbon atoms (e.g., malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid etc.) and unsaturated aliphatic dicarboxylic acids having 2 to 9 carbon atoms (e.g., maleic acid, fumaric acid, citraconic acid, mesaconic acid etc.).

[0016] Examples of aliphatic tricarboxylic acids are saturated aliphatic tricarboxylic acids having 2 to 9 carbon atoms (e.g., tricarballylic acid, 1,2,3-butanetricarboxylic acid etc.).

[0017] The above-mentioned aliphatic carboxylic acids may have 1 or 2 hydroxyl groups. Such aliphatic carboxylic acids include glycolic acid, lactic acid, glyceric acid, tartronic acid, malic acid, tartaric acid, citric acid and so on.

[0018] The aliphatic carboxylic acid is preferably an aliphatic monocarboxylic acid, more preferably an aliphatic monocarboxylic acid having 2 to 9 carbon atoms, and still more preferably a saturated aliphatic monocarboxylic acid having 2 or 3 carbon atoms. Examples of particularly preferable aliphatic carboxylic acids include acetic acid and so on.

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[0019] Examples of aromatic carboxylic acids used as the above-organic acid are benzoic acid and salicylic acid, with preference given to benzoic acid.

[0020] For example, a complex of GH and zinc in the present invention is produced by mixing GH and a water-soluble zinc salt at a mixing ratio (molar ratio) of about 1:1.6 to about 1:2.4, preferably about 1:1.8 to about 1:2.2 in a aqueous solvent (e.g., aqueous solutions containing ethanol, acetonitril or acetone at a concentration (for example, about 1 to about 10%(W/W)) which does not exert an adverse influence on the solubility of GH and a water-soluble zinc salt, preferably water). The said complex may be a compound (complex salt, double salt, salt, and organic metal compound etc.) formed by intermolecular binding between GH and zinc or a mixture of compounds which differ in their binding patterns. The composition ratio (molar ratio) of GH and zinc in the complex of GH and in the present invention is within the scope of about 1:1.6 to about 1:2.4, preferably about 1:1.8 to about 1:2.2, more preferably about 1:2. In complex of GH and zinc of the present invention, although it is preferred that all of GH and zinc contained at a molar ratio of about 1:1.6 to about 1:2.4 is in the form of a complex, GH and/or zinc which do not form a complex may be present.

[0021] The pH of the aqueous solution resulting from the above mixing must be such that the bioactivity of GH is not affected, and such that each solubility of GH and zinc salt is not lowered in excess. Although the mixing procedure is normally conducted in distilled water, it may be conducted in water adjusted to be weakly acidic, neutral, or weakly alkaline pH (pH 6 to 9) as necessary. The concentration of GH and water-soluble zinc salt in the water may range within each solubility.

[0022] The thus-obtained complex of GH and zinc in water is substantially water-soluble since no precipitate is visibly found in the water. A substantially water-soluble complex of GH and zinc means that the solubility of the complex in 1ml of water (pH 6 to 8) at normal temperature is more than about 2mg.

[0023] This complex of GH and zinc in water is used for producing a pharmaceutical composition, preferably a sustained-release preparation after being vacuum dried or lyophylized and micronized.

[0024] The obtained powder of the complex of GH and zinc is fine-grained and is easier to handle than bulky powder of GH free from zinc, and is very useful for producing a sustained-release preparation on a large scale. For example, a complex of GH and zinc can be obtained as a powder with a mean particle diameter of less than about 10 μm, preferably about 4 to about 7 μm.

[0025] In the case where the complex is dispersed into an organic solvent containing hereinafter-mentioned biodegradable polymer, particles having a small diameter are very useful for obtaining an enhanced entrapment ratio of GH and an improved release. For example, an entrapment ratio of GH in the sustained-release preparation is preferably more than about 90% with regard to the sustained-release of GH, an initial burst ratio of GH is preferable less than about 50%.

[0026] The content of the complex of GH and zinc in the sustained-release preparation of the present invention is normally about 0.1% (W/W) to about 40% (W/W), preferably about 1% (W/W) to about 20% (W/W).

[0027] The biodegradable polymer is exemplified by high-molecular polymers being slightly soluble or insoluble in water, such as aliphatic polyesters (e.g., homopolymers, copolymers or mixtures thereof synthesized from one or more α-hydroxycarboxylic acids such as glycolic acid, lactic acid, hydroxybutyric acid etc.), hydroxydicarboxylic acids such as malic acid etc., hydroxytricarboxylic acids such as citric acid etc. and others, poly-α-cyanoacrylic acid esters, polyamino acids such as poly- γ-benzyl-L-glutamic acid and so on. These may be used in mixture at appropriate ratios. The type of polymerization may be random, block or graft.

[0028] The biodegradable polymer is preferably an aliphatic polyester (e.g., a homopolymer, copolymer or mixture thereof synthesized from one or more α-hydroxycarboxylic acids such as glycolic acid, lactic acid, hydroxybutyric acid etc., hydroxydicarboxylic acids such as malic acid etc., hydroxytricarboxylic acids such as citric acid etc. and others).

[0029] Among the above-mentioned aliphatic polyesters, homopolymers or copolymers synthesized from one or more α -hydroxycarboxylic acids (e.g., glycolic acid, lactic acid, hydroxybutyric acid etc.) are preferred from the viewpoint of reliable biodegradability and biocompatibility. More preferably, the aliphatic polyester is a copolymer synthesized from one or more α-hydroxycarboxylic acids (e.g., glycolic acid, lactic acid, hydroxybutyric acid etc.). Also, these copolymers may be used in mixture.

[0030] Although the above-described α-hydroxycarboxylic acid may be of the D-, L- or D,L-configuration, it is preferable that the ratio of the D-/L-configuration (mole%) falls within the range from about 75/25 to about 25/75. The ratio of the D-/L-configuration (mole%) is more preferably about 60/40 to about 30/70.

[0031] Examples of copolymers of the above-described α-hydroxy-carboxylic acid include copolymers of glycolic acid with another α-hydroxy acid, which is preferably lactic acid, 2-hydroxybutyric acid etc.

[0032] The α -hydroxycarboxylic acid copolymer is preferably a lactic acid-glycolic acid copolymer, a 2-hydroxybutyric acid-glycolic acid copolymer etc., more preferably, the α-hydroxycarboxylic acid copolymer is a lactic acid-glycolic acid copolymer etc.

[0033] With respect to the lactic acid-glycolic acid copolymer (hereinafter generally called lactic acid-glycolic acid polymer or PLGA), it is preferable that the content ratio (lactic acid/glycolic acid ratio, hereinafter called L/G) (mole/mole %) be about 100/0 to about 40/60. The content ratio is more preferably about 90/10 to about 45/55, and more

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preferably about 80/20 to about 45/55. The weight-average molecular weight of the lactic acid-glycolic acid copolymer is about 3,000 to about 20,000, preferably about 3,000 to about 16,000 more preferably about 3,000 to about 14,000.

[0034] Also, the degree of dispersion of the lactic acid-glycolic acid copolymer (weight-average molecular weight/number-average molecular weight) is preferably about 1.2 to about 4.0, more preferably about 1.5 to about 3.5.

[0035] The lactic acid-glycolic acid copolymer can be synthesized by a known process, such as the method described in Japanese Patent Unexamined Publication No. 28521/1986. It is preferable that the copolymer be synthesized by catalyst-free dehydration polymerization condensation.

[0036] With respect to the 2-hydroxybutyric acid-glycolic acid copolymer, it is preferable that glycolic acid accounts for about 10 to about 75 mole % and 2-hydroxybutyric acid for the remaining portion. More preferably, glycolic acid accounts for about 20 to about 75 mole %, and still more preferably about 30 to about 70 mole %. The weight-average molecular weight of the 2-hydroxybutyric acid-glycolic acid copolymer is preferably about 2,000 to about 20,000. The degree of dispersion of the 2-hydroxybutyric acid-glycolic acid copolymer (weight-average molecular weight/number-average molecular weight) is preferably about 1.2 to about 4.0, more preferably about 1.5 to about 3.5. A 2-hydroxybutyric acid-glycolic acid copolymer can be synthesized by a known process, such as that described in Japanese Patent Unexamined Publication Nos. 28521/1986 and 112465/1993. It is preferable that the copolymer be synthesized by catalyst-free dehydration polymerization condensation.

[0037] Preferable example homopolymers of the above-described α-hydroxycarboxylic acid include homopolymer of lactic acid. The weight-average molecular weight of the homopolymer of lactic acid is about 3,000 to about 20,000, preferably about 3,000 to about 14,000.

[0038] A homopolymer of lactic acid can be synthesized by a known process, such as that described in Japanese Patent Unexamined Publication No. 28521/1986. It is preferable that the homopolymer be synthesized by catalyst-free dehydration polymerization condensation.

[0039] The above-described 2-hydroxybutyric acid-glycolic acid copolymer may be used in a mixture with polylactic acid. Although the polylactic acid may be of the D- or L-configuration or a mixture thereof, it is preferable that the ratio of the D-/L-configuration (mole%) fall within the range from about 75/25 to about 20/80. The ratio of the D-/L-configuration (mole%) is more preferably about 60/40 to about 25/75, and still more preferably about 55/45 to about 25/75. The weight-average molecular weight of polylactic acid is preferably about 1,500 to about 20,000, more preferably about 1,500 to about 10,000. Also, the degree of dispersion of the polylactic acid is preferably about 1.2 to about 4.0, more preferably about 1.5 to about 3.5.

[0040] For producing polylactic acid, two methods are known: ring-opening polymerization of lactide, a dimer of lactic acid, and dehydration polymerization condensation of lactic acid. For obtaining a polylactic acid of relatively low molecular weight for the present invention, direct dehydration polymerization condensation of lactic acid is preferred. This method is, for example, described in Japanese Patent Unexamined Publication No. 28521/1986.

[0041] When a 2-hydroxybutyric acid-glycolic acid copolymer and polylactic acid are used in mixture, their mixing ratio is about 10/90 to about 90/10 (% by weight). The mixing ratio is preferably about 20/80 to about 80/20, and more preferably about 30/70 to about 70/30.

[0042] In the present specification, weight-average molecular weight is defined as the molecular weight obtained by gel permeation chromatography (GPC) with 9 polystyrenes as reference substances with respective weight-average molecular weights of 120,000, 52,000, 22,000, 9,200, 5,050, 2,950, 1,050, 580 and 162. Number-average molecular weight based on GPC measurement is also calculated. The degree of dispersion is calculated from the weight-average molecular weight and the number-average molecular weight. Measurements are taken using a GPC column KF804L × 2 (produced by Showa Denko) and an RI monitor L-3300 (produced by Hitachi, Ltd.) with chloroform as the mobile phase.

[0043] The above-described copolymer synthesized by catalyst-free dehydration polymerization condensation, usually has a terminal carboxyl group.

[0044] In the present invention, the biodegradable polymer preferably has a terminal carboxyl group.

[0045] A biodegradable polymer having a terminal carboxyl group is a polymer in which the number-average molecular weight by GPC determination and that by terminal group determination almost agree.

[0046] By terminal group quantitation, number-average molecular weight is calculated as follows:

[0047] About 1 to 3 g of the biodegradable polymer is dissolved in a mixed solvent of acetone (25 ml) and methanol (5 ml), and the solution is quickly titrated with a 0.05 N alcoholic solution of potassium hydroxide while being stirred at room temperature with phenolphthalein as an indicator to determine the terminal carboxyl group content; the number-average molecular weight based on terminal group quantitation is calculated using the following equation:

$$\text{Number-average molecular weight based on terminal group quantitation} = 20{,}000\ A/B$$

A: Weight mass (g) of the biodegradable polymer

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B: Amount (ml) of the 0.05 N alcoholic solution of potassium hydroxide added until the titration end point is reached.

[0048] For example, in the case of a polymer having a terminal carboxyl group synthesized from one or more α -hydroxy acids by catalyst-free dehydration polymerization condensation, the number-average molecular weight based on GPC measurement and the number-average molecular weight based on terminal group quantitation almost agree. On the other hand, in the case of a polymer having essentially no terminal carboxyl group synthesized from a cyclic dimer by ring-opening polymerization using a catalyst, the number-average molecular weight based on terminal group quantitation is significantly higher than the number-average molecular weight based on GPC determination. This difference makes it possible to clearly differentiate a polymer having a terminal carboxyl group from a polymer having no terminal carboxyl group.

[0049] While the number-average molecular weight based on terminal group quantitation is an absolute value, the number-average molecular weight based on GPC determination is a relative value that varies depending on various analyti-cal conditions (e.g., kind of mobile phase, kind of column, reference substance, slice width chosen, baseline chosen etc.); it is therefore difficult to have an absolute numerical representation of the latter. However, the fact that the number-average molecular weight based on GPC determination almost agrees with the number-average molecular weight based on terminal group quantitation means that the number-average molecular weight based on terminal group quantitation falls within the range from about 0.5 to about 2 times, preferably from about 0.8 to about 1.5 times as high as the number-average molecular weight based on GPC determination. Also, the fact that the number-average molecular weight based on terminal group quantitation is significantly higher than the number-average molecular weight based on GPC determination means that the number-average molecular weight based on terminal group quantitation is about 2 times or more as high as the number-average molecular weight based on GPC determination..

[0050] As the biodegradable polymer of the present invention, a metal salt (also referred to as a complex) of the above-described biodegradable polymer is preferably used. For instance, a polyvalent metal salt of each kind of biodegradable polymer disclosed in WO 97/01331, preferably a divalent metal salt, especially a zinc salt of lactic acid-glycolic acid copolymer, is preferably used. Biodegradable polymers can be produced by a process described in WO 97/01331 and modifications thereof.

[0051] When the polyvalent metal salt of the biodegradable polymer is zinc, the polymer may be produced by reacting the biodegradable polymer with zinc oxide in an organic solvent.

[0052] In said process, the biodegradable polymer and zinc oxide are first allowed to exist together in an organic solvent to prepare a solution of a complex of a biodegradable polymer and zinc oxide in the organic solvent. Although the concentration of the biodegradable polymer in the solution varies depending on the molecular weight and the type of the organic solvent, it is, for instance, about 0.1 to about 80%(W/W), preferably about 1 to about 70%(W/W) and more preferably about 2 to about 60%(W/W). Although the amount of zinc oxide added varies depending on the type of organic solvent, it is, for instance, about 0.001 to about 2% (W/W), preferably about 0.01 to about 1.5%(W/W) and more preferably about 0.1 to about 1%(W/W), based on the amount of the biodegradable polymer.

[0053] Regarding the order of addition of the biodegradable polymer and zinc oxide to the organic solvent, zinc oxide both in a powder state or in a dispersed state in the organic solvent can be added to a solution of the biodegradable polymer in the organic solvent, conversely, a solution of the biodegradable polymer in the organic solvent can be added to a dispersion of zinc oxide in the organic solvent. Furthermore, the organic solvent can be added after the biodegradable polymer and zinc oxide both in a powder state have been admixed.

[0054] The conditions required to produce a solution of a complex of a biodegradable polymer and zinc oxide, such as complex of PLGA and zinc oxide, from a biodegradable polymer and zinc oxide can be changed according to the type of biodegradable polymer used, the particle diameter of zinc oxide, the type of organic solvent, and the composition ratio. When PLGA is, for example, employed as the polymer, a complex of PLGA and zinc oxide can be obtained by the above reaction usually at about 0 to about 30°C, preferably about 2 to about 25°C, for about 1 to about 168 hours, preferably about 12 to about 96 hours, more preferably about 24 to about 72 hours. The production of a complex of PLGA and zinc oxide in the present invention can be confirmed visibly since zinc oxide which is in a dispersed state at the time of addition dissolves in the organic solvent to give a clear solution. The reaction time is not limited to the above ranges and can be determined using turbidity as an index.

[0055] Although this reaction proceeds simply by the co-presence of PLGA and zinc oxide in the organic solvent, the reaction carried out under stirring or shaking advantageously reduces the reaction time. Furthermore, the reaction carried out under ultrasonication is equally preferred. As the reaction temperature becomes higher, the reaction time becomes shorter.

[0056] The thus obtained complex of biodegradable polymer and zinc oxide is applied to the next process, preferably as a solution in an organic solvent, or if necessary as a solid after removal of the organic solvent.

[0057] The sustained-release preparation of the present invention is produced by removing the organic solvent from dispersion, preferably a solid-in-oil dispersion in which a GH and zinc containing complex at molar ratio of about 1:1.6 to about 1:2.4, preferably as a powder, is dispersed into a solution of a biodegradable polymer (hereafter also means

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"biodegradable polymer" including a metal salt of the biodegradable polymer) in an organic solvent (oil phase). Methods of producing a sustained-release preparation include the in-water drying method, phase separation method, spray drying method, and modifications thereof.

[0058] Methods of producing a sustained-release preparation, e.g., microcapsules, are described below.

(a) In-water drying method (S/O/W method)

[0059] In this method, a solution of a biodegradable polymer in an organic solvent is first prepared. The organic solvent used to produce the sustained-release preparation of the present invention preferably has a boiling point not higher than 120 °C. Such organic solvents include halogenated hydrocarbons (e.g., dichloromethane, chloro-form, carbon tetrachloride etc.), alcohols (e.g., ethanol, methanol), acetonitrile and so on. These may be used as a mixture at appropriate ratios. The organic solvent is preferably dichloromethane and acetonitrile, and still more preferably dichloromethane. The concentration of the biodegradable polymer in the organic solvent solution is normally about 0.01 to about 80% (W/W), preferably about 0.1 to about 70% (W/W), and more preferably about 1 to about 60% (W/W), depending on the molecular weight of the biodegradable polymer, kinds of organic solvent and so on.

[0060] To the organic solvent solution (oil phase) of the biodegradable polymer thus obtained, a complex of GH and zinc is added or dispersed. In this operation, the amount of complex of GH and zinc added is set so that the complex of GH and zinc weight ratio to biodegradable polymer is up to about 0.4, preferably about 0.2. As a method of dispersing, a powder of a complex of GH and zinc may be added and dispersed uniformly, and the lyophilized bulk of the complex of GH and zinc is added directly and dispersed uniformly by atomizing and mixing in an oil phase.

[0061] The organic solvent suspension (S/O type dispersion) thus prepared is added to an aqueous phase(water phase) to form an S/O/W type emulsion using a turbine type mechanical stirrer, ultrasonic equipment or the like, followed by evaporation of the solvent in the oil phase, to yield microcapsules. The volume of the aqueous phase is normally chosen over the range of about 1 to about 10,000 times, preferably about 5 to about 2,000 times, and more preferably about 10 to about 1,000 times, the volume of the oil phase.

[0062] An emulsifier may be added to the external aqueous phase. The emulsifier may be any one, as long as it is capable of forming a stable S/O/W type emulsion. Examples of such emulsifiers include anionic surfactants, nonionic surfactants, polyoxyethylene castor oil derivatives, polyvinylpyrrolidone, polyvinyl alcohol, carboxymethyl cellulose, lecithin, gelatin, hyaluronic acid and so on. These may be used in combination as appropriate. The emulsifier concentration in the external aqueous phase is preferably about 0.001 to about 20% (W/V), more preferably about 0.01 to about 10% (W/V), and still more preferably about 0.05 to about 5% (W/V).

[0063] The thus obtained microcapsules are recovered by centrifugation or filtration, washed with distilled water to remove the emulsifier etc. adhering to the surface of microcapsules, redispersed in distilled water, and lyophilized. Then, if necessary, water and the organic solvent in the microcapsules are further removed by heating. The heating may be conducted under reduced pressure. Regarding the heating conditions, heating and drying are conducted at a temperature not lower than a glass transition temperature of the biodegradable polymer and not so high as to cause aggregation of each microcapsule particle. The heating and drying are conducted preferably at a temperature ranging from the glass transition temperature of the biodegradable polymer to a temperature which is about 30°C higher than the glass transition point obtained using a differential scanning calorimeter when the temperature is increased at a rate of about 10 to about 20°C per minute.

(b) Phase separation method (Coacervation method)

[0064] In this method, a coacervating agent is gradually added to the above described S/O type dispersion under stirring to precipitate and solidify microcapsules. The amount of the coacervating agent used is about 0.01 to about 1,000 times by volume, preferably about 0.05 to about 500 times by volume, especially preferably about 0.1 to about 200 times by volume. Any coacervating agent can be used, as long as it is a polymeric, mineral oil or vegetable oil compound miscible with the organic solvent for dissolution of a biodegradable polymer and it does not dissolve the biodegradable polymer used. Specifically, examples of such coacervating agents include silicone oil, sesame oil, soybean oil, corn oil, cottonseed oil, coconut oil, linseed oil, mineral oil, n-hexane and n-heptane. Two or more of these may be used in combination. The thus obtained microcapsule are recovered by filtration, and washed repeatedly with heptane etc. to remove the coacervating agent. Further, washing is conducted in the same manner as in the above (a), followed by lyophilization.

(c) Spray-drying method

[0065] In this method, the above described S/O type dispersion is sprayed via a nozzle into the drying chamber of a spray drier to volatilize the organic solvent in fine droplets in a very short time to yield microcapsules. Examples of

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the nozzle include, for instance, a two-fluid nozzle type, a pressure nozzle type and a rotary disc type. It is also advantageous, if necessary , to spray an aqueous solution of the above-described antiaggregation agent via another nozzle in order to prevent aggregation of each microcapsule particle. The thus obtained microcapsule is washed in the same manner as in the above (a), if necessary followed by heating (if necessary under reduced pressure) to remove water and the organic solvent.

[0066] The sustained-release preparation of the present invention is preferably used in the form of fine particles. This is so that the sustained-release preparation does not cause undue pain to the patient when administered via an injection needle for ordinary subcutaneous or intramuscular injection. The mean particle diameter of the sustained-release preparation, for example, is about 0.1 to about 300 μm, preferably about 1 to about 150 μm, and more preferably about 2 to about 100 μm.

[0067] In the present invention, the microcapsule may be fine particles (called microspheres) comprising the active ingredient (complex of GH and zinc) and a base for the microcapsule (biodegradable polymer). Typically, they include microcapsules containing one core of active ingredient in one particle, or microcapsules containing many cores of active ingredient in one particle.

[0068] The sustained-release preparation of the present invention, for example, can be administered as microcapsules, in the form of various dosage forms of non-oral preparations (e.g., intramuscular, subcutaneous or visceral injections or indwellable preparations, nasal, rectal or uterine transmucosal preparations etc.) or oral preparations (e.g., capsules such as hard capsules, soft capsules etc., solid preparations such as granules and powders etc., liquid preparations such as suspensions etc.).

[0069] In the present invention, the sustained-release preparation is preferably used for injection. When the sustained-release preparation is a microcapsule, for instance, it can be prepared as an aqueous suspension by suspending microcapsules in water, along with a dispersing agent (e.g., surfactants such as polysorbate (Tween 80, Bio Rad) and HCO-60 (Nikko Chemicals), polysaccharides such as carboxymethyl cellulose, sodium alginate and sodium hyaluronate etc.), a preservative (e.g., methyl paraben, propyl paraben etc.), an isotonizing agent (e.g., sodium chloride, mannitol, sorbitol, glucose etc.), etc., to yield a sustained-release preparation for injection of practical use. Alternatively, the sustained-release preparation of the present invention is prepared as an oily suspension by dispersing microcapsules, along with a vegetable oil such as sesame oil or corn oil with or without a phospholipid such as lecithin, or a medium-chain fatty acid triglyceride (e.g., MIGLYOL 812, Huls A.G. (Marl, Germany)), to yield a sustained-release preparation for injection of practical use.

[0070] When the sustained-release preparation is a microcapsule, for instance, its mean particle size is chosen over the range from about 0.1 to about 300 μm as long as the requirements concerning degree of dispersion and needle passage are met, when it is to be used as an injectable suspension. Preferably, the particle size falls within the range from about 1 to about 150 μm, more preferably about 2 to about 100 μm.

[0071] The above-described microcapsule can be prepared as a sterile preparation, without limitation, for example, by the method in which the entire production process is sterile, the method in which gamma rays are used as sterilant, and the method in which an antiseptic is added.

[0072] The sustained-release preparation of the present invention is of low toxicity and can be safely used in mammals (e.g., humans, bovines, swines, dogs, cats, mice, rats, rabbits etc.).

[0073] The sustained-release preparation of the present invention is useful for treating or preventing adult GH hyposecretion, Turner's syndrome, pituitary dwarfism, chronic renal diseases, achondroplasia, adult hypopituitarism, Down syndrome, Silver syndrome, hypochondroplasia, juvenile chronic arthritis and static heart diseases etc.

[0074] Depending on duration of the release, target disease, subject animal species and other factors, the dose of the sustained-release preparation may be set at any level, as long as the effective concentration of GH in the body is maintained. For instance, when the sustained-release preparation is designed for two weeks release and administered to patients for pituitary dwarfism, the dose of an effective ingredient can be chosen from the range of preferably about 0.01 to about 5mg/kg body weight, more preferably about 0.03 to about 1mg/kg body weight, per an adult, administered once every two weeks.

[0075] The complex of GH and zinc of the present invention has low toxicity and while the complex of GH and zinc can be administrated as it is, it is usually administered in the form of a composition formulated by conventional methods using pharmaceutically acceptable carriers or diluents for pharmaceutical compositions adequately selected from excipients (e.g. calcium carbonate, kaolin, sodium hydrogencarbonate, lactose, corn starch, crystalline cellulose, talc, fine granulated sugar and porous substance), binders (e.g. dextrin, gum, α-starch, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and furran), thickeners (e.g. natural rubbers and cellulose derivatives), disintegrants (e.g. carboxymethyl cellulose calcium, closcarmellose sodium, clospovidone, low-substituted hydroxypropyl cellulose and partial α-starch), solvents (e.g. water for injection, physiological saline, ringels solution, alcohol, propylene glycol, sesame oil and corn oil), dispersing agents (e.g. Tween 80, HCO 60, carboxymethyl cellulose and sodium alginate), suspending agents (e.g. sodium lauryl sulfate and benzalkonium chloride), dissolution acids (e.g. polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, torisaminomethane, triethanolamine, sodium carbonate and

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sodium citrate), anesthetizing agents (e.g. benzylalcohol), buffers (e.g. phosphate, acetate, carbonate and citrate), lubricants (e.g. magnesium stearate, calcium stearate, talc, starch and sodium benzoate), colorants (e.g. tar pigment, caramel, iron sesquioxide, titanium oxide and riboflavins), falvoring agents (e.g. sweeteners and perfume), stabilizers (e.g. sodium sulfite and ascorbic acid) and preservatives (e.g. parabens and sorbic acid) in adequate amounts respectively. The pharmaceutical composition of the present invention which may contain the above-mentioned carriers or diluents for pharmaceutical compositions, contains an effective amount of the complex of GH and zinc for preventing and treating the above-diseases in a similar way to the above-sustained-release preparation. The content of the complex of GH and zinc of the present invention in the pharmaceutical composition ranges usually from about 0.1 to about 100 weight % relative to the whole weight of the pharmaceutical composition.

[0076] Although the sustained-release preparation may be stored at normal temperature or in a cold place, it is preferable to store it in a cold place. Normal temperature and a cold place as mentioned herein are as defined by the Pharmacopoeia of Japan, specifically, 15 to 25°C for normal temperatures and under 15°C for cold places.

Examples

[0077] The present invention will be explained in more detail by the following Examples, Reference Examples, Comparative Examples and Experimental Examples. The scope of the present invention is not intended to be restricted by said Examples. In the present specification and Examples, amino acid abbreviations are based on those recommended by the IUPAC-IUB Commission on Biochemical Nomenclature, or those used commonly in the related field, and as shown below. In the case that amino acids have optical isomers, they represent L-type unless otherwise specified.

SDS:	Sodium dodecylsulfate
Gly:	Glycine
Ala:	Alanine
Val:	Valine
Leu:	Leucine
Ile:	Isoleucine
Ser:	Serine
Thr:	Threonine
Cys:	Cystein
Met:	Methionine
Glu:	Glutamic acid
Gln:	Glutamine
Asp:	Aspartic acid
Asn:	Asparagine
Lys:	Lysine
Arg:	Arginine
His:	Histidine
Phe:	Phenylalanine
Tyr:	Tyrosine
Trp:	Tryptophan
Pro:	Proline
Asx:	Asp + Asn
Glx:	Glu + Gln

Reference Example 1

Construction of expression vector for GH using T7 promoter

[0078] The structure gene of GH was isolated as about 0.75 kb of EcoRI-EcoRV fragment from plasmid pHGH107 (ATCC 31538 or ATCC 40011) described in Japanese Patent Publication No. 12996/1994. On the other hand, T7 promoter and ampicillin resistant gene were isolated as about 4.6 kb of NdeI-BamHI fragment from pET-3C [Rosenberg et al., Gene, 56, 125 (1987)]. Both of the two fragments were treated with T4 DNA polymerase (DNA blunting kit; Takara Shuzo, Inc.) and ligated with T4 DNA ligase, followed by introduction into Escherichia coli JM109 and selection of ampicillin resistant transformant. From the obtained 12 colonies, plasmids were prepared and digested with PstI. As a result, it was found that GH gene was inserted in a correct direction in the plasmids from the 6 colonies. The plasmid obtained from one transformant among the 6 colonies was named as pTGA201.

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Reference Example 2

Expression of Met-GH in Escherichia coli

[0079] Escherichia coli JM109 was transformed with λ phage (Studie, Supura) having RNA polymerase gene of T7 phage. Thereafter, into the obtained Escherichia coli JM109 (DE3), GH expression vector pTGA201 obtained in Reference Example 1 was introduced to obtain Escherichia coli JM109 (DE3)/pTGA201.

[0080] Escherichia coli JM109 (DE3)/pTGA201 was inoculated into a flask of 2 liter capacity containing 1 liter of LB medium [1% peptone, 0.5% yeast extract, 0.5% sodium chloride] and 50 μ g/ml ampicillin and then subjected to rotary shaking cultivation at 30°C for 16 hours. The resultant culture liquid was then transferred to a 50 liter jar fermentor containing 20 liter of LB medium [0.02 % antiforming agent (New Pole LB-625; San-yo Kasei Kogyo), 50 μ g/ml ampicillin], after which it was subjected to cultivation under aeration and agitation at 37°C for 6 hours. The resultant culture liquid was then transferred to a 500 liter jar fermentor containing 360 liter of a liquid production medium [1.68 % sodium hydrogen phosphate, 0.3 % potassium dihydrogen phosphate, 0.1 % ammonium chloride, 0.05 % sodium chloride, 0.024 % magnesium sulfate, 0.02 % antiforming agent (New Pole LB-625), 0.0005 % thiamine hydrochloride, 1.5 % glucose, 1.5 % casamino acid], after which it was subjected to cultivation under aeration and agitation at 37°C. When the Klett value was about 500, 5.95 mg/L/minute of isopropyl- β -D-thiogalactopyronoside (IPTG) was added to the medium and the cultivation was further continued for 4 hours. The culture liquid was centrifuged to obtain about 4.5 kg of wet cells which were frozen at -80°C.

[0081] The above-described transformant Escherichia coli JM109 (DE3)/pTGA201 has been deposited FERM BP-5632 at the NIBH (National Institute of Bioscience and Human-Technology) and IFO 16001 at the IFO (Institute Fermentation Osaka).

Reference Example 3

Activation of Met-GH

[0082] Two kg of wet cells obtained in Reference Example 2 was dissolved in 6 1 of 50 mM Tris-HCl and guanidine hydrochloride (pH 8.0), followed by centrifugation (10000 rpm, 120 minutes). To 6 liters of the resultant supernatant, was added 18 liter of a solution (pH 8.0) containing 50 mM Tris-HCl, 0.28 mM GSSG and 0.7 M Arg to adjust pH 8.0, followed by standing at 4°C for 5 days to continue activation of Met-GH.

Reference Example 4

Purification of Met-GH

[0083] The solution obtained in Reference Example 3 was subjected to salting-out and concentration by Pellicon cassette system (PTGC membrane; Millipore Corporation) and with adding a solution (pH 8.0) of 20 mM Tris-HCl and 2.5 M urea until electric conduction became not more than 10 mS. The obtained concentrate was centrifuged (10000 rpm, 60 minutes) to obtain 5 liter of supernatant. The supernatant was loaded on DEAE-Toyopearl 650M column (20 cm ϕ × 84 cm, Tosoh) equilibrated with a solution (pH 8.0) of 20 mM Tris-HCl and 2.5 M urea, followed by adsorption and washing. The column was eluted with using a linear concentration gradient consisting of 0-25 % solution B (B = 20 mM Tris-HCl, 2.5 M urea, 1M NaCl, pH 8.0) at 300 ml/minute of flow rate for 100 minutes. The eluted solution containing Met-GH of 10 liter was again subjected to salting-out and concentration by Pellicon cassette system (PTGC membrane; Millipore). The concentrated solution was passed through DEAE-5PW column (21 cm ϕ × 30 cm, Tosoh) using HPLC method (Gilson HPLC system; Gilson). The column was eluted using a pH gradient consisting of 70-85 % solution B (A = 50 mM Tris-HCl and 2.5 M urea (pH 8.0); B = 50 mM MES [2-(N-morpholino)ethane sulfonate] and 2.5 M urea (pH 4.0)) at 320 ml/minute of flow rate for 70 minutes. To the obtained Met-GH fraction 6 liter, was added 2 M Tris-HCl (pH 7.8) to adjust to pH 7.2, followed by salting-out and concentration by Pellicon cassette system (PTGC membrane; Millipore) to obtain 9,979 mg of Met-GH.

Reference Example 5

Removal of N-terminal Met

[0084] To 1650 ml solution of Met-GH obtained in Reference Example 4, was added 413 ml of a solution containing 35 mM copper sulfate, 2.5 M glyoxylic acid and 6 M pyridine and the mixture was stirred and allowed to stand at 25°C for 1 hour. The reaction solution was passed at a flow rate of 3 liter/h through Sephadex G-25 column (11.3 cm ϕ ×

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125 cm, Pharmacia) equilibrated with a solution (pH 8.0) of 20 mM Tris-HCl and 2.5 M urea and the column was washed with the same solution to collect the fraction of diketone derivative of Met-GH. The eluted fraction was directly added to a 4 liter solution of 4M acetic acid, 4 M sodium acetate, 80 mM o-phenylenediamine and 3 M urea with stirring. After the elution; the reaction solution (8 liters) was allowed to stand at 4°C for 3 days. The solution was subjected to salting-out by Pellicon cassette system (PTGC membrane; Millipore). The concentrated solution (4 liters) was passed at a flow rate of 3 liter/h through Sephadex G-25 column (11.3 cm ϕ × 140 cm, Pharmacia) equilibrated with a solution (pH 8.0) of 20 mM Tris-HCl and 2.5 M urea to collect the fraction of GH (4.7 liter). The obtained fraction was passed through a DEAE-5PW column (21 cm ϕ × 30 cm, Tosoh) using HPLC method (Gilson HPLC system; Gilson). The column was eluted using a pH gradient consisting of 70-85 % solution B (A = 50 mM Tris-HCl and 2.5 M urea (pH 8.0); B = 50 mM MES [2-(N-morpholino)ethane sulfonate] and 2.5 M urea (pH 4.0)) at a flow rate of 320 ml/minute for 70 minutes to collect 10 liter fraction of GH. To the obtained GH fraction was added 500 ml solution of 2 M Tris-HCl (pH 7.8) to adjust to pH 7.2, followed by concentration with Minitan II (PTGC membrane; Millipore). The concentrated solution 500 ml was passed at a flow rate of 2 liter/h through Sephacryl S-100 column (11.3 cm ϕ × 50 cm, Pharmacia) equilibrated with distilled water to collect the GH fraction 1651 ml, and followed by filtration with Millipack 60 (Millipore) to obtain GH solution 1487 ml (3309 mg of GH).

Reference Example 6

Determination of Feature of GH

(a) Analysis with SDS-polyacrylamide gel electrophoresis

[0085] To the GH solution obtained in Reference Example 5 was added the same volume of Sample buffer [Laemmli, Nature, 227, 680 (1970)] containing 100 mM DTT, and the mixture was heated at 95°C for 2 minutes, followed by electrophoresis with Multi Gel 10/20 (Daiichi Pure Chemicals). After electrophoresis, the gel was stained with Coomassie brilliant blue and only one single band at about 22 kd of the purified protein was obtained.

(b) Analysis of amino acid composition

[0086] Analysis of amino acid was used for the determination of amino acid composition was done with an amino acid analyzer (L-8500A, Hitachi). The amino acid composition of GH obtained agreed with that predicted from cDNA sequence of GH (Table 1).

Table 1

Analysis of amino acid composition		
Amino acid	Number of residues per 1 mole	Values predicted from cDNA sequence of GH
Asx	20.2	20
Thr[1)]	10.0	10
Ser[1)]	16.7	18
Glx	27.0	27
Pro	8.1	8
Gly	8.2	8
Ala	7.6	7
Cys[2)]	N.D.	4
Val	7.0	7
Met	3.0	3
Ile	7.7	8
Leu	27.9	26
Tyr	8.1	8
Phe	12.7	13
His	3.2	3
Lys	8.9	9
Arg	10.9	11
Trp	0.8	1

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[0087] Acid hydrolysis (6N HCl, 4% thioglycolic acid, 110°C, Mean value of those obtained after 24 and 48 hours of hydrolysis)

1) Value extrapolated on the assumption that hydrolysis time was 0 hours.
2) Undetected

Analysis was carried out using about 20 μ g of GH.

(c) Analysis of N-terminal amino acid sequence

[0088] The N-terminal amino acid sequence of GH was determined using a gas-phase protein sequencer (Applied Biosystems, 477A model). The N-terminal amino acid sequence of GH obtained agreed with that predicted from cDNA sequence of GH (Table 2).

Table 2

Analysis of N-terminal amino acid sequence		
Residue No.	PTH[1)]-amino acid detected (pmol)	amino acid predicted from cDNA sequence of GH
1	Phe (949)	Phe
2	Pro (404)	Pro
3	Thr (422)	Thr
4	Ile (744)	Ile
5	Pro (283)	Pro
6	Leu (514)	Leu
7	Ser (136)	Ser
8	Arg (36)	Arg
9	Leu (377)	Leu
10	Phe (408)	Phe
11	Asp (77)	Asp
12	Asn (230)	Asn
13	Ala (435)	Ala
14	Met (334)	Met
15	Leu (398)	Leu
16	Arg (67)	Arg
17	Ala (488)	Ala
18	His (30)	His
19	Arg (42)	Arg
20	Leu (406)	Leu

1) phenylthiohydantoin

[0089] Analysis was carried out using 1nmol of GH.

(d) Analysis of C-terminal amino acid

[0090] Analysis of C-terminal amino acid was done by determination of C-terminal amino acid with amino acid analyzer (L-8500A, Hitachi). The C-terminal amino acid of GH obtained agreed with that predicted from cDNA sequence of GH (Table 3).

Table 3

Analysis of C-terminal amino acid	
C-terminal amino acid	Yield (%)
Phe	52

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Vapor-phase hydrazinolysis (100°C, 3.5 hours)
Analysis was carried out using 18nmol of GH.

(e)Determination of GH activity

[0091] GH purified and obtained in Reference Example 5 had a cell growth enhancing activity to Nb 2 cells according to the method described in Journal of Clinical Endocrinology and Metabolism, 51, 1058 (1980) almost similar to a standard product (Chemicon International, USA).

Example 1

(1)Production of complex of GH and zinc

[0092] To 120ml of aqueous solution of genetic recombinant type GH (2mg/ml) obtained according to Reference Example 5, 0.5 ml of two kinds of aqueous solution of zinc acetate whose concentration was set so that the molar ratio of zinc to 1 mole of GH was 1.8 and 2.0, were added independently and were lyophilized to yield complex of GH and zinc (about 230mg).

(2)Production of microcapsule containing GH

[0093] 1.89 g of lactic-glycolic acid copolymer (lactic acid/glycolic acid = 50/50, average molecular weight converted into polystyrene = 12,000, viscosity = 0.145dl/g) was dissolved in 4 ml of dichloromethane, and after 10 mg of zinc oxide was added, it was stirred (60rpm) at 25°C to be dissolved completely. To this solution of polymer in an organic solution, 100mg of complex of GH and zinc obtained in the above (1) was added and was atomized by Polytron(Kinematica). The obtained S/O dispersion was added to 800ml of 0.1% aqueous solution of polyvinyl alcohol, and stirred and emulsified by homomixer. After drying in water for 2 hours, it was washed with distilled water and lyophilized to yield microcapsules containing GH (1.07g(1:1.8), 0.91g(1:2.0)).

Comparative Example 1

(1) Production of GH powder

[0094] To 120ml of aqueous solution of genetic recombinant type GH (2mg/ml) obtained according to Reference Example 5, 0.5 ml of various kinds of aqueous solution of zinc acetate whose concentration was set so that the molar ratio of zinc to 1 mole of GH were 0, 3.0, 4.0, 5.0 and 6.0, were added independently and was lyophilized to yield GH powder (about 230mg).

(2) Production of microcapsule containing GH

[0095] By the same method of Example 1-(2), microcapsule containing GH (0.95g(1:0), 1.23g(1:3), 1.13g(1:4), 1.2g (1:5), 1.27g(1:6)) was obtained by using the GH powder described in the above-described (1).

Experimental Example 1

[0096] By using microcapsules produced in Example 1-(2) and Comparative Example 1-(2), the following experiments were conducted.

(1)Content of GH

[0097] 300 μl of acetonitrile was added to 4 mg of microcapsules produced in Example 1-(2) or Comparative Example 1-(2), the base lactic acid-glycolic acid copolymer was dissolved in it, and 700 μl of aqueous solution which contained 0.02% bovine serum albumin-0.05% trifluoro acetic acid was added by stirring to elute GH. In the supernatant obtained by the centrifugation, the content of GH in the microcapsule was determinated by high performance liquid chromatography. The result is shown in Table 4.

[0098] As illustrated by Table 4, more than 90% entrapment ratio of GH was obtained in the case of using the complex of the present invention which contains GH and zinc at a molar ratio of 1.8 or 2.0 of zinc to 1 mole of GH.

[0099] It is clear that the sustained-release preparation containing a complex of GH and zinc in the present invention has an excellent entrapment ratio of GH.

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(2) Release in vivo

[0100] Microcapsules produced in Example 1-(2) and Comparative Example 1-(2) were subcutaneously administered to imunosuppressed SD rats (male, 6 weeks old) in the amount of 6 mg GH/rat. Blood was collected periodically and the serum concentration was assayed with radioimuunoassay kit (Ab beads HGH : Eiken Kagaku). Immunosuppressed SD rats were obtained by administering Prograph® (Fujisawa Pharm.) in the amount of 0.4 mg/rat on 3 days before administration of microcapsule and in the amount of 0.2 mg/rat on the administration day and 4, 7, 11 and 14 days after the administration. The amount of GH released on the first day and 1-18 days after the administration of microcapsule were calculated based on pharmaco kinetic parameters (AUC and clearance) obtained by the changes of serum GH concentration. The initial burst amount GH was obtained by ratio of the amount of GH released during the first day after the administration to the amount of GH administered. The result is shown in the Table 4.

[0101] As shown in Table 4, in microcapsules containing the complex of GH and zinc at a molar ratio of 1:1.8 or 1:2.0, the initial burst amount of GH (amount released until 1 day (24 hours) after administration) was low (less than about 30%) and the amount of GH release after 1 day (amount released from 1 day after administration (24 hours to 18 days after administration)) was high (more than about 50 %). In the microcapsule produced in Comparative Example 1-(2), an effective sustained release was not obtained because the initial burst amount was high and the amount of release after it was low.

[0102] It is clear that the sustained-release preparation containing a complex of GH and zinc in the present invention has an excellent sustained-release.

Table 4

microcapsule	GH/zinc molar ratio	entrapment ratio(%)	amount of GH release		
			1 day	1-18 days	initial burst ratio (%)
Example 1	1:1.8	92	1.60	2.31	26.7
	1:2.0	92	1.23	2.68	20.5
Comparative Example 1	1:0	88	3.26	1.96	54.3
	1:3.0	73	4.32	1.95	72.0
	1:4.0	75	4.83	1.97	80.5
	1:5.0	70	5.99	1.44	83.2
	1:6.0	73	4.46	1.91	74.3

Experimental Example 2

[0103] To 2ml of aqueous solution of genetic recombinant type GH (2mg/ml) obtained according to Reference Example 5, 50 μ l of various kinds of aqueous solution of zinc acetate whose concentration was set so that the molar ratio of zinc to 1 mole of GH were 0, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 3.0, 4.0, 5.0 and 6.0, were added independently and lyophilized. The obtained lyophilized powder was dispersed in 2 ml of dichloromethane, atomized and micronized by Vortex mixer. The distribution of particle size was determined by using laser diffraction apparatus of determining distribution of particle size (SALD2000A; Shimazu). The results are shown in Figure 1. In Figure 1, particle size(mean particle diameter : μ m) is shown by ●.

[0104] As shown by Figure 1, the complex of GH and zinc at a molar ratio of 1:1.6 to 1:2.4 in the present invention showed the mean particle diameter being less than 5 μm.

[0105] It is clear that the complex of GH and zinc in the present invention is fine particle.

Experimental Example 3

[0106] To 1ml of aqueous solution of genetic recombinant type GH (2mg/ml) obtained according to Reference Example 5, 25 μ l of various kinds of aqueous solution of zinc acetate whose concentration was set so that the molar ratio of zinc to 1 mole of GH were 0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 were added independently, and was centrifugated for 5 minutes at 12,000 rpm/minute. The obtained supernatant was filtered through 0.45 μ m filter and the concentration of GH was quantitatively analyzed by high performance liquid chromatography to calculate the ratio formed of water-insoluble complex (ratio of GH in water-insoluble complex to total amount of GH added (%)). The result is shown in Figure 2. In Figure 2, the ratio of water-insoluble complex formed is shown by O.

[0107] As shown by Figure 2, in the case that the zinc molar ratio to 1 mole of GH is less than 2.0, the co-existing water-insoluble component was less than 30% and the complex was substantially water-soluble.

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[0108] It is clear that the complex of GH and zinc in the present invention is substantially water-soluble.

Claims

1. A complex of human growth hormone and zinc containing human growth hormone and zinc at a molar ratio of about 1:1.6 to about 1:2.4.

2. A complex of claim 1, which is water-soluble.

3. A complex of claim 1, wherein the mean particle diameter of the complex is less than about 10 μ m.

4. A sustained-release preparation, which comprises the complex of any of claims 1 to 3 and a biodegradable polymer.

5. A preparation of claim 4, wherein the biodegradable polymer is an aliphatic polyester.

6. A preparation of claim 5, wherein the aliphatic polyester is a polymer of lactic acid and glycolic acid.

7. A preparation of claim 6, wherein the content ratio of a copolymer of lactic acid and glycolic acid is 100/0 to 40/60 (mole %).

8. A preparation of claim 5, wherein the weight-average molecular weight of the aliphatic polyester is about 3,000 to about 20,000.

9. A preparation of claim 5, wherein the aliphatic polyester is a salt of polyvalent metal.

10. A preparation of claim 9, wherein the polyvalent metal is zinc.

11. A preparation of claim 4, wherein the preparation is a microcapsule.

12. A preparation of claim 12, wherein the microcapsule is for injection.

13. A preparation of claim 4, wherein the initial burst ratio of growth hormone is less than about 50%.

14. A method for producing a complex of human growth hormone and zinc, which comprises mixing human growth hormone and zinc salt at a molar ratio of about 1:1.6 to about 1:2.4.

15. A method for producing micronized human growth hormone, which comprises forming a complex of human growth hormone and zinc containing human growth hormone and zinc at a molar ratio of about 1:1.6 to about 1:2.4 and atomizing them.

16. Use of a complex of human growth hormone and zinc containing human growth hormone and zinc at a molar ratio of about 1:1.6 to about 1:2.4 for producing a sustained-release preparation containing human growth hormone.

17. A method for producing a sustained-release preparation containing human growth hormone, which comprises dispersing a complex of human growth hormone and zinc containing human growth hormone and zinc at a molar ratio of about 1:1.6 to about 1:2.4 in an oil phase containing a biodegradable polymer to make a solid-in-oil emulsion, adding the solid-in-oil emulsion to water phase to make a solid-in-oil-in-water emulsion, and then in-water drying the solid-in-oil-in-water emulsion.

18. A pharmaceutical composition which comprises an effective amount of the complex of claim 1 in admixture with a pharmaceutically acceptable carrier or diluent.

19. A pharmaceutical composition for treating or preventing pituitary drawfism, which comprises an effective amount of the complex of claim 1 in admixture with a pharmaceutically acceptable carrier or diluent.

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Figure 1

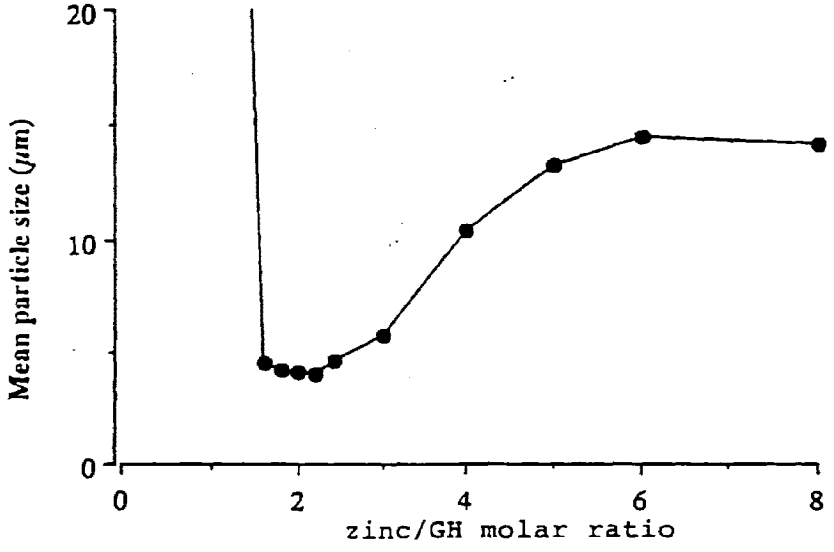
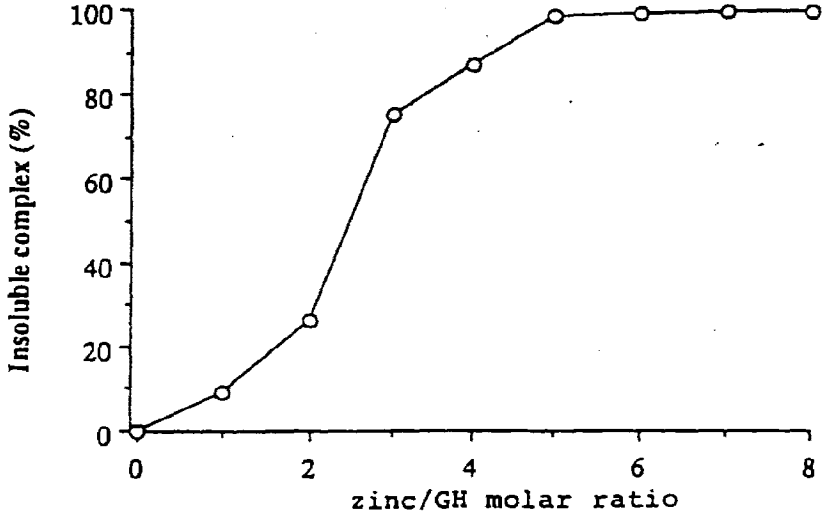


Figure 2



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TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PRIOR PATENT	Docket No.: 056291-5004-01

In re Application of: **EVANS et al.**
Application No.: **10/872,784**
Filed: **June 22, 2004**
For: **FORMULATION**

The owner*, **AstraZeneca AB**, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§ 154 to 156 and 173, as shortened by any terminal disclaimer, of prior Patent No. **6,774,122**. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §§ 154 to 156 and 173 of any patent granted on the second application, as shortened by any terminal disclaimer filed prior to the patent grant, in the event that any such granted patent: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. § 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. [ ] For submissions on behalf of an organization (*e.g.*, corporation, partnership, university, government agency, etc.) the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. [X] The undersigned is an attorney of record.

10/18/04
Signature Date

Donald J. Bird Reg. No. 25,323
Typed or printed name

(202) 739-5320
Telephone Number

[x] Terminal disclaimer fee under 37 C.F.R. §1.20(d)

[x] PTO suggested wording for terminal disclaimer was
[x] unchanged. [ ] changed (if changed, an explanation should be supplied).

*Statement under 37 C.F.R. § 3.73(b) is required if the terminal disclaimer is signed by the assignee (owner).

10/20/2004 SSESHE1 00000045 10872784

04 FC:1814 110.00 DA

InnoPharma Exhibit 1046.0130

Application Number	Application No.	Applicant(s)	
	10/872,784	EVANS ET AL.	

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Document Code - DISQ	**This patent is subject to a Terminal Disclaimer**	
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9629 7590 03/17/2008

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EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
03/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

InnoPharma Exhibit 1046.0132

Office Action Summary	Application No.	Applicant(s)	
	10/872,784	EVANS ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-18-2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

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DETAILED ACTION

This is a continuation of US 09/756,291, filed 1/9/2001, now patent 6,774,122. The instant application also claims the benefit of UNITED KINGDOM 0000313.7, filed 01/10/2000 and UNITED KINGDOM 0008837.7, filed 04/12/2000.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 24-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dukes (EP 0 346 014) in view of Lehmann et al. (US Patent Re. 28,690), GB 1 569 286 (herein after referred as '286), Osborne et al., Journal of National Cancer Institute, 1995;87(10):746-750, and Remington (Remington's Pharmaceutical Sciences, 18th ed., 1990, page 219), all of the references are of record in the parent application.

Dukes teaches antiestrogen agents, including fulvestrant, are useful in treating postmenopausal symptoms such as urogenital atrophy affecting the vagina (See page 3, lines 56-page 4, line 1; also page 7, line 28-29). Dukes teaches that antiestrogen agent, including fulvestrant, may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol (See page 7, line 20-24).

Dukes does not expressly teach the dosage of fulvestrant to be 45mg. Dukes does not expressly teach the employment of benzyl benzoate, in the percent amount of 60% w/v or less, or 50% w/v or less, or 45% w/v or less, 40% w/v or less, or 35% w/v or less, or 30% w/v or less, 25% w/v or less, or 10-25% w/v, or 12-18% w/v, as part of the vehicle herein. Dukes does not expressly teach the total amount of the fulvestrant-containing composition administered. Dukes does not expressly teach weight amount of castor oil and benzyl alcohol. Dukes does not expressly teach the employment of ethanol as part of the vehicle herein. Dukes does not expressly teach the dosage of fulvestrant to be 250mg. Dukes does not expressly teach the plasma concentration of fulvestrant herein.

Lehmann et al. teaches that benzyl benzoate and castor oil are well-known solvent useful as conventional carriers for steroids (See col. 1, line 21-26).

'286 teaches an intramuscular injection of testosterone derivative containing castor oil/benzoate in a ratio of 6:4 (See page 1, line 17).

Osborne et al. teaches fulvestrant as useful in treating human breast cancer (See pages 747- 748, Result Section).

Remington teaches that ethanol is one of the most commonly used solvents in pharmaceutical industry (See page 219).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein claimed weight percent, with fulvestrant in the dosage herein, in a method of treating postmenopausal symptoms such as urogenital atrophy in the vagina.

One of ordinary skill in the art would have been motivated to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein claimed weight percent, with fulvestrant, in the dosage herein, in a method of treating postmenopausal symptoms such as urogenital atrophy or treating breast cancer because fulvestrant is known to be useful in treating urogenital atrophy, a benign disease of the female reproductive tract in the vagina and breast cancer. Castor oil and benzyl alcohol are known to be effective as vehicle for fulvestrant. Ethanol is a commonly used pharmaceutical solvent. Benzyl benozate is known to be effective as solvent for steroidal compounds. Since fulvestrant is a estrogen derivative, benzyl benzoate would be reasonably expected to be useful as a solvent for fulvestrant. Therefore, combining one or more agents, which are known to be useful as commonly used solvents, such as benzyl benzoate, ethanol, castor oil, and benzyl alcohol, together and incorporated such combination with an estrogen derivatives, fulvestrant, would be reasonably expected to be useful in formulating a pharmaceutical composition. Furthermore, employing such fulvestrant-containing composition to treat urogenital atrophy in vagina would be reasonably expected to be effective. Moreover, the optimization of result effect

parameters (e.g., amount of excipients, dosage range, and dosing regimens) is obvious as being within the skill of the artisan, absent evidence to the contrary.

One of ordinary skill in the art would have been motivated to maintain the plasma concentration of fulvestrant herein because maintaining the therapeutic plasma level of the active compounds would be considered obvious as being within the purview of the skilled artisan, absent evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1617

/San-ming Hui/
Primary Examiner, Art Unit 1617

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BIB DATA SHEET

CONFIRMATION NO. 2093

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/872,784	06/22/2004	514	1617	056291-5004-01

APPLICANTS

John R. Evans, Macclesfield, UNITED KINGDOM;
Rosalind U. Grundy, Macclesfield, UNITED KINGDOM;

**** CONTINUING DATA ***************************

This application is a CON of 09/756,291 01/09/2001 PAT 6,774,122

**** FOREIGN APPLICATIONS ***************************

UNITED KINGDOM 0000313.7 01/10/2000
UNITED KINGDOM 0008837.7 04/12/2000

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

08/13/2004

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ Yes ☐ No	☑ Yes ☐ No	/SAN-MING R HUI/ Examiner's Signature	☐ Initials	UNITED KINGDOM	1	11	2

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004
UNITED STATES

TITLE

Formulation

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InnoPharma Exhibit 1046.0139

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10872784	EVANS ET AL.
	Examiner	**Art Unit**
	San-ming Hui	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/03/2008								
	24	✓								
	25	✓								
	26	✓								
	27	✓								
	28	✓								
	29	✓								
	30	✓								
	31	✓								
	32	✓								
	33	✓								
	34	✓								

InnoPharma Exhibit 1046.0140

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10872784	EVANS ET AL.
	Examiner	Art Unit
	San-ming Hui	1617

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST: fulvestrant, breeast cancer,	3-3-08	SH

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

InnoPharma Exhibit 1046.0141

FORM PTO-1449 (modified)
To: U.S. Department of Commerce
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

OIPE
OCT 18 2004
PATENT & TRADEMARK OFFICE

Date: October 18, 2004

Atty. Dkt. No.	M#	Client Ref.
	056291-5004-01	

Applicant: Evans et al.

Appln. No.: 10/872,784

Filing Date: June 22, 2004

Prior Examiner: Hui, Sang Ming R. | Prior Group Art Unit: 1617

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR	2,822,316	02/1958	Richter et al.			
	BR	2,983,649	05/1961	Ercoli et al.			
	CR	3,541,209	11/1970	Neumann et al.			
	DR	4,048,309	09/1977	Chen et al.			
	ER	4,048,310	09/1977	Chen et al.			
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	HR	5,095,129	03/1992	Ottow et al.			
	IR	5,183,814	02/1993	Dukes			

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		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	JR	0 138 504	04/1985	EPA	Bowler et al.					
	KR	0 346 014	12/1989	EPA	Dukes					
	LR	6241	09/1968	France	Schering AK		X			
	MR	817,241	07/1959	GB	Francecso Vismara, S.p.A.					
	NR	1 569 286	06/1980	GB	Schering AK					
	OR	1 207 571	10/1970	GB	Takeda Chemical Industries, Ltd.					
	PR	1 126 892	09/68	GB	Schering AK					
	QR	681014	02/1968	South Africa	Kimbel					
	RR	682530	04/1968	South Africa	Ufer et al.					

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	SR	Anschel, "Lösungsmittel und Lösungsvermittler in Injektionen", Pharm, Ind., 1965, Vol. 27 (11a), pp. 781-787			X	
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	VR	Dukes et al., "Antiuterotrophic effects of pure antioestrogen. ICI 182,780, ...the uterus in ovariectomized monkeys", J. Endocrinology, 1992, Vol. 135, pp. 239-247				

Examiner | Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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InnoPharma Exhibit 1046.0142

FORM PTO-1449 (modified) To: U.S. Department of Commerce Patent and Trademark Office	Atty. Dkt. No.	M#	Client Ref.
		056291-5004-01	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Applicant: Evans et al.

Appln. No.: 10/872,784

Filing Date: June 22, 2004

Date: October 18, 2004 Page 2 of 4 Prior Examiner: Hui, Sang Ming R. Prior Group Art Unit: 1617

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR	5,484,801	01/1996	Al-Razzak et al.			
	BR	5,733,902	03/1998	Schneider			
	CR	5,929,030	07/1999	Hamied et al.			
	DR	Re. 28,690	01/1976	Lehmann et al.			
	ER						
	FR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	GR	549118	03/1977	Soviet Union	Prokofeva		X			
	HR	676284	07/1979	Soviet Union	Bikkulov et al.		X			
	IR	WO 95/12383	05/1995	WIPO	Fang et al.		X			
	JR	WO 96/19997	07/1996	WIPO	Chwalisz et al.		X			
	KR	WO 97/21440	06/1997	WIPO	Ferdinando et al.					
	LR	WO 97/37653	10/1997	WIPO	Grosse-Bley et al.		X			
	MR	WO 97/40823	11/1997	WIPO	Perry et al.					
	NR	WO 98/11902	03/1998	WIPO	Grosse-Bley et al.		X			

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	OR	Howell et al., "Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer", British Journal of Cancer, 1996, Vol. 74, pp. 300-308
	PR	Martindale, 32nd Ed., "Alcohol", Pharmaceutical Press, 1999, pp. 1099-1101
	QR	Martindale, 32nd Ed., "Benzoates" and "Benzyl Alcohol"; Pharmaceutical Press, 1999, pp. 1102-1104
	RR	Martindale, 32nd Ed., "Caster Oil"; 32nd Ed., Pharmaceutical Press, 1999, p. 1560
	SR	Migally, "Effect of Castor Oil and Benzyl Benzoate Used as a Vehicle for Antiandrogens on the Adrenal Cortex", Archives of Andrology 2, 1979 pp. 365-369
	TR	Pellegrino, "Use of 17 α Hydroxyprogesterone Caproate in Threatened Abortion", Current Therapeutic Research, Vol. 4, No. 6, June, 1962, pp. 301-305
	UR	Piver et al., "Medroxyprogesterone Acetate (Depo-Provera) vs. . . . Women with Metastatic Endometrial Adenocarcinoma", Cancer, Vol. 45, American Cancer Society, 1980, pp. 268-272

Examiner	Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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InnoPharma Exhibit 1046.0143

FORM PTO-1449 (modified) To: U.S. Department of Commerce Patent and Trademark Office	Atty. Dkt. No.	M#	Client Ref.
		056291-5004-01	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Applicant: Evans et al.		
	Appln. No.: 10/872,784		
	Filing Date: June 22, 2004		
Date: October 18, 2004 Page 3 of 4	Prior Examiner: Hui, Sang Ming R.	Prior Group Art Unit: 1617	

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR						
	BR						
	CR						
	DR						
	ER						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	FR									
	GR									
	HR									
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	JR									
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	LR	Riffkin et al., "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones", Journal of Pharmaceutical Sciences, Vol. 53, No. 8, August 1964, pp. 891-895
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	OR	Vidal, Le Dictionnaire, "Gravibinan", 1995, pp 660-661
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	RR	Wakeling et al., "A Potent Specific Pure Antiestrogen with Clinical Potential", Cancer Research, 1991, Vol. 51, pp. 3867-3873
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	TR	Mackey et al, "Tolerability of intramuscular injections of testosterone ester in oil vehicle", Human Reproduction, vol. 10, no. 4, pp, 869-865, 1995

Examiner	Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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FORM PTO-1449 (modified)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date: October 18, 2004 Page 4 of 4

Atty. Dkt. No.	M#	Client Ref.
	056291-5004-01	

Applicant: Evans et al.

Appln. No.: 10/872,784

Filing Date: June 22, 2004

Prior Examiner: Hui, Sang Ming R. | Prior Group Art Unit: 1617

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR						
	BR						
	CR						
	DR						
	ER						
	FR						
	GR						
	HR						
	IR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	JR									
	KR									
	LR									
	MR									
	NR									
	OR									
	PR									

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	QR	Howell et al., "Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer", The Lancet, Jan. 7, 1995, pp. 29-30
	RR	Osborne et al., "Comparison of the Effects of a Pure Steroidal Antiestrogen With Those of Tamoxifen in a Model of Human Breast Cancer", Journal of the National Cancer, May 1995, Vol. 87, No. 10, pp. 746-750
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	TR	Remington's Pharmaceutical Sciences, 18th ed., 1990, p. 219

Examiner | Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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FORM PTO-1449 (modified)
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Atty. Dkt. No.	M#	Client Ref.
	056291-5004-01	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Applicant: Evans et al.

Appln. No.: 10/872,784

Filing Date: June 22, 2004

Date: October 18, 2004 Page 1 of 1

Prior Examiner: Hui, Sang Ming R.

Prior Group Art Unit: 1617

OCT 18 2004 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR	2001/0006963 A1	07/2001	Lachnit-Fixson et al. *English equivalent of JP 11-501649			
	BR						
	CR						
	DR						
	ER						
	FR						
	GR						
	HR						
	IR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name	English Abstract		Translation Readily Available	
						Enclosed	No	Enclose	No
	JR	11-501649	02/1999	Japan					
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	LR	1207571	10/1970	GB	Takeda Chemical Industries English equivalent of JP-43-27327-B				
	MR	09-208496	12/1997	Japan	Toshihiro et al.	X			
	NR	10-152438	06/1998	Japan	Koji et al.	X			
	OR	10/203982	04/1998	Japan					
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	QR	11-158200	06/1999	JP					
	RR	0905143 A2	03/1999	EP	Yamagata et al. English equivalent of JP Pub. 11-158200				
	SR								

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

	TR	
	UR	
	VR	
	WR	

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EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	"9721440".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L2	2	"5183814".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L3	1606205	castor oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L4	57823	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L5	87	fulvestrant and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L6	681	oil and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L7	2	"4659516".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L8	5	"346014".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L9	9311	(benzyl adj benzoate) or (phenylmethyl adj benzoate)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26

InnoPharma Exhibit 1046.0147

L10	1445775	solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L11	4443	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L12	2	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (estrogen or estradiol or estrone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L13	3	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (testosterone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L14	10	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L15	893	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) and(steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L16	893	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) and (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L17	57823	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L18	2772	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26

InnoPharma Exhibit 1046.0148

L19	1701	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L20	951	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L21	2	((((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent) same steroid	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L22	937	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L23	937	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L24	52202	breast adj cancer	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:26
L25	593	breast adj cancer and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:28
L26	113	breast adj cancer same fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:28
L27	367	cancer same fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/03/03 02:28

3/3/08 2:59:01 AM
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PATENT
ATTORNEY DOCKET NO.: **056291-5004-01**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	Confirmation No. **2093**
EVANS et al.	)	
Application No.: **10/872,784**	)	Group Art Unit: **1617**
Filed: **June 22, 2004**	)	Examiner: **Hui, San-ming R**
FOR: **FORMULATION**	)	Date: **August 21, 2008**

AMENDMENT AND RESPONSE

This is in response to the Action mailed March 17, 2008, the time for responding to which has been extended to and including September 17, 2008 by Petition and authorization for payment of fees submitted herewith. Please amend the claims as presented below.

Table of Contents is presented on page 2 of this paper.
Table of References discussed is presented on page 3 of this paper.
Amendments to the Claims begin on page 4 of this paper.
Remarks/Arguments begin on page 6 of this paper.

Applicants wish to express their appreciation to the Examiner for taking the time for the personal interview on July 15, 2008, with the undersigned, Dr. Gellert and two other representatives of Applicants' assignee, which interview will also be discussed further below.

The Examiner's attention is called to the accompanying Declaration of Dr. Paul Richard Gellert and Attachments thereto (hereinafter "the **Gellert Declaration**"), portions of which were presented at the interview, and additional portions of which provide further factual and documentary support for the patentability arguments presented during the interview.

It is believed that arguments presented in this response and the factual and documentary support provided by the Gellert Declaration establish the patentability of the amended claims presented below and should place this application in condition for allowance. Therefore early and favorable consideration is respectfully requested. However, if any outstanding issues nevertheless remain, it is respectfully requested that the Examiner telephone the undersigned to expedite the resolution of such issues and the allowance of this application.

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For convenience of reference, the Remarks will be presented under the section headings listed in the following Table of Contents, beginning on the page noted:

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TABLE OF REFERENCES

Tab	Author/Inventor	Reference Citation/Patent
1	Cornelius (US '863)	US Patent 4,212,863
2	Dukes (EP '014)	EP 0 346 014 A1 (corresponds to US Patent 5,183,814)
3	Dukes (US '814)	US Patent 5,183,814 (corresponds to EP 0 346 013 A1)
4	Gupta (1999)	P.K. Gupta and G.A. Brazeau (eds). *Injectable Drug Development:Techniques to Reduce Pain and Irritation.* Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999)
5	Huber (US '520)	US Patent 3,164,520
6	Lopatin (1972)	P.V. Lopatin, V. P. Safonov, T. P. Litvinova and L. M. Yakimenko. Use of nonaqueous solvents to prepare injection solutions. *Pharm. Chem. J.* ***6***:724-733 (1972)
7	Mackey (1995)	M.A. Mackey, A.J. Conway and D.J. Handelsman. Tolerability of intramuscular injections of testosterone ester in oil vehicle. *Hum. Reprod.***10**: 862-865 (1995)
8	Nema (1997)	S. Nema, R.J. Washkuhn, and R.J. Brendel. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* **51**:166-71 (1997)
9	PDR (1973)	*Physicians' Desk Reference (27th edition).* 1277-1278, 1350-1354, 1391-1392 Medical Economics Company, Oradell, NJ (1973)
10	Powell (1998)	M. F. Powell, T. Nguyen, and L. Baloian. Compendium of excipients for parenteral formulations. *PDA J. Pharm. Sci. Technol.* **52**:238–311 [pages 238-255 provided] (1998)
11	Riffkin (1964)	C. Riffkin, R. Huber and C.H. Keysser. Castor oil as a vehicle for parenteral adminstation of steroid hormones. *J.Pharm.Sci.* **53**: 891-5 (1964)
12	Strickley I (1999)	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) -Part I. *PDA J. Pharm. Sci. Technol.* **53**:324–349 (1999)
13	Strickley II (2000)	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part II *PDA J. Pharm. Sci. Technol.* **54**:69–96 (2000)
14	Strickley III (2000)	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part III. *PDA J. Pharm. Sci. Technol.* **54**:152–169 (2000)
15	Wang (1980)	Y.C. J. Wang and R. R. Kowal. Review of excipients and pH's for parenteral products used in the United States. *J. Parenteral Drug Assoc.* **34**:452–462 (1980).

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IN THE CLAIMS:

This listing of claims will replace all prior versions and listing of claims in the application.

Listing of the claims:

Claims 1-34 (**cancelled**).

Claim 35 (**new**): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of from 10 to 30 % weight of a mixture of ethanol and benzyl alcohol per volume of formulation and from 10 to 25 % weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle, whereby a therapeutically significant blood plasma fulvestrant concentration of at least 2.5ngml^{-1} is attained for at least 2 weeks after injection.

Claim 36 (**new**): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of from 10 to 30 % weight of a mixture of ethanol and benzyl alcohol per volume of formulation and from 10 to 25 % weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle, whereby the formulation comprises at least 45mgml^{-1} of fulvestrant.

Claim 37 (**new**): The method as claimed in claim 35 or 36 wherein the formulation comprises a mixture of from 15 to 25 % weight of a mixture of ethanol and benzyl alcohol per volume of formulation and from 12 to 20 % weight of benzyl benzoate per volume of formulation.

Claim 38 (**new**): The method as claimed in claim 35 or 36 wherein the formulation comprises a mixture of from 8.5 to 11.5 % weight of ethanol per volume of formulation, from 8.5 to 11.5 % weight of benzyl alcohol per volume of formulation and 12 to 18 % weight of

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benzyl benzoate per volume of formulation.

Claim 39 (**new**): The method as claimed in claim 35 wherein the blood plasma fulvestrant concentration is attained for at least 3 weeks after injection.

Claim 40 (**new**): The method as claimed in claim 35 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks after injection.

Claim 41 (**new**): The method as claimed in claim 35 wherein a therapeutically significant blood plasma fulvestrant concentration of at least $3ngml^{-1}$ is attained for at least 2 weeks after injection.

Claim 42 (**new**): The method as claimed in claim 35 wherein a therapeutically significant blood plasma fulvestrant concentration of at least $8.5ngml^{-1}$ is attained for at least 2 weeks after injection.

Claim 43 (**new**): The method as claimed in claim 35 wherein a therapeutically significant blood plasma fulvestrant concentration of at least $8.5ngml^{-1}$ is attained for at least 4 weeks after injection.

Claim 44 (**new**): The method as claimed in claim 35 or 36 wherein the total volume of the formulation administered to said human is 6ml or less, and the concentration of fulvestrant in said formulation is at least $45mgml^{-1}$.

Claim 45 (**new**): The method as claimed in claim 35 or 36 wherein the total volume of the formulation administered to said human is 6ml or less, and the total amount of fulvestrant in said volume of formulation is 250mg or more.

Claim 46 (**new**): The method as claimed in claim 35 or 36 wherein the benign or malignant disease is breast cancer.

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REMARKS

This Amendment and Response is being filed as a follow-up to the personal interview with Examiner Hui on July 15, 2008, in order to formally present the amended claims and the patentability arguments that were discussed at the interview, and to formally present and supplement by means of the accompanying Gellert Declaration the factual and documentary support for the arguments presented at the interview.

(1) Applicants' Summary of Personal Interview July 15, 2008

Applicants wish to thank the Examiner for extending a personal interview in this Application on July 15, 2008 to the undersigned and three representatives of Applicants' assignee, AstraZeneca AB.

Attending this interview on behalf of Applicants, in addition to the undersigned US attorney, were Dr. Paul Gellert, the declarant on the attached Gellert Declaration and a Senior Principal Scientist for AstraZeneca; Dr. Allen Giles, a European Patent Attorney with AstraZeneca; and Dr. Balvinder Matharu, a patent trainee for AstraZeneca, all working out of the AstraZeneca facilities at Mereside, Alderley Park, Macclesfiled, England.

In order to facilitate the discussion during the interview, the undersigned faxed to Examiner Hui on July 14, 2008, a partial draft of the Gellert Declaration (having the substantive content of paragraphs 1-9 of the attached Gellert Declaration and **Attachments A, B and C**), and a partial draft of this Amendment and Response, including the amended claims and the substance of the "Introduction and Background" and "Claim Amendment" portions of the present Amendment and Response (Sections (2) and (3) of the Remarks).

During the course of the interview the Examiner was also given a copy of a corrected version of Table 1 from the present application with an attached explanation of the corrections (see **Attachment D** to the Gellert Declaration); a two page document showing the structure and solubility of certain steroids in castor oil and sesame oil compared to the structure and solubility of fulvestrant, and the solubility of certain steroids in benzyl benzoate (see **Attachment E** to the Gellert Declaration); and a copy of Huber (US '520) referred to in Attachment E, which is included as **Tab 5** of the **Compendium** of **Attachment F** to the Gellert Declaration.

All of the above-noted drafts and documents that were provided to Examiner Hui were

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discussed during the interview, as were the subject application (as published), the present Action and, generally, the applied references.

The undersigned briefly commented on the prior art cited in the obviousness rejection as disclosing, separately or in various sub-combinations, each of the fulvestrant, castor oil, ethanol, benzyl alcohol and benzyl benzoate components of the formulation administered in the claimed method. Then the undersigned and Dr. Gellert went through a summary of Applicants' argument as outlined in the Introduction and Background portion of partial draft response and the additional data presented with the draft portion of the Gellert Declaration that had been sent to the Examiner prior to the interview.

In brief summary it was argued (and it is believed was demonstrated) that the skilled formulator tasked with developing an intramuscular (IM) injectable formulation for the sustained release of fulvestrant, would have conducted a literature review for previously approved and/or commercially marketed injectable formulations to identify potential solvents and cosolvents meriting further consideration. A preformulation solubility screen would then have been conducted to determine the solubility of fulvestrant separately in a range of pure solvents, including potential solvents and cosolvents identified in the literature review. Based on the results of these preformulation investigations, the experienced formulator would have selected a castor oil based vehicle, but would have been *led away* from adding benzyl benzoate as a cosolvent for fulvestrant when attempting to increase the fulvestrant concentration in the castor oil vehicle up to the target level. Many commercialized steroids were *more* soluble in benzyl benzoate than in the oil base of the vehicle as disclosed in **Riffkin (1965)**, [1] and benzyl benzoate could thus act as a cosolvent. However, fulvestrant is even *less* soluble in benzyl benzoate than it is in castor oil and therefore its addition to castor oil would have been expected (and has been shown) to *further decrease* the ability of the resulting castor oil-based vehicle to dissolve fulvestrant.

It was therefore unexpected and surprising when Applicants found that the addition of benzyl benzoate to a castor oil/alcohol mixture would *increase* the solubility of fulvestrant in the formulation as presently claimed, permitting the target fulvestrant concentration to be attained

[1] See Table of References at page 3 above; a copy of each reference is included in **Attachment F** to the Gellert Declaration under the Tab number indicated in the Table of References.

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with a more desirable lower level of alcohol cosolvent. It was pointed out at the interview that this unexpected positive effect of benzyl benzoate on the solubility of fulvestrant in the castor oil/alcohol mixture is shown by the data in Table 3 of the Evans specification. Moreover, the data from the additional testing overseen by Dr. Gellert and presented in **Attachment C** to his Declaration demonstrates that this unexpected positive benzyl benzoate effect is present across the broader range of formulation composition as presently claimed.

Dr. Gellert additionally commented at the interview on certain transcription and other errors in Tables 3 and 1 of the Evans Application relative to the underlying laboratory notebook data and other source materials, and provided clarification by means of handwritten notations on copies of these Tables, which are **Attachments A** and **D** to his Declaration.

At the conclusion of the interview Examiner Hui indicated that the allowability of the amended claims would be viewed favorably in light of the factual presentation of the draft Gellert Declaration and the arguments presented at the interview. The recitations and Attachments to the draft Gellert Declaration discussed at the interview have been retained in the executed Gellert Declaration submitted herewith. The executed Gellert Declaration also includes additional support for the unobviousness of the presently claimed invention, backed up by literature and patent documents in the Compendium and discussion further below.

(2) Introduction and Background

The invention as presently claimed and disclosed in the subject application is broadly directed toward a method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract in a human by administration of an intramuscular injection of a sustained release pharmaceutical formulation comprising fulvestrant.

Even relative to other difficult to formulate steroidal based compounds, fulvestrant is a *particularly* lipophilic molecule having *extremely* low aqueous solubility. The invention therefore addresses the objective of defining (a) a pharmaceutically acceptable solvent or mixture of solvents (b) that will dissolve a sufficient quantity of fulvestrant [at least 250 mg] (c) to form a small enough volume of formulation that is acceptable for injection [6 ml or less] and will provide (d) a fulvestrant concentration of at least $45mgml^{-1}$ [claim 36] and/or (e) the sustained

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release of fulvestrant whereby a therapeutically significant blood plasma fulvestrant concentration of at least 2.5ngml^{-1} is attained for at least 2 weeks [claim 35].

The person of ordinary skill in the art involved in developing formulations for the parenteral administration of new, difficultly soluble compounds such as fulvestrant would be a person having specialized training and experience in developing pharmaceutical formulations and methods for their administration. Such person would be aware of commercialized sustained release injectable steroidal formulations, such as those included in Table 1 of the Evans specification, which commonly use oil to solubilize the compound and may have various additional excipients. The Evans specification acknowledges, as relevant here, that such known formulations include oils such as castor oil and may include one or more other excipients such as benzyl alcohol, ethanol and benzyl benzoate. However, such person would begin the development of a suitable formulation for fulvestrant by determining the solubility of fulvestrant in various single solvents that have previously been used in injectable formulations.

A selection of such solubility data for fulvestrant is listed in Table 2 of the Evans specification, from which it can be seen that fulvestrant is significantly more soluble in castor oil than any of the other oils tested. However, as noted in paragraph [0017] of the Evans specification, [2] the solubility of fulvestrant in castor oil alone would not meet the above criteria. Table 2 shows a very high solubility of fulvestrant in benzyl alcohol and ethanol, and adding an alcohol component to the castor oil would be seen as a clear choice to the skilled person. Dukes (US '814) took this approach in his Example 3, where his formulation contained 50 mg of fulvestrant, 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml, or about 40% w/v benzyl alcohol. While this may have provided acceptable solubility of fulvestrant in an experimental quantity of formulation to demonstrate selective oestrogen therapy in rats, the Evans specification in paragraph [0015] notes that this very high alcohol concentration would complicate manufacture on a commercial scale, and that there is a need to lower the alcohol concentration whilst preventing precipitation of fulvestrant from the formulation. Moreover, the skilled person would want to reduce the level of alcohol cosolvents to minimize their potential to adversely impact performance including tolerability.

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[2] Reference made herein and in the Gellert Declaration to paragraphs of the Evans specification refer to the numbered paragraphs of the published application, US 2005/0043285 A1, published February 24, 2005.

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The focus of the present invention, therefore, resulted from the discovery by Applicants of the unexpected positive effect of benzyl benzoate in significantly *increasing the solubility* of fulvestrant when added to a castor oil/alcohol mixture, whereby the needed therapeutic amount of fulvestrant could be dissolved in a small enough volume of formulation for injection without need for an excessive amount of alcohol. This was truly surprising since the solubility of fulvestrant in benzyl benzoate is significantly lower than the solubility of fulvestrant either in the alcohol component or in castor oil. See Table 2 and specification paragraphs [0019] and [0051] of the Evans Application. This positive effect of benzyl benzoate in significantly increasing fulvestrant solubility in the castor oil/alcohol mixture is demonstrated by the data in Table 3 of the specification, and is confirmed and amplified by the further evidence presented in the Gellert Declaration and tabulated in Attachment C thereto.

The Examiner will note that the claims presented above cover a broader range of total alcohol and benzyl benzoate content than the rejected previously pending claims. However, it will be apparent from the above summary and the following discussion that the inventive step (non-obviousness) of the present invention does not reside in any particular range of solvent concentration, but lies in Applicants' counter-intuitive addition of benzyl benzoate to the fulvestrant formulation, and the unexpected positive effect of this benzyl benzoate addition on increasing fulvestrant solubility. The further data provided by the Gellert Declaration confirms that the addition of benzyl benzoate unexpectedly significantly increases the solubility of fulvestrant over the broader range of formulation composition as presently claimed.

(3) Discussion of Claim Amendments

Claims 24-34 are newly cancelled above (claims 1-23 having been previously cancelled) and replaced by new claims 35-46. The cancellation of these claims is without disclaimer or prejudice to Applicant's right to prosecute any subject matter that may have been deleted thereby in one or more continuing applications.

As with cancelled claims 24-34, new claims 35-46 are directed toward a method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a

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pharmaceutical formulation as recited in the various claims. As in cancelled claim 24, the method of new independent claim 35 provides that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5ngml^{-1} is attained for at least 2 weeks after injection." As in cancelled claim 29, the method of new independent claim 36 provides a formulation that "comprises at least 45mgml^{-1} of fulvestrant." As in cancelled claims 26 and 31, new dependent claim 46 is specifically directed toward the method wherein the hormonal dependent benign or malignant disease is breast cancer.

The particular ranges of formulation composition or other characteristics recited in new claims 35-46 find support in the specification as follows:

- Support for the recitation in new independent claims 35 and 36 of "from 10 to 30 % weight of a mixture of ethanol and benzyl alcohol per volume of formulation and from 10 to 25 % weight of benzyl benzoate per volume of formulation" is found in the published specification, *inter alia*, at line 13 of paragraph [0031] and at line 16 of paragraph [0036].
- Support for the recitation in new dependent claim 37 of "from 15 to 25 % weight of a mixture of ethanol and benzyl alcohol per volume of formulation and from 12 to 20 % weight of benzyl benzoate per volume of formulation" is found in the published specification, *inter alia*, at line 13 of paragraph [0031] and at line 17 of paragraph [0036].
- As with cancelled claims 24 and 29, support for the recitation in new dependent claim 38 of "from 8.5 to 11.5 % weight of ethanol per volume of formulation" and "from 8.5 to 11.5 % weight of benzyl alcohol per volume of formulation" is found in the published specification, *inter alia*, at lines 9-14 of paragraph [0031] wherein one of the preferred ranges of pharmaceutically-acceptable alcohol (total) is "17-23%w/v" at line 14. The immediately following paragraph [0032], lines 3-7, discloses that the pharmaceutically-acceptable alcohol is "preferably a mixture of two alcohols," specifically noting a mixture of ethanol and benzyl alcohol, and that "preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts." Support for the recitation of "12 to 18 % weight of benzyl benzoate per volume of formulation" is found, *inter alia*, at line 17 of paragraph [0036].
- Support for the recitation in new dependent claim 39 of "wherein the blood plasma

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fulvestrant concentration is attained for at least 3 weeks after injection" is found in the published specification, *inter alia*, at lines 1-2 of paragraph [0048].

- Support for the recitation in new dependent claim 40 of "wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks after injection" is found in the published specification, *inter alia*, at lines 2-3 of paragraph [0048].
- Support for the recitation in new dependent claim 41 of "wherein a therapeutically significant blood plasma fulvestrant concentration of at least $3ngml^{-1}$ is attained" is found in the published specification, *inter alia*, at line 3 of paragraph [0047].
- Support for the recitation in new dependent claim 42 of "wherein a therapeutically significant blood plasma fulvestrant concentration of at least $8.5ngml^{-1}$ is attained" is found in the published specification, *inter alia*, at line 3 of paragraph [0047].
- Support for the recitation in new dependent claim 43 of "wherein a therapeutically significant blood plasma fulvestrant concentration of at least $8.5ngml^{-1}$ is attained for at least 4 weeks after injection" is found in the published specification, *inter alia*, at line 3 of paragraph [0047] and at lines 2-3 of paragraph [0048].
- Support for the recitation in new dependent claim 44 of "wherein the total volume of the formulation administered to said human is 6ml or less, and the concentration of fulvestrant in said formulation is at least $45mgml^{-1}$" is found in the published specification in paragraph [0027].
- Support for the recitation in new dependent claim 45 of "wherein the total volume of the formulation administered to said human is 6ml or less, and the total amount of fulvestrant in said volume of formulation is 250mg or more" is found in the published specification in paragraph [0028].
- Support for the recitation in new dependent claim 46 of "wherein the benign or malignant disease is breast cancer" is found in the published specification, *inter alia*, at lines 1-7 of paragraph [0058] and in paragraph [0062].

It should be clear from the above paragraphs, all limitations of new claims 35-46 find support in the specification, and these new claims are believed to be in proper form in all respects. Accordingly, entry of these amendments is believed to be in order and is respectfully

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requested. Following entry of these amendments, claims 35-46 remain pending in this application.

(4) Claim Rejections - 35 USC § 103

Claims 24-34 have been rejected under 35 USC § 103(a) as being unpatentable over Dukes, EP 0 346 014 (hereinafter "Dukes (EP '014)")[3] in view of Lehmann *et al*, US Patent Re 28,690 (hereinafter "Lehmann"), GB 1 569 286 (hereinafter "GB '286), Osborne *et al.*, Journal of National Cancer Institute, 1995;87(10):746-750 (hereinafter "Osborne"), and Remington's Pharmaceutical Sciences (hereinafter "Remington"). The Examiner applies these references to the rejection as follows:

- Dukes is said to teach that antiestrogen agents, including fulvestrant, are useful in treating postmenopausal symptoms such as urogenital atrophy affecting the vagina (citing page 3, lines 56-page 4, line 1; also page 7, line 28-29). Dukes is said to further teach that antiestrogen agents, including fulvestrant, may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol (citing page 7, 20-24).
- Lehmann *et al.* is said to teach that benzyl benzoate and castor oil are well-known solvent useful as conventional carriers for steroids (citing col. 1, line 21-26).
- GB '286 (also by Lehmann) is said to teach an intramuscular injection of testosterone derivative containing castor oil/benzoate in the ratio of 6:4 (citing page 1, line 17).
- Osborne *et al.* is said to teach fulvestrant as useful in treating human breast cancer (citing pages 747-748).
- Remington is said to teach that ethanol is one of the most commonly used solvents in pharmaceutical industry (citing page 219).

The Examiner concluded at page 4 of the Action that combining one or more agents, which are known to be useful as commonly used solvents, such as benzyl benzoate, ethanol, castor oil, and benzyl alcohol, together and incorporating such combination with an estrogen derivative, fulvestrant, would be reasonably expected to be useful in formulating a

[3] This Dukes reference (Dukes (EP '014)) is the European counterpart of US 5,183,814 (Dukes (US '814)) noted in paragraph [0014] of the published specification.

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pharmaceutical composition; and that employing such fulvestrant-containing composition to treat urogenital atrophy would be reasonably expected to be effective.

The Examiner further concluded that the optimization of parameters such as the amount of excipients, dosage range, and dosing regimens, is "obvious as being within the skill of the artisan, absent evidence to the contrary," and that maintaining the plasma concentration of the active compound as claimed would be considered "obvious as being within the purview of the skilled artisan, absent evidence to the contrary."

Applicants respectfully traverse this obviousness ground for rejection based on the following arguments and the support therefore provided by the Gellert Declaration.

(5) Applicants' Response, Arguments and Declaration Support for the Patentability of the Presently Pending Claims

The invention as disclosed and presently claimed in the subject application is broadly directed toward a method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract in a human by administration of an intramuscular (IM) injection of a sustained release pharmaceutical formulation comprising fulvestrant. Fulvestrant is the non-proprietary name for the subsequently approved and commercialized drug now known as Faslodex®.

The invention is focused in particular on the discovery of a novel and unobvious formulation for this extremely difficult to formulate molecule, which formulation is suitable for intramuscular injection to a human patient and is capable of dissolving the therapeutic target amount of fulvestrant in a small enough volume for IM administration, and which formulation provides for the satisfactory sustained release of fulvestrant over an extended period of time as specified in the present claims.

Oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. One approach to oestrogen deprivation is to antagonize oestrogens with antioestrogens, that is, to administer drugs that bind to and compete for oestrogen receptors present in the nuclei of oestrogen-responsive tissue. Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for oestrogen receptor binding but their effectiveness is often limited by the partial agonism they display, which results

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in incomplete blockade of oestrogen-mediated activity (specification paragraphs [0002-0003]). Fulvestrant, on the other hand, binds oestrogen receptors with high affinity, but without the partial agonism of the traditional non-steroidal antioestrogens. Fulvestrant therefore is capable of eliciting complete ablation of the trophic effects of oestrogens, and is thus characterized as a "pure" antioestrogen, or an Estrogen Receptor-Downregulator (E.R.D) (specification paragraph [0004]. As such, fulvestrant completely blocks the growth stimulatory action of oestradiol on human breast cancer cells, and the uterotrophic action of oestradiol, and is useful in the treatment of oestrogen-dependent indications such as breast cancer and gynaecological conditions, such as endometriosis (specification paragraphs [0007], [0058] and [0062]).

However, developing an IM injectable formulation for fulvestrant that would achieve the satisfactory sustained release of the drug over an extended period of weeks presented a particularly difficult challenge to the experienced formulator. Fulvestrant is a *particularly* lipophilic molecule having *extremely* low aqueous solubility, even relative to other difficult to formulate steroidal based compounds, and it is also poorly soluble in most of the oils and cosolvents that have been used in formulating commercialized steroidal compositions (specification paragraphs [0011-0013], including Table 1, and [0015], including Table 2).

Dr. Gellert notes in ¶ 11 of his Declaration that in about early 2000 [the earliest priority claimed for the Evans Application] the skilled person responsible for developing a sustained release injectable formulation suitable for administration to humans for a new steroidal compound such as fulvestrant, would have had specialized training and experience in developing pharmaceutical formulations and methods for their administration. In developing such a formulation for fulvestrant, the objective would have been to formulate an intramuscular (IM) injection that would provide for the satisfactory sustained release of fulvestrant over a period of at least two weeks and preferably over a period of at least four weeks to reduce the frequency of administration, and would have a target fulvestrant content of at least 45 mg/mL so as to provide a fulvestrant dose of at least 250 mg in a single 5-6 mL injection. (Gellert Declaration, ¶ 11).

Given the nature of fulvestrant and above objectives, the traditional administration options to explore were intramuscular injection of a sustained release *aqueous or oil suspension* or an *oil-based solution* (depot) containing at least 250 mg of fulvestrant that could be administered in a single injection volume of no more than 5 or 6 mL. (Gellert Declaration ¶ 12).

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Because of the extremely low solubility of fulvestrant in water and the objective of formulating a single injection to contain at least 250 mg of fulvestrant, a reasonable starting point would have been to investigate administering fulvestrant as a *suspension* -- as an intramuscular injection of an aqueous or oil suspension of fulvestrant. However, the formulator would have found that injection of an aqueous suspension of fulvestrant resulted in extensive local tissue irritation at the injection site as well as a poor release profile, such as reported in paragraph [0042] of the Evans Application. (Gellert Declaration ¶ 13).

Once finding that injectable suspensions were not an acceptable option with fulvestrant, the experienced formulator would then have moved on to further explore whether fulvestrant could be administered in the form of a sustained release *oil-based solution* at the target fulvestrant concentration of at least 45 mg/mL. (Gellert Declaration ¶ 13). This would require a determination as to whether 250 mg of fulvestrant could be solubilized in no more that than 5-6 mL of an oil-based vehicle that is suitable for IM injection in a human and also provides satisfactory sustained release of fulvestrant.

The experienced formulator, knowing the complexity of this task, would have adopted a rational, systematic approach to identify specific oils, cosolvents and other excipients that were possible candidates for further consideration to meet the formulation objectives. This would have included a literature review of approved and/or commercially marketed injectable formulations in order to identify candidate oils, cosolvents and other excipients (as well as their concentrations) that had already been determined to be safe and effective in similar formulations, in hope of simplifying the regulatory approval process. A preformulation solubility screen would then have been conducted, separately measuring the solubility of fulvestrant in a range of pure solvents, including the potential oil and cosolvent candidates that had been identified in the literature review, to identify those that could help to achieve the target fulvestrant concentration. Such a preformulation approach is explained in detail and documented with contemporaneous texts in paragraphs 14-24 of the Gellert Declaration. Moreover, the text and tables in the Evans Application indicate that a similar approach had been followed. (Gellert Declaration ¶ 14 *et seq.*).

Thus, in paragraph 14 of his Declaration, Dr. Gellert notes that as a part of the preformulation phase, the experienced formulator would have conducted a literature review or

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otherwise would have become familiar with commercially marketed injectable formulations, particularly injectable sustained release formulations of steroids or other relatively insoluble compounds such as those listed in Table 1 of the Evans Application, with the objective of identifying potential oil vehicles, co-solvents and other excipients that already had been found to be tolerated and/or to have passed through regulatory review, and which might be candidates for further consideration and testing for the fulvestrant formulation. This review also would have provided guidance with respect to concentration levels of such co-solvents and other excipients that generally had been found acceptable in sustained release oil-based intramuscular injections administered to humans.

Dr. Gellert documents the objectives for carrying out such a preformulation review, at about the time of the Evans *et al.* invention, with quotations from contemporaneous pharmaceutical formulation texts, including Nema (1997) at page 166:

> Generally, a knowledge of which excipients have been deemed safe by the FDA or are already present in a marketed product provides increased assurance to the formulator that these excipients will probably be safe for their new drug product. ... Regulatory bodies may view an excipient previously approved in an injectable dosage form favorably, and will frequently require less safety data.

noting that the purpose of this Nema paper was thus "to present the various excipients that have been included in the formulation of injectable products marketed in the USA."[4]

Similar objectives were intended to be served by the compilations of commercial formulations in Strickley I (1999), Strickley II (2000) and Strickley III (2000):

> This compilation will also be useful for those interested in knowing what additives are currently used in injectable products and at what concentrations they are administered in practice. This compilation only focuses on marketed formulations and does not delve into the subject of preclinical or drug discovery formulations associated with early-stages pharmacokinetics or proof-of-concept pharmacodynamics, where the formulation scientist is not bound by regulatory constraints.

[4] Nema (1997) does caution, however, that there is no guarantee that the new drug product will be safe as excipients are combined with other additives and/or with a new drug, creating unforeseen potentiation or synergistic toxic effects.

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(Strickley I (1999) at 324). Powell (1998) similarly states at page 238 with respect to its compilation of commercially used excipients:

> Thus, the formulation scientist is often faced with a dilemma -- which excipients are truly available for use (based on what has been used previously), and which are not? ... And at what concentrations, and by what route? ...
>
> Herein are listed the excipients found in most of the approved and marketed parenteral formulations, given systematically by excipient name. In this format it is easy to determine what concentrations were used, the route of administration, the main rationale for addition of that excipient, the drug that was formulated, the manufacturer, brand name, etc.

(Gellert Declaration ¶ 14).

Dr. Gellert reports in paragraph 15 of his Declaration that the formulator, in conducting this literature review, would have noted reference to a number of intramuscular injectable sustained release oil-based steroidal formulations that had been commercially marketed. Dr. Gellert lists, for example, the following formulations found in the literature references cited below:

- Strickley I (1999), Table VII:

  Haloperidol Decanoate/Haldol decanoate (50-100 mg/mL in sesame oil, benzyl alcohol 1.2%);

  Testosterone Enanthate/Delatestryl (200 mg/mL in sesame oil, chlorobutanol 5 mg/mL);

- PDR (1973) at pages 1277-1278

  Proluton/progesterone (50 mg/mL in sesame oil, 150 mg/ml benzyl benzoate, 5 mg/ml benzyl alcohol, 1 mg/ml propylparaben);

- PDR (1973) at pages 1349-1354

  Deladumone/Testosterone Enanthate & Estradiol Valerate (90 & 4 mg/mL in sesame oil, 0.5% chlorobutanol);

  Deladumone OB/Testosterone Enanthate & Estradiol Valerate (180 & 8 mg/mL in sesame oil, 2% benzyl alcohol);

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Delalutin/hydroxyprogesterone caproate (250 mg/mL in 52% castor oil, 46% benzyl benzoate, 2% benzyl alcohol);

Delestrogen/estradiol valerate (20 mg/mL in 78% castor oil, 20% benzyl benzoate, 2% benzyl alcohol and 40 mg/mL in 58% castor oil, 40% benzyl benzoate, 2% benzyl alcohol);

Delatestryl/Testosterone Enanthate (200 mg/mL in sesame oil, 0.5% chlorobutanol);

Delaluteval 2X/hydroxyprogesterone caproate & estradiol valerate (250 mg/mL & 5 mg/mL in castor oil, 45% benzyl benzoate, 1.6% benzyl alcohol);

- PDR (1973) at pages 1391-1392

  Prolixin Enanthate/FluphenazineEnanthate (25 mg/mL in sesame oil, 1.5% benzyl alcohol);

- Wang (1980):

  Depo-Testosterone/testosterone cypionate (100 mg/mL in 87.4% cottonseed oil, 0.1 mL benzyl benzoate, 9.45 mg benzyl alcohol as a preservative);

- Mackey (1995):

  Testoviron Depot/testosterone enanthate (250 mg/mL in castor oil and benzyl benzoate);

as well as a number of other commercialized oil based long-acting IM injectable formulations reported on Table 1 of the Evans Application. (Gellert Declaration ¶ 15).

As a further part of the preformulation phase, Dr. Gellert explains in paragraph 16 of his Declaration that the experienced formulator would have conducted a preformulation solubility screen, separately measuring the solubility of fulvestrant in a range of pure solvents, including the potential oil and co-solvent candidates that had been identified in the above literature review as being suitable for inclusion in intramuscular injection formulations. This is documented, for example, in Gupta (1999), Chapter 17 at page 402, under the heading "Formulation Development":

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> The activities necessary to develop a parenteral product can be placed into the following three broad areas: preformulation, formulation, and scale-up. While there are alternative development perspectives, all development ultimately needs to accomplish the same activities. Preformulation includes the characteristics of the bulk drug plus initial screening for excipient compatibility with the drug.

Such "Preformulation studies" are said in Gupta (1999) to "provide fundamental data and experience necessary to develop formulations for a specific compound" including, as item 8.1 in the outline of areas of specific interest, a determination of "solubility" in "selected solvents" (at 403). "Significant formulation activities begin with initial preformulation data and knowledge of the specific route of administration" (at 405), which "formulation activities include the identification and selection of a suitable vehicle (aqueous, nonaqueous or co-solvent system) ..." (at 404). It is further noted that "injection volume is one of the most important considerations in the formulation development of a commercial product" (at 405). When carrying out such a preformulation solubility screen with fulvestrant, the formulator would have found that fulvestrant had extremely low solubility in water, low solubility in most oils (but highest in castor oil), low solubility in benzyl benzoate, and the highest solubility in ethanol and benzyl alcohol, such as reported in Table 2 of the Evans Application. (Gellert Declaration ¶ 16).

With the information on prior commercialized formulations and the fulvestrant solubility data from the preformulation screen (such as reported in Table 2 of the Evans Application), Dr. Gellert notes that the experienced formulator would have selected castor oil as the oil vehicle because of the higher solubility of fulvestrant in castor oil relative to the other oils tested. Nevertheless, he would have appreciated that the target fulvestrant concentration of at least 45 mg/mL could not be achieved with castor oil alone, and that a co-solvent would be required. (Gellert Declaration ¶ 17).

Dr. Gellert further explains in paragraph 18 of his Declaration that a number of the commercialized formulations that would have been identified in the literature review (including the castor oil-based formulations) have a substantial benzyl benzoate component, which may be present as a co-solvent. He cites, for example, Delalutin noted in paragraph 15 above, which is reported in PDR (1973) and noted in Table 1 of the Evans Application, and is one of the

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formulations discussed in the Riffkin (1964) article entitled, "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones" (see Riffkin n. 6). Delalutin is 250 mg/mL 17-hydroxyprogesterone caproate dissolved in 52% castor oil, 46% benzyl benzoate and 2% benzyl alcohol. However, Riffkin Table II reports that the solubility of 17-hydoxyprogesterone caproate in castor oil alone is only 55.6 mg/mL, but the solubility of 17-hydroxyprogesterone caproate in benzyl benzoate is substantially higher, being at least 250 mg/mL (see example 4 of Huber (US '520) and Attachment E discussed below). Even if not needed as a cosolvent, Riffkin (1964) notes that "the addition of benzyl alcohol or benzyl benzoate to castor oil resulted in a lower and more favorable viscosity, making it easier to inject" (paragraph bridging pages 893-894). (Gellert Declaration ¶ 18).

However, Dr. Gellert points out that in paragraph 19 of his Declaration that the skilled formulator would have appreciated from the fulvestrant solubility data generated in the preformulation screen that fulvestrant had very different solubility characteristics relative to the steroids of previous commercial formulations. Attachment E is a compilation showing the chemical structures and relative solubilities in castor oil and sesame oil of the compounds named in Riffkin (1964) Table II compared to the structure and the solubility of fulvestrant in these oils. It can be seen that the solubility of fulvestrant in castor oil and in sesame oil (20 mg/mL and 0.58 mg/mL, respectively, from Table 2 of the Evans Application) is appreciably lower than the solubility of the other steroids in these oils (taken from Table II of Riffkin (1964)). The second page of Attachment E tabulates the concentration in benzyl benzoate of five named steroids, taken from Examples 1-5 of Huber (US '520), ranging from 200 to 400 mg/ml.[5] By comparison, the solubility of fulvestrant in benzyl benzoate is reported in Table 2 of the Evans Application as being only 6.15 mg/mL, and only 3.8 mg/mL as determined in the recently conducted tests reported in Attachment C. (Gellert Declaration ¶ 19).

He concludes in paragraph 20 of his Declaration that the experienced formulator thus would have expected that benzyl benzoate would not act as a co-solvent for fulvestrant in castor oil because the solubility of fulvestrant in benzyl benzoate was significantly lower than its

[5] Data taken from the Examples of Huber (US '520); these are concentrations used in the examples and not necessarily the actual maximum solubility of each steroid in benzyl benzoate, which may be higher. Huber was a co-author on Riffkin (1964).

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solubility in castor oil. Dr. Gellert further notes that addition of benzyl benzoate to castor oil, for whatever reason, would have been expected to decrease, rather than increase, the solubility of fulvestrant in the resulting castor oil/benzyl benzoate mixture. This is confirmed in Table 4 of the Evans Application, which reports a fulvestrant solubility of only 12.6 mg/mL in the castor oil vehicle containing only 15% benzyl benzoate, compared to the 20 mg/mL solubility of fulvestrant in castor oil alone as reported in Table 2.[6] (Gellert Declaration ¶ 20).

Based on the solubility data determined in the preformulation screen (such as reported in Table 2 of the Evans Application), Dr. Gellert notes in paragraph 21 of his Declaration that ethanol and/or benzyl alcohol would have been seen as the best co-solvent candidates for raising the fulvestrant solubility to the 45 mg/mL target in the castor oil vehicle, and would also function to lower the viscosity of the resulting formulation and make it easier to inject. Consistent with this solubility data, Dukes (US '814) added 40% w/v benzyl alcohol in order to dissolve 50 mg/mL fulvestrant in the castor oil-based formulation used in the experimental rat studies of his Example 3. It thus would have been apparent that 40% w/v benzyl alcohol could function as a co-solvent in castor oil to achieve the target fulvestrant concentration. Nevertheless, Dr. Gellert states that the skilled formulator would have been concerned with using such a high alcohol content in intramuscular injectable formulations for administration to a human. (Gellert Declaration ¶ 21).

First of all, he notes, the experienced formulator would want to minimize the amount of co-solvents and excipients in any injectable formulation. For example, as stated in Gupta (1999), Chapter 17, "Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parental Products" at page 414:

> Cosolvents are commonly used to enhance drug solubility and stability. Cosolvents may include ethanol, propylene glycol, polyethylene glycols, and glycerin. These components have intrinsic effects on biologic tissue and can alter the properties of other excipients, thus influencing the tissue damage or pain caused by a product. There is a dearth of literature on the pain caused by

[6] Dr. Gellert also notes that in the further tests that were recently conducted under his guidance (paragraphs 7-9 and Attachments B and C to the Gellert Declaration), the solubility of fulvestrant in castor oil alone was again tested and found to be 21.4 mg/mL, and the solubility of fulvestrant in benzyl benzoate alone was again tested and found to be only 3.8 mg/mL, which further confirms that benzyl benzoate would not be expected to act as a cosolvent for fulvestrant in castor oil.

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> cosolvents, but there is also a growing body of knowledge on the tissue damage that they can cause. It is not certain that tissue damage is always directly correlated with the injection pain, but minimization of both pain on injection and potential for tissue damage should be included in the product development plan.

Dr. Gellert finds further support from Gupta (1999), Chapter 11, titled Cosolvent Use in Injectable Formulations, page 217:

> Ideally, it is best to select and use solvents that would maximize the solubility of the compound. Maximizing the solubility of a compound in a particular cosolvent system would result in lower total levels of the non-aqueous solvent(s) being administered to the patient, thereby lowering the chance for potential side effects.

Although this quotation from Gupta (1999) is focusing on non-aqueous solvents in aqueous formulation, Dr. Gellert points out that this objective would have applied to aqueous and oil-based systems alike, in that the precedent of commercialized formulations identified in the literature review would have confirmed that fixed oils, such as castor oil, have long been commercially used and accepted as the major component of oil-based sustained release intramuscular injectable steroidal formulations. On the other hand, co-solvents such as ethanol or benzyl alcohol have generally been used only in far lesser concentrations, as discussed in the following paragraph. (Gellert Declaration ¶ 22).

Thus, in paragraph 23 of his Declaration, Dr. Gellert documents that the use of such a high content of either benzyl alcohol or ethanol would have been contrary to precedent, as shown from the review of commercialized oil-based intramuscular injectable sustained release formulations. The literature review as of early 2000 would have shown that any benzyl alcohol in such formulations was almost always present as a preservative in a concentration of about 2% or less, occasionally at a concentration of up to 5%, but only rarely at higher concentrations. With respect to benzyl alcohol Dr. Gellert notes, for example:

- Gupta (1999), Chapter 11 at page 229 stating that benzyl alcohol "is typically used in concentrations of up to 2 percent as a preservative and up to 5 present as a solvent," and then discussing reported toxicities.

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- Nema (1997), Table V at page 168, reporting that benzyl alcohol was present as an antimicrobial preservative in 74 injectable formulations (not limited to oil-based IM formulations) at concentrations of from 0.75-5% (note that benzyl alcohol is not included at all in Nema Table I, "Solvents and Co-solvents");
- Powell (1998), the benzyl alcohol listing at pages 244-246, particularly those indicated as being used in IM formulations;
- Strickley I (1999) at page 329 notes the inclusion of 2% benzyl alcohol in an IM lorazapam formulation in a propylene glycol vehicle, but does not include benzyl alcohol at all in Table VI listing "Cosolvents Used in Parenteral Formulations;"
- Lopatin (1972) noting in Table 3 at page 727 opposite Benzyl alcohol, "Toxic. Used in concentration of not over 3%. Has irritant action in concentration of 5%;"
- Cornelius (US '863), col. 1, lines 30-35 stating, "It is known that the solubility of steroids in vegetable or animal oils can be increased by the addition of excipients such as benzyl alcohol and benzyl benzoate. An objection to the use of such excipients, and specifically benzyl alcohol in somewhat higher concentrations, is that these agents may irritate the tissues."

The literature review as of early 2000 also would have shown that, with few exceptions, ethanol was not included in such formulations in excess of about 10%. With respect to ethanol, Dr. Gellert cites, for example:

- Gupta (1999), Chapter 11 at page 225 noting that ethanol has been used at levels up to 50 percent, but these levels typically are associated with pain on injection;
- Strickley I (1999), Table VI, "List of Cosolvents Used in Parenteral Formulations" more specifically lists the ethanol content in IM formulations for specifically identified drugs, which concentrations range only from 2.5 to 10%; an IM/IV lorazapam formulation in a propylene glycol vehicle is noted at page 329 as having 18% alcohol, but is not included with the IM formulations in Table VI;
- Nema (1997), Table I, "Solvents and Co-solvents" at page 167, lists ethanol as being in 24 formulations with a concentration range of 0.6-80% (for Prograf); note that this is misleading, however, since Prograf is a *concentrate* for intravenous infusion only,

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and is to be diluted 250 to 1000 times before administration;

- Powell (1998) lists "alcohol" at page 242 and "ethyl alcohol" at page 255, wherein the ethanol concentration for IM formulations ranges from 0.61-10%.

(Gellert Declaration ¶ 23).

Thus, Dr. Gellert continues in paragraph 24 of this Declaration, even though Dukes (US '814) had demonstrated that the target 45 mg/mL fulvestrant concentration could be achieved by adding 40% benzyl alcohol to the castor oil vehicle, the precedent of commercialized IM oil-based systems would have motivated the experienced formulator to substantially reduce the benzyl alcohol content of the formulation intended for human use, and this commercial precedent would have made him very reluctant to replace benzyl alcohol with the substantial amount of ethanol that would be needed to maintain the target fulvestrant concentration. Benzyl benzoate clearly would not be considered to solve this dilemma, but rather would be expected to have a negative effect on fulvestrant solubility since fulvestrant was even less soluble in benzyl benzoate than in castor oil, that is, one would have expected that adding benzyl benzoate would require still more alcohol to maintain the target fulvestrant concentration.[7] (Gellert Declaration ¶ 24).

Dr. Gellert thus concludes, in paragraph 25 of his Declaration, that under these circumstances, the discovery by Evans *et al.*, that the addition of benzyl benzoate to the castor oil/alcohol mixture actually increases the solubility of fulvestrant such that more fulvestrant could be dissolved in a given volume of formulation, was unexpected and truly surprising. This positive benzyl benzoate effect on fulvestrant solubility in the resulting formulation is shown in Table 3 of the specification (and is not changed by the above-noted corrections), and is confirmed and demonstrated over a broader range of formulation composition by the additional set of experiments conducted under his guidance and discussed in paragraphs 7-9 of the Gellert

[7] It should be noted that even apart from this solubility issue, there would have been no motivation to add benzyl benzoate for viscosity reduction since the significant quantity of alcohol would serve the dual function of acting as a co-solvent as well as reducing the injection viscosity and making it easier to inject, whereas the benzyl benzoate would be expected to have a negative effect on the fulvestrant solubility.

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Declaration, the results of which are reported in Attachment C. (Gellert Declaration ¶ 25). These additional experiments will be discussed further in Section (7) below of these Remarks.

(6) Corrections/Clarifications to Evans Application

During the course of Dr. Gellert's study of the Evans Application and the underlying data, he became aware of several transcription or other errors between certain disclosures of Tables 1, 2 and 3 of the Evans Application and the underlying laboratory notebook data or other source material for these disclosures. Dr. Gellert points out the existence and nature of these errors in paragraphs 4, 5 and 10 of his Declaration.

Thus, in paragraph 4 of his Declaration, Dr. Gellert points out that in Table 2 of the Evans Application, the solubility of fulvestrant in castor oil appears to have been transcribed incorrectly from the original source, the laboratory notebook. The value in the latter is 24.5 mg/ml and not 20 mg/ml. He also reports that in other experiments to determine the solubility of fulvestrant in castor oil and also in benzyl benzoate, some variability was observed. (Gellert Declaration ¶ 4).

In paragraph 5 of his Declaration, Dr. Gellert points out that in Table 3 of the Evans Application, the given solubility values were generated at 4°C and not at 25°C as is stated in the title of Table 3. He also notes that for fulvestrant formulations, it is preferable that the fulvestrant remains completely in solution at both 4°C and 25°C, and that the 4°C temperature corresponds to the storage temperature (2°C to 8°C in the FDA approved label for Faslodex), and the 25°C temperature corresponds to the administration temperature (ambient temperature). In addition, Dr. Gellert notes that the specified solubility values on this Table 3 are mean values calculated from analysis of replicate samples from one or more trials. The individual values are shown in handwriting in the amended version of Table 3 in Attachment A to his Declaration. He additionally notes that it appears that the mean values for the last three compositions in Table 3 have been incorrectly calculated. The corrected mean values, together with the correction of the temperature from "25°C" to read "4°C", are also shown in handwriting in the amended version of Table 3 in Attachment A. (Gellert Declaration ¶ 5).

Dr. Gellert evaluated the transcription and other errors against the original application disclosures and concluded that these do not change the ultimate conclusions made from the data

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as originally reported. He specifically confirmed that the addition of 15% w/v benzyl benzoate to compositions having total alcohol concentrations in castor oil of 10%, 15%, 20% and 30% w/v unexpectedly provides a positive effect on fulvestrant solubility, significantly increasing the solubility of fulvestrant in the compositions despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil. (Gellert Declaration ¶ 6).

Moreover, an additional set of experiments has been conducted at 25°C under Dr. Gellert's guidance to obtain consistent data with reduced variability from a single set of rigorously controlled solubility experiments and to demonstrate that the unexpected increase of solubility of fulvestrant by adding benzyl benzoate into compositions containing ethanol, benzyl alcohol and castor oil, is present across the broader range of composition encompassed by the claims presented herein. These additional experiments will be discussed in Section (7) of these Remarks below.

Dr. Gellert additionally points out in paragraph 10 of his Declaration that during the course of his study of the Evans Application and the underlying source materials it was drawn to his attention that some of the composition data given for Delestrogen and Delalutin somehow had been shifted one column to the right. Thus, for Delestrogen, the 78% and 58% figures shown under the BzBz column should have been under the OIL column; the 20% and 40% figures shown under the BzOH column should have been under the BzBz column; and the 2% figures shown under EtOH should have been under the BzOH column. Similarly for Delalutin, the "up to 2%" shown under the EtOH column should have been under the BzOH column. This Table 1 reports that the source of this data was J.Pharm.Sci (1964) 53(8) 891, which is Riffkin (1964), and Dr. Gellert verified the corrected data from the entries for Delalutin and Delestrogen in PDR (1973). A copy of Table 1 from the Evans Application is reproduced as Attachment D to the Gellert Declaration, on which the above corrections have been made in handwriting, as well as additional minor corrections as noted in paragraph 10 of his Declaration. Attachment D also includes a one page explanation by Dr. Gellert of the corrections to this Table 1. (Gellert Declaration ¶ 10).

(7) Additional Tests and Data in Attachment C

In paragraphs 4 and 5 of his Declaration Dr. Gellert has pointed out several transcription and/or other errors relating to the solubility data reported in Tables 2 and 3 of the Evans

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Application relative to the underlying laboratory notebook data. Thus in Table 2, the solubility of fulvestrant in castor oil has been reported as 20 mg/ml whereas the value in the underlying laboratory notebook is 24.5 mg/ml. Dr. Gellert also observed some variability in other experiments to determine the solubility of fulvestrant in castor oil and also in benzyl benzoate. It was also observed that the solubility values in Table 3 had been generated at 4°C and not at 25°C as stated in the title of Table 3. Moreover, the specified solubility values on Table 3 are mean values calculated from analysis of replicate samples from one or more trials.

Therefore, an additional set of experiments was conducted at 25°C under Dr. Gellert's guidance to obtain consistent data with reduced variability from a single set of rigorously controlled solubility experiments, to demonstrate that the unexpected increase of solubility of fulvestrant by adding benzyl benzoate into compositions containing ethanol, benzyl alcohol and castor oil, is present across the broader range of composition encompassed by the amended claims presented above. The solubility of fulvestrant in benzyl benzoate and in castor oil was also measured in the same set of experiments using the same batch of benzyl benzoate and the same batch of castor oil as were used to make up the compositions. The Experimental Test Procedure is described in Attachment B to Dr. Gellert's Declaration. (Gellert Declaration ¶ 7).

The results from these solubility experiments are shown in the table in Attachment C. These results show that the solubility of fulvestrant in castor oil alone (21.4 mg/ml) is significantly greater than the solubility of fulvestrant in benzyl benzoate alone (3.8 mg/ml) and demonstrate the unexpected increase in fulvestrant solubility on the addition of 10, 15 and 25% w/v benzyl benzoate, in place of an equivalent amount of castor oil, to compositions having total alcohol concentrations in castor oil of 10%, 15%, 20%, 25% and 30% w/v. (Gellert Declaration ¶ 8).

As Dr. Gellert observes in paragraph 9 of his Declaration, the results that were obtained from these experiments conducted under rigorously controlled conditions and with an expanded range of compositions, as shown in Attachment C, confirm the ultimate conclusions drawn from the results shown in Table 3 of the original application disclosure, namely that the addition of 10% to 25% w/v benzyl benzoate to compositions having total alcohol concentrations in castor oil of between 10% to 30% w/v unexpectedly provides a positive effect on fulvestrant solubility, significantly increasing the solubility of fulvestrant in the compositions despite fulvestrant

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having a lower solubility in benzyl benzoate than in either alcohol or castor oil. (Gellert Declaration ¶ 9).

(8) Fourth Information Disclosure Statement

A Fourth Information Disclosure Statement is submitted herewith together with a form PTO-1449 formally citing those references discussed in the Gellert Declaration in support of patentability that were not previously cited in this Application. A copy of each of the cited references (except for U.S. patents) is also submitted with this Information Disclosure Statement.

Also submitted with this Fourth Information Disclosure Statement as **Attachment I** is a copy of European patent 1250138 which granted on the European counterpart of the present application; as **Attachment II** is a copy of the file from the European Patent Office for the opposition pending against European patent 1250138. Attachment I is included to give the Examiner easy reference to the 33 claims in issue in the Opposition.

The Examiner will note that all of documents D1 through D7 cited in the opposition have already been cited and considered by the Examiner in the present application *except for* document D5, being US Patent 4,388,307 to Cavanak (Cavanak US '307), and document D6, being German language EP 0310542A1 to Schneider (Schneider EP '542). As discussed further below, Cavanak US '307 is no more relevant to the present claims than the documents already cited and considered in this Application, and any relevant subject matter in Schneider EP '542 is already in the present record through US 5,733,902 to Schneider (Schneider US '902), which has been formally cited and acknowledged as having been considered by the Examiner. While not identical in wording, both Schneider EP '542 and Schneider US '902 claim priority from application DE 37 33478 filed October 1, 1987.

However, to complete the present record, Cavanak US '307 and Schneider EP '542 (with English language translation) are formally cited on the form PTO-1449 accompanying the Fourth Information Disclosure Statement.

Cavanak US '307 refers to galenic compositions containing "hydrophobic and/or lipophilic peptides which are insoluble or difficulty soluble in conventional pharmaceutical vehicles, in particular cyclosporins" (col. 1, line 66 to col. 2, line 2). The focus of this reference is on the particular benefits to cyclosporin compositions of carriers comprising certain classes of

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glycerides (col. 1, lines 51-56), specifically at least one of component (a), being "a trans esterification product of a natural or hydrogenated vegetable oil triglyceride and a polyalkylene polyol," component (b) being "a saturated fatty acid triglyceride," and component (c) being "a mono- or di-glyceride" (col. 1, lines 57-65). The Opposer (at pages 5-6 of the Opposition) cites as the relevant portion of this document the discussion of "further excipients" that may be included in the cyclosporin/glyceride composition, specifically the disclosure at column 5, lines 25, 31-32 and 34, which in context read as follows:

> The pharmaceutical compositions according to the invention may be formulated with or without further excipients.
>
> In particular solubilizing agents and solvents may be present in a concentration of up to 60% of the total composition, if desired, in order to attain satisfactory concentration of peptide.
>
> (i) Ethanol may be used as a further solubilizing agent/solvent. The *ethanol content by weight may be for example 2 to 5% for parenteral compositions* and 1 to 20% for oral compositions, calculated on the total composition.
>
> (ii) For parenteral composition, *an alternative* further solubilizing agent/solvent is *benzoic acid benzyl ester. This may be present at from 5 to 40% of by weight.*
>
> (iii) A vegetable oil, such as olive oil or corn oil, may be present in both oral and parenteral compositions as Vehicle. The vegetable oil content by weight may be for example for 35 to 60%, calculated on the total composition.

(Cavanak US '307, col. 5, lines 18-38). The reference notes as "especially advantageous" a composition comprising "a cyclosporin and a carrier comprising a component (a) together with (i) ethanol and (iii) a vegetable oil" (col. 5, lines 48-53), and all claims are directed toward such a composition. Ethanol and the benzoic acid benzyl ester are taught and exemplified as alternative solubilizing agents (see above quote and the examples, wherein the exemplified compositions contain *either* ethanol *or* benzoic acid benzyl ester).

It is respectfully submitted that the prior art commercialized oil based sustained release injectable *steroidal* compositions listed in Table 1 of the present application, which include an ethanol-containing oil-based steroidal composition (Parabolan) and several benzyl benzoate-containing oil-based steroidal compositions, are more relevant to the present invention than the disclosure of Cavanak US '307, which relates to a *cyclosporin* composition in a glyceride-

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containing vehicle. In any event, most significantly, there very clearly is no suggestion in this reference of the unexpected benzyl benzoate positive effect on the solubility of fulvestrant in a castor oil/alcohol mixture vehicle, as detailed above and in the Gellert Declaration.

Document D6 (Schneider EP '542) is cited in the opposition for the disclosure in example 8, of "an oily solution in castor oil/benzyl benzoate of an antioestrogenic steroid." Example 8 in Schneider EP '542 is identical to example 8 in Schneider US '902, which has already been considered by the Examiner. Moreover, Table 1 in the present Application already acknowledges several steroidal compositions in castor oil and benzyl benzoate.

Also submitted with this further Information Disclosure Statement as **Attachment III** is a copy of the Supplementary European Search Report in a divisional application filed from European Patent 1250138, the European counterpart of the present application. This Search Report is based on the same claims that are involved in the Opposition, a copy of which has been included in **Attachment I** to this Information Disclosure Statement. It will be noted that documents D6 and D7 in this Search Report correspond to documents D6 and D5, respectively, discussed above with respect to the Opposition, and are categorized only as "A: technological background."

(9) Conclusion

As detailed in the Gellert Declaration and the supporting contemporaneous literature references, the skilled person taxed with developing an IM injectable formulation for the sustained release of fulvestrant would have followed a systematic approach, including a preformulation literature review and preformulation solubility screen. In doing so, the skilled formulator would have been *led away* from adding benzyl benzoate as a cosolvent for fulvestrant when attempting to increase the fulvestrant concentration in the castor oil vehicle up to the target level. Instead, considering the low solubility of fulvestrant in benzyl benzoate relative to castor oil, it would have been expected that the addition of benzyl benzoate would have *further decreased* the ability of the resulting castor oil-based vehicle to dissolve fulvestrant. Therefore it was unexpected and surprising when Applicants found that the addition of benzyl benzoate to a castor oil/alcohol mixture would increase the solubility of fulvestrant in the formulation as presently claimed, permitting the target fulvestrant concentration to be attained with a more desirable lower level of alcohol cosolvent.

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In view of this teaching away, and the surprising and unexpected benzyl benzoate positive effect on fulvestrant solubility found when Applicants nevertheless added benzyl benzoate to a castor oil/alcohol mixture, it is submitted that the present claims are not rendered obvious by the prior art. Moreover, the additional test data generated under Dr. Gellert's direction establishes that this positive benzyl benzoate effect applies to the broader range of formulation composition as presently claimed. Accordingly, it is believed that all claims are in condition for allowance, and a Notice to that effect is respectfully requested. However, if any issues remain, it is respectfully requested that the Examiner telephone the undersigned to expedite the resolution of any such issues and the allowance of this application.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: August 21, 2008 By: _____

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PATENT
ATTORNEY DOCKET NO.: **056291-5004-01**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	Confirmation No. **2093**
EVANS et al.	)	
Application No.: **10/872,784**	)	Group Art Unit: **1617**
Filed: **June 22, 2004**	)	Examiner: **Hui, San-Ming R**
FOR: **FORMULATION**	)	

DECLARATION UNDER 35 U.S.C. § 1.132
OF PAUL RICHARD GELLERT

PAUL RICHARD GELLERT of AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK declares:

1. I graduated from the University of Oxford in Chemistry in 1984. I undertook postgraduate research with Professor Brian Howard in the Physical Chemistry Laboratory at the University of Oxford leading to the award of a D.Phil in 1988. From February 1988 until the present I have been employed by AstraZeneca, (formerly Zeneca and ICI) initially as a Senior Research Scientist and subsequently as a Team Leader/Manager, Principal Scientist and, since 2004, a Senior Principal Scientist.

2. I have worked in the formulation and drug delivery area throughout my career with AstraZeneca, where my research and development work has covered a range of formulation types including sustained released injections, including fulvestrant.

3. During the course of my study of the subject application (hereinafter "the Evans Application") and the underlying data, I have become aware of several transcription or other errors between certain disclosures of the subject application and the underlying laboratory notebook data. One purpose of this Declaration is to point out the existence

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and nature of these errors and to report further testing that has been carried out under my guidance to obtain additional data (paragraphs 4-10 below and Attachments A-D). A further purpose of this Declaration is to set out and document the manner in which an experienced formulator would likely have approached the task of developing a sustained release injectable formulation suitable for human use for a steroidal compound such as fulvestrant in about early 2000, which I understand is when the priority applications supporting the Evans Application were filed (paragraphs 11 - 25 below and Attachment E). Citations to literature and patent references in this Declaration will be in the format Lead Author (Date), and the full citations are given in the Table of References at the end of this Declaration. A copy of each cited reference (or cited portions of the longer references) is included in Attachment F under the Tab number noted in the Table of References.

4. In Table 2 of the Evans Application, the solubility of fulvestrant in castor oil appears to have been transcribed incorrectly from the original source, the laboratory notebook. The value in the latter is 24.5 mg/ml and not 20 mg/ml. In other experiments to determine the solubility of fulvestrant in castor oil and also in benzyl benzoate, some variability was observed.

5. In Table 3 of the Evans Application, the given solubility values were generated at 4°C and not at 25°C as is stated in the title of Table 3. For fulvestrant formulations, it is preferable that the fulvestrant remains completely in solution at both 4°C and 25°C. The 4°C temperature corresponds to the storage temperature (2°C to 8°C in the FDA approved label for Faslodex), and the 25°C temperature corresponds to the administration temperature (ambient temperature). In addition, the specified solubility values on this Table 3 are mean values calculated from analysis of replicate samples from one or more trials. The individual values are shown in handwriting in the amended version of Table 3 in Attachment A. In addition, it appears that the mean values for the last three compositions have been incorrectly calculated. The corrected mean values, together with the correction of the temperature from "25°C" to read "4°C", are also shown in handwriting in the amended version of Table 3 in Attachment A.

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6. I have evaluated the transcription and other errors against the original application disclosures and conclude that these do not change the ultimate conclusions made from the data as originally reported. The addition of 15% w/v benzyl benzoate to compositions having total alcohol concentrations in castor oil of 10%, 15%, 20% and 30% w/v unexpectedly provides a positive effect on fulvestrant solubility, significantly increasing the solubility of fulvestrant in the compositions despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

7. An additional set of experiments has been conducted at 25°C under my guidance to obtain consistent data with reduced variability from a single set of rigorously controlled solubility experiments and to demonstrate that the unexpected increase of solubility of fulvestrant by adding benzyl benzoate into compositions containing ethanol, benzyl alcohol and castor oil, is present across the broader range of composition encompassed by the claims being presented with this Declaration. The solubility of fulvestrant in benzyl benzoate and in castor oil was also measured in the same set of experiments using the same batch of benzyl benzoate and the same batch of castor oil as were used to make up the compositions. The Experimental Test Procedure is described in Attachment B.

8. The results from these solubility experiments are shown in the table in Attachment C. These results show that the solubility of fulvestrant in castor oil alone (21.4 mg/ml) is significantly greater than the solubility of fulvestrant in benzyl benzoate alone (3.8 mg/ml) and demonstrate the unexpected increase in fulvestrant solubility on the addition of 10, 15 and 25% w/v benzyl benzoate, in place of an equivalent amount of castor oil, to compositions having total alcohol concentrations in castor oil of 10%, 15%, 20%, 25% and 30% w/v.

9. Thus, the results that were obtained from experiments conducted under rigorously controlled conditions and with an expanded range of compositions, as shown in Attachment C, confirm the ultimate conclusions drawn from the results shown in Table 3 of the original application disclosure, namely that the addition of 10% to 25% w/v benzyl

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benzoate to compositions having total alcohol concentrations in castor oil of between 10% to 30% w/v unexpectedly provides a positive effect on fulvestrant solubility, significantly increasing the solubility of fulvestrant in the compositions despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

10. During the course of my study of the Evans Application and the underlying source materials it was drawn to my attention that some of the composition data given for Delestrogen and Delalutin somehow had been shifted one column to the right. Thus, for Delestrogen, the 78% and 58% figures shown under the BzBz column should have been under the OIL column; the 20% and 40% figures shown under the BzOH column should have been under the BzBz column; and the 2% figures shown under EtOH should have been under the BzOH column. Similarly for Delalutin, the "up to 2%" shown under the EtOH column should have been under the BzOH column. This table reports that the source of this data was J.Pharm.Sci (1964) 53(8) 891, which is Riffkin (1964) elsewhere referred to in this Declaration, and I have also verified the corrected data from the entries for Delalutin and Delestrogen in PDR (1973). A copy of Table 1 from the Evans Application is reproduced as Attachment D, on which these corrections have been made in handwriting, and I have additionally more correctly noted that Delalutin is 17-hydroxy progesterone *caproate*, and that the "COMP" designation for Delalutin should be "BMS" (Bristol-Myers Squibb). Attachment D also includes a one page explanation of the corrections to this Table 1.

11. In about early 2000, a person responsible for developing a sustained release injectable formulation suitable for administration to humans for a new steroidal compound such as fulvestrant, would have had specialized training and experience in developing pharmaceutical formulations and methods for their administration. In developing such a formulation for fulvestrant, the objective would have been to formulate an intramuscular (IM) injection that would provide for the satisfactory sustained release of fulvestrant over a period of at least two weeks and preferably over a period of at least four weeks to reduce the frequency of administration, and would have a target fulvestrant content of at

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least 45 mg/mL so as to provide a fulvestrant dose of at least 250 mg in a single 5-6 mL injection. From my personal experience and knowledge of the literature at about that time, I believe that such an experienced formulator would likely have approached the task of developing a formulation for fulvestrant in about the following manner.

12. Given the foregoing objective, the experienced formulator would have appreciated that the traditional administration options to explore were intramuscular (IM) injection of a sustained release aqueous or oil suspension or an oil-based solution (depot) containing at least 250 mg of fulvestrant in a volume of vehicle that is tolerable for injection, *i.e.*, no more than 5 or 6 mL.

13. Because of the extremely low solubility of fulvestrant in water, a reasonable starting point would have been to investigate intramuscular injection of an aqueous or oil suspension of fulvestrant. However, the formulator would have found that injection of an aqueous suspension of fulvestrant resulted in extensive local tissue irritation at the injection site as well as a poor release profile, such as reported in paragraph [0042] of the Evans Application. Since suspensions thus were not an acceptable option for fulvestrant, the experienced formulator would have moved on to further explore whether 250 mg of fulvestrant could be solubilised in no more than 5-6 mL of an oil-based vehicle, *i.e.*, to achieve the target fulvestrant concentration of at least 45 mg/mL.

14. In the preformulation phase, the experienced formulator would have conducted a literature review or otherwise would have become familiar with commercially marketed injectable formulations, particularly injectable sustained release formulations of steroids or other relatively insoluble compounds such as those listed in Table 1 of the Evans Application, with the objective of identifying potential oil vehicles, co-solvents and other excipients that already had been found to be tolerated and/or to have passed through regulatory review, and which might be candidates for further consideration and testing for the fulvestrant formulation. This review also would have provided guidance with respect to concentration levels of such co-solvents and other excipients that generally had been found acceptable in sustained release oil-based intramuscular injections administered to

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humans. This objective is confirmed, for example, in Nema (1997) at page 166:

> Generally, a knowledge of which excipients have been deemed safe by the FDA or are already present in a marketed product provides increased assurance to the formulator that these excipients will probably be safe for their new drug product. ... Regulatory bodies may view an excipient previously approved in an injectable dosage form favorably, and will frequently require less safety data.

The purpose of this Nema paper was thus "to present the various excipients that have been included in the formulation of injectable products marketed in the USA."[1] Similar objectives were intended to be served by the compilations of commercial formulations in Strickley I (1999), Strickley II (2000) and Strickley III (2000):

> This compilation will also be useful for those interested in knowing what additives are currently used in injectable products and at what concentrations they are administered in practice. This compilation only focuses on marketed formulations and does not delve into the subject of preclinical or drug discovery formulations associated with early-stages pharmacokinetics or proof-of-concept pharmacodynamics, where the formulation scientist is not bound by regulatory constraints.

(Strickley I (1999) at 324).

Powell (1998) similarly states at page 238 with respect to its compilation of commercially used excipients:

> Thus, the formulation scientist is often faced with a dilemma -- which excipients are truly available for use (based on what has been used previously), and which are not? ... And at what concentrations, and by what route? ...
>
> Herein are listed the excipients found in most of the approved and marketed parenteral formulations, given systematically by excipient name. In this format it is easy to determine what concentrations were used, the route of administration, the main rationale for addition of that excipient, the drug that was formulated, the manufacturer, brand name, etc.

15. From the literature review, the formulator would have noted reference to a number of intramuscular injectable sustained release oil-based steroidal formulations that had been

[1] Nema (1997) does caution, however, that there is no guarantee that the new drug product will be safe as excipients are combined with other additives and/or with a new drug, creating unforeseen potentiation or synergistic toxic effects.

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commercially marketed:

- Strickley I (1999), Table VII:

  Haloperidol Decanoate/Haldol decanoate (50-100 mg/mL in sesame oil, benzyl alcohol 1.2%);

  Testosterone Enanthate/Delatestryl (200 mg/mL in sesame oil, chlorobutanol 5 mg/mL);

- PDR (1973) at pages 1277-1278

  Proluton/progesterone (50 mg/mL in sesame oil, 150 mg/ml benzyl benzoate, 5 mg/ml benzyl alcohol, 1 mg/ml propylparaben);

- PDR (1973) at pages 1349-1354

  Deladumone/Testosterone Enanthate & Estradiol Valerate (90 & 4 mg/mL in sesame oil, 0.5% chlorobutanol);

  Deladumone OB/Testosterone Enanthate & Estradiol Valerate (180 & 8 mg/mL in sesame oil, 2% benzyl alcohol);

  Delalutin/hydroxyprogesterone caproate (250 mg/mL in 52% castor oil, 46% benzyl benzoate, 2% benzyl alcohol);

  Delestrogen/estradiol valerate (20 mg/mL in 78% castor oil, 20% benzyl benzoate, 2% benzyl alcohol and 40 mg/mL in 58% castor oil, 40% benzyl benzoate, 2% benzyl alcohol);

  Delatestryl/Testosterone Enanthate (200 mg/mL in sesame oil, 0.5% chlorobutanol);

  Delaluteval 2X/hydroxyprogesterone caproate & estradiol valerate (250 mg/mL & 5 mg/mL in castor oil, 45% benzyl benzoate, 1.6% benzyl alcohol);

- PDR (1973) at pages 1391-1392

  Prolixin Enanthate/FluphenazineEnanthate (25 mg/mL in sesame oil, 1.5% benzyl alcohol);

- Wang (1980):

  Depo-Testosterone/testosterone cypionate (100 mg/mL in 87.4% cottonseed oil, 0.1 mL benzyl benzoate, 9.45 mg benzyl alcohol as a preservative);

- Mackey (1995):

  Testoviron Depot/testosterone enanthate (250 mg/mL in castor oil and benzyl

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benzoate);

as well as a number of other commercialized oil based long-acting IM injectable formulations reported on Table 1 of the Evans Application.

16. As a further part of the preformulation phase, the experienced formulator would have conducted a preformulation solubility screen, separately measuring the solubility of fulvestrant in a range of pure solvents, including the potential oil and co-solvent candidates that had been identified in the above literature review as being suitable for inclusion in intramuscular injection formulations. See, for example, Gupta (1999), Chapter 17 at page 402, under the heading "Formulation Development":

> The activities necessary to develop a parenteral product can be placed into the following three broad areas: preformulation, formulation, and scale-up. While there are alternative development perspectives, all development ultimately needs to accomplish the same activities. Preformulation includes the characteristics of the bulk drug plus initial screening for excipient compatibility with the drug.

"Preformulation studies" are said to "provide fundamental data and experience necessary to develop formulations for a specific compound" including, as item 8.1 in the outline of areas of specific interest, a determination of "solubility" in "selected solvents" (at 403). "Significant formulation activities begin with initial preformulation data and knowledge of the specific route of administration" (at 405), which "formulation activities include the identification and selection of a suitable vehicle (aqueous, nonaqueous or co-solvent system) ..." (at 404). It is further noted that "injection volume is one of the most important considerations in the formulation development of a commercial product" (at 405). When carrying out such a preformulation solubility screen with fulvestrant, the formulator would have found that fulvestrant had extremely low solubility in water, low solubility in most oils (but highest in castor oil), low solubility in benzyl benzoate, and the highest solubility in ethanol and benzyl alcohol, such as reported in Table 2 of the Evans Application.

17. With the information on prior commercialized formulations and the fulvestrant solubility data from the preformulation screen (such as reported in Table 2 of the Evans

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Application), the experienced formulator would have selected castor oil as the oil vehicle because of the higher solubility of fulvestrant in castor oil relative to the other oils tested. Nevertheless, he would have appreciated that the target fulvestrant concentration of at least 45 mg/mL could not be achieved with castor oil alone, and that a co-solvent would be required.

18. A number of the commercialized formulations that would have been identified in the literature review (including the castor oil-based formulations) have a substantial benzyl benzoate component, which may be present as a co-solvent. See, for example, Delalutin noted in paragraph 15 above, which is reported in PDR (1973) and noted in Table I of the Evans Application, and is one of the formulations discussed in Riffkin (1964), "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones" (see Riffkin n. 6). Delalutin is 250 mg/mL 17-hydroxyprogesterone caproate dissolved in 52% castor oil, 46% benzyl benzoate and 2% benzyl alcohol. However, Riffkin Table II reports that the solubility of 17-hydoxyprogesterone caproate in castor oil alone is only 55.6 mg/mL, but the solutility of 17-hydroxyprogesterone caproate in benzyl benzoate is substantially higher, being at least 250 mg/mL (see example 4 of Huber (US '520) and Attachment E discussed below). Even if not needed as a cosolvent, Riffkin (1964) notes that "the addition of benzyl alcohol or benzyl benzoate to castor oil resulted in a lower and more favorable viscosity, making it easier to inject" (paragraph bridging pages 893-894).

19. However, the skilled formulator would have appreciated from the fulvestrant solubility data generated in the preformulation screen that fulvestrant had very different solubility characteristics relative to the steroids of previous commercial formulations. Attachment E is a compilation showing the chemical structures and relative solubilities in castor oil and sesame oil of the compounds named in Riffkin (1964) Table II compared to the structure and the solubility of fulvestrant in these oils. It can be seen that the solubility of fulvestrant in castor oil and in sesame oil (20 mg/mL and 0.58 mg/mL, respectively, from Table 2 of the Evans Application) is appreciably lower than the solubility of the other steroids in these oils (taken from Table II of Riffkin (1964)). The second page of Attachment E tabulates the concentration in benzyl benzoate of five named steroids, taken

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from Examples 1-5 of Huber (US '520), ranging from 200 to 400 mg/ml.[2] By comparison, the solubility of fulvestrant in benzyl benzoate is reported in Table 2 of the Evans Application as being only 6.15 mg/mL, and only 3.8 mg/mL as determined in the recently conducted tests reported in Attachment C.

20. The experienced formulator thus would have expected that benzyl benzoate would *not* act as a co-solvent for fulvestrant in castor oil because the solubility of fulvestrant in benzyl benzoate was significantly lower than its solubility in castor oil. The addition of benzyl benzoate to castor oil, for whatever reason, would have been expected to *decrease, rather than increase*, the solubility of fulvestrant in the resulting castor oil/benzyl benzoate mixture. This is confirmed in Table 4 of the Evans Application, which reports a fulvestrant solubility of only 12.6 mg/mL in the castor oil vehicle containing only 15% benzyl benzoate, compared to the 20 mg/mL solubility of fulvestrant in castor oil alone as reported in Table 2.[3]

21. Based on the solubility data determined in the preformulation screen (such as reported in Table 2 of the Evans Application), ethanol and/or benzyl alcohol would have been seen as the best co-solvent candidates for raising the fulvestrant solubility to the 45 mg/mL target in the castor oil vehicle, and would also function to lower the viscosity of the resulting formulation and make it easier to inject. Consistent with this solubility data, Dukes (US '814) added 40% w/v benzyl *alcohol* in order to dissolve 50 mg/mL fulvestrant in the castor oil-based formulation used in the experimental rat studies of his Example 3. It thus would have been apparent that 40% w/v benzyl alcohol could function as a co-solvent in castor oil to achieve the target fulvestrant concentration. Nevertheless, the skilled formulator would have been concerned with using such a high alcohol content in intramuscular injectable formulations for administration to a human.

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[2] Data taken from the Examples of Huber (US '520); these are concentrations used in the examples and not necessarily the actual maximum solubility of each steroid in benzyl benzoate, which may be higher. Huber was a co-author on Riffkin (1964).

[3] It should be noted that in the further tests that were recently conducted under my guidance (paragraphs 7-9 above and Attachments B and C hereto), the solubility of fulvestrant in castor oil alone was again tested and found to be 21.4 mg/mL, and the solubility of fulvestrant in benzyl benzoate alone was again tested and found to be only 3.8 mg/mL, which further confirms that benzyl benzoate would not be expected to act as a cosolvent for fulvestrant in castor oil.

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22. First of all, the experienced formulator would want to minimize the amount of co-solvents and excipients in any injectable formulation. For example, as stated in Gupta (1999), Chapter 17, "Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parental Products" at page 414:

> Cosolvents are commonly used to enhance drug solubility and stability. Cosolvents may include ethanol, propylene glycol, polyethylene glycols, and glycerine. These components have intrinsic effects on biologic tissue and can alter the properties of other excipients, thus influencing the tissue damage or pain caused by a product. There is a dearth of literature on the pain caused by cosolvents, but there is also a growing body of knowledge on the tissue damage that they can cause. It is not certain that tissue damage is always directly correlated with the injection pain, but minimization of both pain on injection and potential for tissue damage should be included in the product development plan.

See also Gupta (1999), Chapter 11, titled Cosolvent Use in Injectable Formulations, page 217:

> Ideally, it is best to select and use solvents that would maximize the solubility of the compound. Maximizing the solubility of a compound in a particular cosolvent system would result in lower total levels of the non-aqueous solvent(s) being administered to the patient, thereby lowering the chance for potential side effects.

This objective would have applied to aqueous and oil-based systems alike, in that the precedent of commercialized formulations identified in the literature review would have confirmed that fixed oils, such as castor oil, have long been commercially used and accepted as the major component of oil-based sustained release intramuscular injectable steroidal formulations. On the other hand, co-solvents such as ethanol or benzyl alcohol have generally been used only in far lesser concentrations, as discussed in the following paragraph.

23. Thus, use of such a high content of either benzyl alcohol or ethanol would have been contrary to precedent as shown from the review of commercialized oil-based intramuscular injectable sustained release formulations. The literature review as of early 2000 would have shown that any benzyl alcohol in such formulations was almost always

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present as a preservative in a concentration of about 2% or less, occasionally at a concentration of up to 5%, but only rarely at higher concentrations. With respect to benzyl alcohol see, for example:

- Gupta (1999), Chapter 11 at page 229 stating that benzyl alcohol "is typically used in concentrations of up to 2 percent as a preservative and up to 5 present as a solvent," and then discussing reported toxicities.
- Nema (1997), Table V at page 168, reporting that benzyl alcohol was present as an antimicrobial preservative in 74 injectable formulations (not limited to oil-based IM formulations) at concentrations of from 0.75-5% (note that benzyl alcohol is not included at all in Nema Table I, "Solvents and Co-solvents";
- Powell (1998), the benzyl alcohol listing at pages 244-246, particularly those indicated as being used in IM formulations;
- Strickley I (1999) at page 329 notes the inclusion of 2% benzyl alcohol in an IM lorazapam formulation in a propylene glycol vehicle, but does not include benzyl alcohol at all in Table VI listing "Cosolvents Used in Parenteral Formulations;"
- Lopatin (1972) noting in Table 3 at page 727 opposite Benzyl alcohol, "Toxic. Used in concentration of not over 3%. Has irritant action in concentration of 5%;"
- Cornelius (US '863), col. 1, lines 30-35 stating, "It is known that the solubility of steroids in vegetable or animal oils can be increased by the addition of excipients such as benzyl alcohol and benzyl benzoate. An objection to the use of such excipients, and specifically benzyl alcohol in somewhat higher concentrations, is that these agents may irritate the tissues."

The literature review as of early 2000 also would have shown that, with few exceptions, ethanol was not included in such formulations in excess of about 10%. See, for example:

- Gupta (1999), Chapter 11 at page 225 noting that ethanol has been used at levels up to 50 percent, but these levels typically are associated with pain on injection;
- Strickley I (1999), Table VI, "List of Cosolvents Used in Parenteral Formulations" more specifically lists the ethanol content in IM formulations for specifically identified drugs, which concentrations range only from 2.5 to 10%; an IM/IV lorazapam formulation in a propylene glycol vehicle is noted at page 329 as having 18% alcohol, but is not included with the IM formulations in Table VI;

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- Nema (1997), Table I, "Solvents and Co-solvents" at page 167, lists ethanol as being in 24 formulations with a concentration range of 0.6-80% (for Prograf); note that this is misleading, however, since Prograf is a *concentrate* for intravenous infusion only, and is to be diluted 250 to 1000 times before administration;
- Powell (1998), lists "alcohol" at page 242 and "ethyl alcohol" at page 255, wherein the ethanol concentration for IM formulations ranges from 0.61-10%.

24. Thus, even though Dukes (US '814) had demonstrated that the target 45 mg/mL fulvestrant concentration could be achieved by adding 40% benzyl alcohol to the castor oil vehicle, the precedent of commercialized IM oil-based systems would have motivated the experienced formulator to substantially reduce the benzyl alcohol content of the formulation intended for human use, and this commercial precedent would have made him very reluctant to replace benzyl alcohol with the substantial amount of ethanol that would be needed to maintain the target fulvestrant concentration. Benzyl benzoate clearly would not be considered to solve this dilemma, but rather would be expected to have a negative effect on fulvestrant solubility since fulvestrant was even less soluble in benzyl benzoate than in castor oil, that is, one would have expected that adding benzyl benzoate would require still *more* alcohol to maintain the target fulvestrant concentration.[4]

25. Under these circumstances, the discovery by Evans *et al.*, that the addition of benzyl benzoate to the castor oil/alcohol mixture actually increases the solubility of fulvestrant such that more fulvestrant could be dissolved in a given volume of formulation, was unexpected and truly surprising. This positive benzyl benzoate effect on fulvestrant solubility in the resulting formulation is shown in Table 3 of the specification (and is not changed by the above-noted corrections), and is confirmed and demonstrated over a broader range of formulation composition by the additional set of experiments conducted under my guidance and discussed in paragraphs 7-9 above, the results of which are reported in Attachments C.

[4] It should be noted that even apart from this solubility issue, there would have been no motivation to add benzyl benzoate for viscosity reduction since the significant quantity of alcohol would serve the dual function of acting as a co-solvent as well as reducing the injection viscosity and making it easier to inject, whereas the benzyl benzoate would be expected to have a negative effect on the fulvestrant solubility.

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The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punished by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

Signature: P. R. Mullick.

Date: 8th August 2008.

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TABLE OF REFERENCES

Tab	Author/Inventor	Reference Citation/Patent
1	Cornelius (US '863)	US Patent 4,212,863
2	Dukes (EP '014)	EP 0 346 014 A1 (corresponds to US Patent 5,183,814)
3	Dukes (US '814)	US Patent 5,183,814 (corresponds to EP 0 346 013 A1)
4	Gupta (1999)	P.K. Gupta and G.A. Brazeau (eds). *Injectable Drug Development:Techniques to Reduce Pain and Irritation.* Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999)
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6	Lopatin (1972)	P.V. Lopatin, V. P. Safonov, T. P. Litvinova and L. M. Yakimenko. Use of nonaqueous solvents to prepare injection solutions. *Pharm. Chem. J.* ***6***:724-733 (1972)
7	Mackey (1995)	M.A. Mackey, A.J. Conway and D.J. Handelsman. Tolerability of intramuscular injections of testosterone ester in oil vehicle. *Hum. Reprod.* **10**: 862-865 (1995)
8	Nema (1997)	S. Nema, R.J. Washkuhn, and R.J. Brendel. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* **51**:166-71 (1997)
9	PDR (1973)	*Physicians' Desk Reference (27th edition).* 1277-1278, 1350-1354, 1391-1392 Medical Economics Company, Oradell, NJ (1973)
10	Powell (1998)	M. F. Powell, T. Nguyen, and L. Baloian. Compendium of excipients for parenteral formulations. *PDA J. Pharm. Sci. Technol.* **52**:238–311 (1998)
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ATTACHMENT A

TABLE 3

EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT ~~25°C~~ 4°C.

		% w/v							
	Ethanol (96%)	5	5	10	10	10	10	15	15
	Benzyl Alcohol	5	5	5	5	10	10	15	15
	Benzyl Benzoate		15		15		15		15
	Castor Oil	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100
Mean	Fulvestrant Solubility [mgml^{-1}]	27	36	46	54	45	~~68~~ 64	~~78~~ 77	~~102~~ 103
	Individual values [mgml^{-1}]	27.8	35.5	54.0	64.1	48.4	62.9	65.8	80.6
		25.8	36.1	38.6	47.3	41.7	60.8	76.9	101.9
					53.0		63.2	90.0	121.6
					50.3		72.9	73.4	107.4

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ATTACHMENT B:

Experimental Test Procedure for measuring the solubility of fulvestrant in different solvent vehicles at 25°C

1. Solvent vehicles for the solubility experiments were prepared by weighing the required amount of benzyl benzoate, benzyl alcohol and ethanol into a 20 ml volumetric flask and then diluting to volume with castor oil.
2. For each solvent vehicle in which the solubility of fulvestrant was to be determined, 1.0-1.5g of fulvestrant was weighed into each of 3 separate vials (2 dram size) and 5mls of the solvent vehicle was added to each vial, except for the pure castor oil vehicle, where 80mg of fulvestrant were weighed into each of the 3 separate vials and 2mls of the castor oil added to each vial. The reduced amount of fulvestrant and lower volume of solvent vehicle was needed to maintain stirring and achieve adequate mixing with the pure castor oil vehicle due to the combination of its higher viscosity and lower fulvestrant solubility/higher undissolved fulvestrant levels compared to the other solvent vehicles.
3. A magnetic stirrer bar was placed into each vial and the vials were capped and then placed on a magnetic stirrer block maintained at 25 ± 0.5°C.
4. After 5 days of stirring at 25 ± 0.5°C, an aliquot of each fulvestrant/solvent vehicle mixture was removed from each vial and placed into an Eppendorf tube which was then centrifuged at 12000 rpm for 5 minutes at ambient temperature.
5. For all but the fulvestrant/castor oil mixture, 1 ml of the supernatant was then removed from the Eppendorf tube and pipetted into a 10ml or 20ml volumetric flask and then diluted to volume with methanol and mixed to give a sample for analysis. The choice of whether to use a 10ml or 20ml volumetric flask for a particular sample was dependent on the likely concentration of fulvestrant in the sample and the quantifiable concentration range of the HPLC assay method used. For the fulvestrant/castor oil mixture, 100µl of the supernatant was removed from the Eppendorf tube and pipetted into a 1ml volumetric flask and then diluted to volume with methanol and mixed to give a sample for analysis.
6. Step 5 was repeated to give a duplicate sample for analysis. Thus, this gave 2 samples for each of the 3 vials, giving a total of 6 samples for analysis for each solvent vehicle tested.
7. The resultant samples were analysed for fulvestrant content by reverse phase High

InnoPharma Exhibit 1046.0198

Performance Liquid Chromatography (HPLC). The HPLC method that was used is described below at point 9. The fulvestrant content obtained for each sample was used to calculate a value for the concentration of fulvestrant dissolved in the corresponding solvent vehicle after stirring for 5 days at 25°C.

8. The mean solubility of fulvestrant for each different solvent vehicle tested was calculated as the arithmetic mean of the 6 individual values for the concentration of fulvestrant dissolved in the corresponding solvent vehicle.
9. HPLC Method details:

Gradient HPLC Method

Eluent A : 27% Methanol / 32% Acetonitrile / 41% Water

Eluent B : 41% Methanol / 49% Acetonitrile / 10% Water

Column : 15cm 3.5um Symmetry C8 4.6mm i.d.

Detection wavelength : 225 nm

Flow rate : 2 mL min-1

Temperature : 40°C

Injection volume : 10 µL

Gradient programme :

Time (min)	Eluent A (%)	Eluent B (%)
0	100	0
25	100	0
55	0	100
65	0	100
66	100	0
70	100	0

Retention time of fulvestrant: 21minutes approximately

InnoPharma Exhibit 1046.0199

ATTACHMENT C: EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25°C

	% w/v																					
Ethanol (96%)	0	0	5	5	5	5	10	10	10	10	10	10	10	10	12.5	12.5	12.5	12.5	15	15	15	15
Benzyl Alcohol	0	0	5	5	5	5	5	5	5	5	10	10	10	10	12.5	12.5	12.5	12.5	15	15	15	15
Benzyl Benzoate	0	100		10	15	25		10	15	25		10	15	25		10	15	25		10	15	25
Castor oil	100	0	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100
Mean Fulvestrant solubility [mgml^{-1}]	**21.4**	**3.8**	**27.6**	**29.2**	**43.3**	**47.5**	**64.6**	**71.6**	**84.2**	**94.0**	**68.1**	**87.2**	**93.4**	**118.9**	**96.6**	**107.7**	**116.1**	**139.6**	**121.3**	**144.6**	**143.8**	**166.2**
Individual values [mgml^{-1}]	23.2	3.9	29.5	31.2	43.9	48.3	64.2	76.2	83.8	95.2	68.6	90.0	92.5	122.1	104.1	106.1	115.5	138.9	110.0	129.8	148.2	163.3
	17.8	4.0	28.3	26.3	45.1	50.7	66.8	72.1	81.9	97.8	68.9	84.9	92.1	120.3	74.0	86.6	117.9	141.0	120.0	133.5	147.1	164.8
	21.5	3.9	24.5	31.5	44.3	45.4	61.2	66.2	93.2	95.6	71.6	87.6	93.9	120.4	102.0	112.6	118.8	139.4	124.4	150.1	144.4	168.5
	21.8	3.8	26.6	29.3	45.4	45.2	66.0	65.7	84.6	96.1	67.6	88.1	93.0	118.3	98.6	117.9	116.1	142.1	125.6	151.7	144.4	169.7
	22.2	4.0	27.0	29.1	36.9	47.6	65.8	75.4	82.4	88.2	67.0	90.7	93.8	116.8	102.1	107.9	117.0	138.7	123.3	151.2	139.5	165.5
	22.0	3.2	29.6	27.8	44.3	47.6	63.6	73.9	79.1	91.0	64.8	82.1	95.3	115.7	98.4	115.1	111.5	137.9	124.6	151.1	139.1	165.5

InnoPharma Exhibit 1046.0200

ATTACHMENT D

TABLE I

OIL BASED LONG-ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMP'.	SOURCE	OIL	BnBz	BnOH	EtOH	DOSE	DOSING
SUSTANON 100	Testosterone propionate	30 mg	Androgen	Organon	AHPI Data Sheet Comp. 1999	Arachis		0.1 ml		1 ml	3 weeks
	Testosterone phenyl-propionate	60 mg									
	Testosterone isocaproate	40 mg									
	Testosterone decanoate	100 mg									
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250 mg/ml	Progestogen	Schering BC	AHPI Data Sheet Comp. 1999	Castor	up to 40%			2 or 2 ml	1 week
TOCOGESTAN	Hydroxy progesterone enanthate	200 mg	Progestogen	Theramex	Dict. Vidal 1999	Ethyl oleate	40%			2 ml	<1 week
	Progesterone or Tocopherol	50 mg 250 mg									
TROPICDIOLONE	Estroprogestate	2.5 mg	Mixed	Theramex	Dict. Vidal 1997	Olive	45%			1 ml	15 to 30 days
	Nandrolone undecanoate	50 mg									
	Hydroxy-progesterone heptanoate	80 mg									
NORISTERAT	Norethisterone enanthate	200 mg	Contra-ceptive	Schering BC	AHPI Data Sheet Comp. 1999	Castor	YES			1 ml	8 weeks
BENZO-GYNOESTRYL	Estradiol benzhydro-benzoate	5 mg	Estradiol	Roussel	Dict. Vidal 1999	Arachis				1 ml	1 week
PROGESTERONE-RETARD	Hydroxy progesterone caproate	250 mg/ml	Progestogen	Fournier	Dict. Vidal 1999	Castor	YES			1 or 2 ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate	5 mg/ml	Mixed	Schering	Dict. Vidal	Castor	YES			1 or	1-2
	Hydroxy-progesterone caproate	250 mg/ml		BC	1995					2 ml	weeks
PARABOLAN	Trenbolone	76 mg	Androgen	Negma	Dict. Vidal 1997	Arachis		75 mg	45 mg	2.5 ml	2 weeks
DELESTROGEN	Estradiol valerate	20 mg/ml 40 mg/ml	Estradiol	BMS	J Pharm. Sci (1964) 53(8) 891	Castor	20% 10% 5%	20% 10% 5%	5% 2% 2%		
OELALUTIN	17-Hydroxy progesterone caproate	250 mg/ml	Progestogen	~~Duphar~~ BMS	J Pharm. Sci.(1964) 53(8) 891	Castor	YES	YES up to 2%	~~5%~~ 2%		

Bnlz = benzylbenzoate
BnOH = benzylalcohol
EtOH = ethanol. Dict.
Vidal = Dictionnaire Vidal % are w/v and
*approximate as measured directly from a single sample

InnoPharma Exhibit 1046.0202

Corrections to Table 1

In Table 1, the given values for the benzyl benzoate, benzyl alcohol and ethanol levels for the Delestrogen and Delalutin products have been incorrectly entered into the wrong columns. The entries are shown in their correct form in the attached corrected version of Table 1. The error is apparent from a review of the reference J.Pharm Sci (1964) 53 (8) 891 (Riffkin) which is stated in Table 1 as being the Source of the information for the Delestrogen and Delalutin products:

- In the Summary on page 895 of Riffkin, Delestrogen and Delalutin are identified as castor oil based commercially available products containing estradiol valerate at 20 & 40 mg/ml and 17-hydroxy-progesterone caproate at 250 mg/ml respectively.
- Furthermore, details of particular vehicle compositions for estradiol valerate and 17-hydroxy-progesterone caproate are given in Tables V and VI
    - In Table VI, the only 20 mg/ml formulation of estradiol valerate, also referred to as commercially available, has the composition castor oil 78%, benzyl benzoate 20% and benzyl alcohol 2%.
    - In Table VI, the only 40 mg/ml castor oil based formulation of estradiol valerate, has the composition castor oil 58%, benzyl benzoate 40% and benzyl alcohol 2%.
    - In Table V, there are three 250/mg/ml castor oil based formulations of 17-hydroxy-progesterone caproate that all contain benzyl benzoate. Two of these formulations also contain 2% benzyl alcohol and the other formulation does not contain benzyl alcohol ie they all contain up to 2% benzyl alcohol.

- None of the vehicle compositions disclosed in Tables V and VI in Riffkin contain ethanol. Therefore the entries in the Ethanol column of Table 1 for the Delestrogen and Delalutin products must have been incorrectly entered in the wrong column and should have been entered into the Benzyl Alcohol column.
- It is also apparent from Table VI that the 78% and 58% entries in the Benzyl Benzoate column of Table 1 for the Delestrogen products should have been entered into the Oil column and the 20% and 40% entries in the Benzyl Alcohol column should have been entered into the Benzyl Benzoate column
- The exact compositions for the Delestrogen and Delalutin products are confirmed in the Physicians Desk Reference (Edition 27, 1973) on page 1352.

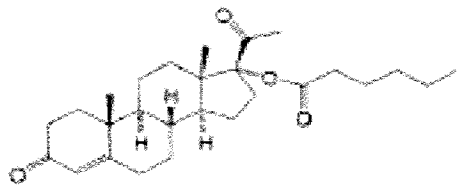
In addition, the name of the steroid given in Table 1 for the Delalutin product should have been 17-hydroxy-progesterone caproate and not just 17-hydroxy-progesterone. Also the entry under the Company column for the same product should read BMS rather than DMS.

InnoPharma Exhibit 1046.0203

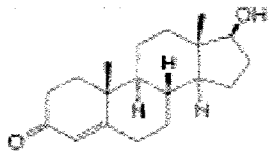
ATTACHMENT E

Structure of compounds disclosed in Riffkin et al.

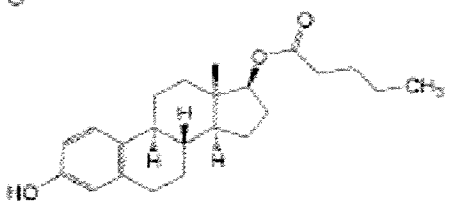
17-Hydroxyprogesterone caproate:



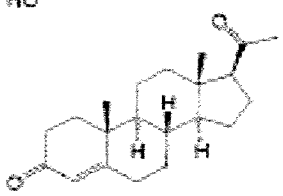
Testosterone:



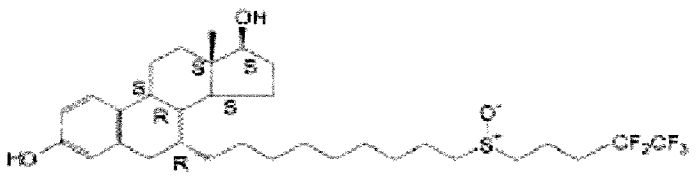
Estradiol valerate:



Progesterone:



On the other hand, fulvestrant has the following structure:



From Riffkin et al. Table II:

Steroid	Solubility [mg/ml] at 25°C	
	Castor oil	Sesame oil
Fulvestrant	20	0.58
17-Hydroxyprogesterone caproate	55.5	23.4
Testosterone	38.6	5.4
Estradiol valerate	60.6	16.1
Progesterone	52.0	22.9

InnoPharma Exhibit 1046.0204

Tabulation of data from Examples of Huber, 3,164,520:

Example	Steroid	Steroid concentration in benzyl benzoate (mg/ml)
1	16,17-dihydroxyprogesterone	200
2	testosterone palmitate	200
3	progesterone	250
4	Progesterone + 17-hydroxyprogesterone caproate	250 + 250
5	Testosterone enanthate	400

InnoPharma Exhibit 1046.0205

ATTACHMENT F

TABLE OF REFERENCES

Tab	Author/Inventor	Reference Citation/Patent
1	Cornelius (US '863)	US Patent 4,212,863
2	Dukes (EP '014)	EP 0 346 014 A1 (corresponds to US Patent 5,183,814)
3	Dukes (US '814)	US Patent 5,183,814 (corresponds to EP 0 346 013 A1)
4	Gupta (1999)	P.K. Gupta and G.A. Brazeau (eds). *Injectable Drug Development:Techniques to Reduce Pain and Irritation.* Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999)
5	Huber (US '520)	US Patent 3,164,520
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8	Nema (1997)	S. Nema, R.J. Washkuhn, and R.J. Brendel. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* **51**:166-71 (1997)
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11	Riffkin (1964)	C. Riffkin, R. Huber and C.H. Keysser. Castor oil as a vehicle for parenteral adminstation of steroid hormones. *J.Pharm.Sci.* **53**: 891-5 (1964)
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14	Strickley III (2000)	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part III. *PDA J. Pharm. Sci. Technol.* **54**:152–169 (2000)
15	Wang (1980)	Y.C. J. Wang and R. R. Kowal. Review of excipients and pH's for parenteral products used in the United States. *J. Parenteral Drug Assoc.* **34**:452–462 (1980).

ATTACHMENT F

ATTACHMENT F - COMPILATION

TAB 1

United States Patent [19]

Cornelius

[11] **4,212,863**

[45] **Jul. 15, 1980**

[54] **HIGHLY CONCENTRATED PHARMACEUTICAL FORMULATIONS OF STEROIDS AND PROCESSES FOR THEIR PREPARATION**

[75] Inventor: **Lammert Cornelius**, Boxmeer, Netherlands

[73] Assignee: **Akzo N.V.**, Arnhem, Netherlands

[21] Appl. No.: **953,877**

[22] Filed: **Oct. 23, 1978**

[30] **Foreign Application Priority Data**

Oct. 29, 1977 [NL] Netherlands 7711916

[51] **Int. Cl.**[2] **A61K 31/56**

[52] **U.S. Cl.** **424/240**

[58] **Field of Search** 424/240, 284

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,791,609	5/1957	Kaplan	424/240
3,025,311	3/1962	Gutsell, Jr. et al.	424/240
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Chemical Abstracts, vol. 82, No. 4 (1975) Paragraph 21, 826(g).

Primary Examiner—Elbert L. Roberts
Attorney, Agent, or Firm—Stevens, Davis, Miller & Mosher

[57] **ABSTRACT**

The invention relates to highly concentrated liquid pharmaceutical formulations of steroids of the oestrane, androstane and (19-nor-)pregnane series comprising tocol or a derivative thereof that is fluid at normal temperature, or mixtures thereof, in an amount of at least 10% by weight of the formulation, and optionally one or more of the usual fluid carriers, such as vegetable oil, benzyl benzoate and/or benzyl alcohol.

10 Claims, No Drawings

InnoPharma Exhibit 1046.0208

HIGHLY CONCENTRATED PHARMACEUTICAL FORMULATIONS OF STEROIDS AND PROCESSES FOR THEIR PREPARATION

The invention relates to highly concentrated pharmaceutical formulations of steroids of the oestrane, androstane and (19-nor-)pregnane series, the said formulations being fluid at normal temperature, and to processes for their preparation.

Injection preparations of steroids are known. Such preparations usually consist of solutions of the steroids in oily carriers, such as arachis oil, sesame oil, olive oil and similar carriers, to which yet other excipients may, if desired, be added, such as benzyl alcohol and benzyl benzoate. Such fluid preparations may be injected almost without damage to tissues, and absorption of the active substance by the organism takes place from the subcutaneous or intramuscular depot thus obtained. The extent and the duration of the absorption depends on various factors including the dosage and concentration of the steroid and the physical properties of the steroid, such as lipophilicity. The upper limit of the concentration is naturally governed by the solubility of the steroid in the carrier. If this solubility is not very great, achievement of the desired effect will necessitate repeating injections at shorter intervals or injecting larger volumes, and there are of course objections to both of these procedures.

It is known that the solubility of steroids in vegetable or animal oils can be increased by the addition of excipients such as benzyl alcohol and benzyl benzoate. An objection to the use of such excipients, and specifically benzyl alcohol in somewhat higher concentration, is that these agents may irritate the tissues.

Other ways of administration to give higher concentrations in the subcutaneous or intramuscular depot are the injection of crystal suspensions or the implantation of solid formulations. The preparation of stable crystal suspensions may give rise to problems, while the surgical intervention, though minor, constitutes an objection to the implantation.

When the preparation and use of a highly concentrated long-acting injection preparation of steroids is therefore desired, for example an injection preparation for the inhibition of ovulation in animals or man, one or more of the above-noted objections will be valid to a greater or lesser extent.

The administration of steroids in solution, for example a solution in oil, by the oral route is also known; see for example the Dutch Patent Application No. 7402689.(=British Pat. No. 1,500,374).

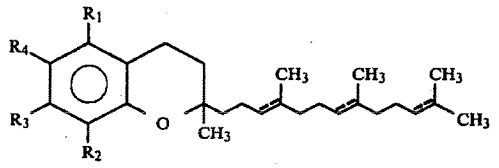
The administration of fluid pharmaceutical preparations by the oral route may be realized in various ways. The prescribed quantity, for example a number of drops or ml, may be taken per spoon, on a sugar lump or together with food. The solution may also be taken "sealed" in a soft gelatine capsule or in microcapsules.

With the oral administration of certain steroids in solution, for example testosterone and esters thereof, the problem may also arise that the solubility (and therefore the amount of active agent per dosage unit) in the known solvents is relatively low, so that either more or larger dosage units must be administered on each occasion or the administration of the preparation must be repeated at shorter intervals. There are objections to both procedures. In such cases there is an obvious need for solutions with greater concentrations.

It has now surprisingly been found that highly concentrated formulations of steroids, said formulations being fluid at normal temperature, and said steroids being of the oestrane, androstane and (19-nor-)pregnane series, may be prepared by dissolving the steroids in tocol or in a derivative thereof which is liquid at normal temperature (15°–30° C.), or in a mixture of two or more of these derivatives whereby the quantity of tocol or derivative thereof in the formulation is at least 10% by weight.

Hence, the invention relates to the highly concentrated steroid formulations thus obtained, and to the processes for their preparation.

Tocol and the derivatives liquid at normal temperature may be represented by the general formula:



where

R_1=H, CH_3 or C_2H_5;

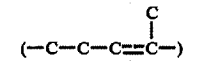
R_2=H, CH_3 or C_2H_5;

R_3=H, CH_3 or C_2H_5;

R_4=H, OH, O-acyl (1–2 atoms) or O-alkyl (1–2 C-atoms); and

the dotted lines denote the optional presence of a carbon-carbon double bond.

The compounds in which the side-chain in the formula given above contain one or two isoprene residues



less than indicated are also included amongst the tocol derivatives noted above.

For tocol itself, R_1=R_2=R_3=H, R_4=OH and the side-chain is saturated. Examples of tocol derivatives are: 5-methyltocol, 7-methyltocol, 8-methyltocol, 5,7-dimethyltocol, 5,8-dimethyltocol, 7,8-dimethyltocol, 5,7,8-trimethyltocol, 8-methyltocotrienol, 7,8-dimethyltocotrienol, 5,8-dimethyltocotrienol, 5,7,8-trimethyltocotrienol, 5,7-di-ethyltocol, 5,7-dimethyl-8-ethyltocol, 5,7-di-ethyl-8-methyltocol, the formates and acetates, as well as the methyl and ethyl esters of these compounds, and 6-desoxytocol. Use is preferably made of tocol, 5,7,8-trimethyltocol(α-tocopherol) or 8-methyltocol(δ-tocopherol). In practice use is generally made of the racemates dl-tocol, dl-α-tocopherol and dl-δ-tocopherol.

During the preparation of a formulation according to the invention, excipients such as benzyl alcohol or benzyl benzoate may optionally also be used, or a quantity of an oily carrier such as arachis oil or sesame oil may be added. Such a use or addition may be desirable in the preparation of injection formulations in order to lower the viscosity and in this way make the preparation easier to inject; in other words, to enable the formulation to be injected through a needle of the desired bore.

The amount of tocol or derivative thereof in the preparation is preferably at least 25% w/w, which means that at least 100 mg and preferably 250 mg tocol

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or derivative thereof is present in a milliliter (about 1000 mg) of solution. The upper limit of the quantity of tocol or derivative thereof is of course determined by the amount of steroid which can be dissolved in the carrier, and depends to some extent on both the steroid and the carrier; it lies between 50 and 90% w/w and is generally between 60 and 80% w/w. This means that the maximum amount of steroid per ml solution (about 1000 mg), again depending on the steroid and the carrier, will be between 100 and 500 mg and generally may be 200–400 mg.

The process offers particular advantages for steroids of the oestrane, androstane and (19-nor-) pregnane series containing at least a 3-oxo-Δ^4-group and an optionally esterified hydroxy group at position 17 and/or 21 (if present), since with these steroids much higher concentrations can be achieved than is possible with the known solvents and concentrations of 100 to 400 mg in the absolute sense are furthermore possible; for certain steroids with the characteristics noted, even concentrations up to 500 mg per ml tocol or derivative thereof are possible.

Examples of oestrane, androstane and (19-nor-) pregnane compounds with at least a 3-oxo-Δ^4-group and an optionally esterified hydroxy group at position 17 and/or 21 (when present) are: testosterone, 19-nor-testosterone (nandrolone), progesterone, 19-nor-progesterone, 17α-hydroxyprogesterone, 17α-hydroxy-19-nor-progesterone, 21-hydroxy-progesterone, 21-hydroxy-19-nor-progesterone, 16α-ethyl-21-hydroxy-progesterone, 16α-ethyl-21-hydroxy-19-nor-progesterone, 16-methylene-17α-hydroxy-progesterone, corticosterone, desoxycorticosterone, cortisone, hydrocortisone, prednisolone, aldosterone and the 17 and/or 21 esters of these steroids derived from organic mono- or di-carboxylic acids with 1 or 2, respectively, to 18 carbon atoms.

Examples of such organic mono- and di- carboxylic acids are aliphatic carboxylic acids such as propionic acid, butyric acid, isocaproic acid, decanoic acid, α-methyldecanoic acid, lauric acid, myristic acid, oleic acid, palmitic acid, trimethylacetic acid, undecenoic acid, malonic acid, succinic acid, glutaric acid and tartaric acid, cyclo-aliphatic carboxylic acids, such as cyclohexane-carboxylic acid, cyclopentylpropionic acid and cyclohexylbutyric acid, araliphatic carboxylic acids such as phenylacetic acid and phenylpropionic acid, and aromatic carboxylic acids such as benzoic acid.

The steroids named may also be further substituted at positions 6, 7 and/or 11, for example by a methyl, ethyl or methylene group, and/or may contain a further double bond, for example a Δ^6 bond.

The preparations obtained according to the invention, depending on the steroid present, may be used for various indications. Preparations based on testosterone and esters thereof may be used as androgenically active preparations in substitution therapy. Preparations based on oestrogens may be used in cases of oestrogen deficiency. Preparations containing nandrolone or esters thereof can find use as anabolic preparations or ovulation-inhibiting preparations. Preparations based on progesterone or progesterone derivatives may be used as progestagenic preparations, not only for the maintenance of a pregnancy but also for prevention of pregnancy (ovulation inhibiting action) and they may furthermore be used for the treatment of endometrial carcinoma. For use as ovulation inhibitors, long-acting esters of 17α-hydroxy-progesterone, such as for example, 17α-hydroxy-progesterone caproate and medroxyprogesterone acetate, are used. Preparations containing corticosteroids may be used in those cases in which mineralocorticoid, glucocorticoid, anti-inflammatory, anti-allergic, anti-shock or analgesic activity is desired.

An interesting application of those preparations according to the invention based on nandrolone esters, in particular nandrolone esters derived from organic carboxylic acids with more than 7 carbon atoms, for example nandrolone phenylpropionate, is the use as an injection preparation for the regulation of oestrus in animals. Such an injection preparation offers particular advantages for the suppression of oestrus in domestic animals such as dogs. Since it is possible, in accordance with the invention, to prepare injection formulations containing well over 300 mg nandrolone ester, for example nandrolone palmitate, per ml, it is possible to suppress oestrus in dogs for more than 3 months with a single injection of 1 ml. Only concentrations of 50 to 100 mg per ml can be obtained with the known solvents such as arachis oil, while the addition of benzyl benzoate and/or benzyl alcohol enables concentrations of 100 to 200 mg per ml to be reached with certain nandrolone esters, for example nandrolone palmitate. For the suppression of oestrus, therefore, either a larger volume (2 to 5 ml) would have to be injected, or the injection would have to be repeated at an earlier date, and there are objections to both these procedures.

On using injection preparations according to the invention based on nandrolone esters for the suppression of oestrus in animals it was furthermore shown that, specifically with the preparations based on nandrolone esters derived from aliphatic carboxylic acids with 9–18 carbon atoms, an additional depot effect (prolonged activity or sustained release effect) appears, so that the very high concentration in the depot, particularly during the initial phase, does not result in an undesirably high blood level; unwanted side-effects as a result of excessively high blood levels do not therefore occur.

Another interesting use of the preparations according to the invention is the oral administration in the form of soft gelatine capsules containing a highly concentrated solution of the steroids in tocol or a derivative thereof. This use is specifically of importance for the oral administration of testosterone and nandrolone, in particular the esters of these steroids derived from organic carboxylic acids.

The activity of both testosterone and nandrolone is much lower on oral administration than on parenteral administration. It is true that this difference proves to be smaller for the esters of these compounds, but it may nevertheless still constitute an adequate reason for choosing the parenteral administration form in preference to the oral form, particularly in those cases where the doses to be administered are relatively high, as, for example, in androgen substitution therapy, and a large number of dosage units or a relatively large dosage unit (swallowing problem!) have or has, respectively, to be given on each occasion or alternatively the dosage has to be repeated at shorter intervals. In such cases, use of the highly concentrated solutions according to the invention can weigh the scales in favour of the medically and technically easier oral dosage form, such as the soft gelatine capsule containing the concentrated solution of, for example, a testosterone or nandrolone ester. Such an oral administration form furthermore offers the advantage that the active agent is made available to the organism in a lipoid solution, which has a favourable effect on the activity of the preparation. In this connec-

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tion see the Belgian Patent Specifications Numbers 826086 and 845613.

It is known that certain tocol derivatives possess vitamin E activity. For many applications, such as suppression of oestrus in animals, this is not objectionable, but for applications in the human sector the vitamin E activity of a preparation according to the invention may be a drawback. It is however known that the various tocols possess differing vitamin E activities, and that tocol itself and certain derivatives, for example 5,7-diethyltocol and 6-desoxytocol, possess little or no vitamin E activity, so that a formulation with the desired low vitamin E activity or a formulation devoid of vitamin E activity can be prepared according to the choice of carrier.

The invention is illustrated by means of the following examples.

EXAMPLE I

Saturated solutions of a number of steroids in 5,7,8-trimethyltocol (α-tocopherol) were prepared at 21° C. The concentration of steroid in mg per ml solution is given in column a of Table A. Column b gives the concentration of steroid in mg per ml in a saturated solution in a solvent comprising equal parts by volume of α-tocopherol and arachis oil, while for comparison column c shows the concentration of steroid in mg per ml in a standard solution in arachis oil.

Table A

Steroid	a	6	c
testosterone	100	40	5
corticosterone	40	2	1
16α-ethyl-21-hydroxy-progesterone-21-decanoate	500	200	50
16α-ethyl-21-hydroxy-progesterone-21-heptanoate	>225	>225	140
dinandrolone oxydiacetate	120	20	10
dinandrolone adipate	180	85	2
testosterone undecanoate	>225	>225	85
nandrolone palmitate	400	200	75

EXAMPLE II

300 g nandrolone palmitate and 250 g α-tocopherol were added to a mixture of 100 g benzyl alcohol and 250 g benzyl benzoate which had been warmed to 70° C. After stirring for a while, a clear solution was obtained. The solution was cooled to room temperature after which the volume was adjusted to 1000 ml by addition, with stirring, of arachis oil (about 100 g). The solution thus obtained was filled into 1000 vials in a volume of 1 ml solution each, after which the vials were closed with oil-resistant rubber stoppers and so-called open "Ciliatto" capsules. The vials were finally heated at 121° C. for 30 minutes in an autoclave.

In a similar way, but using tocol instead of α-tocopherol, and in another batch δ-tocopherol instead of α-tocopherol, solutions were prepared and vials were filled with 1 ml solution containing 300 mg nandrolone palmitate.

The injection preparations thus obtained proved to be eminently suitable for use in the suppression of oestrus in dogs, a single injection of 1 ml made using a syringe fitted with a 19 G needle giving suppression of oestrus lasting at least 3 months.

EXAMPLE III

A sterile solution of testosterone undecanoate in tocol, containing 208.35 g per liter, was made. In the way usual in the pharmaceutical technique, this solution was encapsulated under aseptic conditions in soft gelatine capsules with a volume (contents) of 0.24 ml, so that the testosterone undecanoate content was 50 mg per capsule. The capsule wall (113 mg) consisted of gelatine (77 mg), glycerine (17.5 mg), sorbitol (15.5 mg), parabens (0.5 mg), TiO_2 (0.6 mg) and Cochineal Red A (1.9 mg; dye).

A number of other steroids were dissolved in tocol and encapsulated in soft gelatine capsules in a similar way. Details are given in Table B.

Table B

Steroid	Capsule content (ml)	mg steroid per capsule
Testosterone α-methyldecanoate	0.12	25
Nandrolone decanoate	0.18	50
Nandrolone α-methyl-β-cyclohexylpropionate	0.08	20
Dinandrolone oxydiacetate	0.24	25

EXAMPLE IV

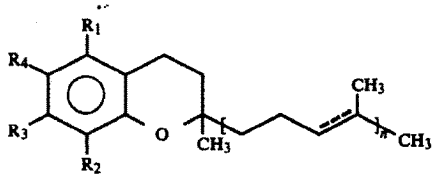
Injection formulations of a number of steroids in a solution based on tocol, benzyl alcohol, benzyl benzoate and arachis oil (50:5:20:25) were prepared in the usual way (see Example II) and filled into 1 ml capsules. The steroids are given in Table C, together with their concentrations in mg per ml solution.

Table C

Steroid	mg per ml
Nandrolone phenylpropionate	200
16α-ethyl-21-hydroxyprogesterone-21-decanoate	350
Dinandrolone oxydiacetate	75
Oestradiol phenylpropionate	50
17α-hydroxyprogesterone caproate	150
Nandrolone palmitate/laurate (2:1)	300

I claim:

1. A highly concentrated liquid pharmaceutical steroid formulation comprising (1) at least one steroid of the oestrane, androstane or (19-nor-)pregnane series containing at least a 3-oxo-Δ^4-group and an hydroxy group at position 17 and or 21 (if present) and (2) a solvent for said steroid comprising at least one of tocol or a derivative thereof that is fluid at normal temperatures and of the formula:



where

R_1=H, CH_3, or C_2H_5;
R_2=H, CH_3, or C_2H_5;
R_3=H, CH_3, or C_2H_5;
R_4=H, OH, O-C_{1-2} acyl, OCH_3, or C_2H_5; and
n=1, 2, or 3;

the dotted lines indicate the optional presence of a carbon atom double bond, with the proviso that said tocol or derivative constitutes at least 10% by weight of said formulation.

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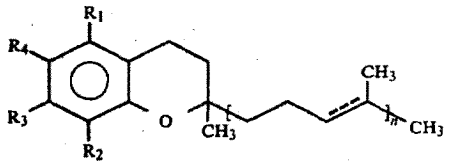
2. The formulation of claim 1, wherein said tocol or derivative thereof is selected from the group consisting of tocol, α-tocopherol and δ-tocopherol.

3. The formulation of claims 1 or 2, wherein said tocol or derivative thereof constitutes at least 25% by weight of said formulation.

4. The steroid formulation of claim 1 where the hydroxy group of the steroid is esterified.

5. The steroid formulation of claim 1 further containing at least one fluid carrier selected from the group consisting of vegetable oils, benzyl benzoate, and benzyl alcohol with the proviso that said tocol or derivative constitutes at least 10% by weight of said formulation.

6. A process for preparing a highly concentrated pharmaceutical steroid formulation comprising dissolving at least one steroid of the oestrane, androstane, or (19-nor-) pregnane series containing at least a 3-oxo-Δ^4-group and an hydroxy group at position 17 and or 21 (if present) in at least one of tocol or a derivative thereof that is liquid at normal temperatures and of the formula:



where

R_1=H, CH_3, or C_2H_5;
R_2=H, CH_3, or C_2H_5;
R_3=H, CH_3, or C_2H_5;
R_4=H, OH, O-C_{1-2} acyl, or C_2H_5; and
n=1, 2, or 3;

the dotted lines indicate the optional presence of a carbon atom double bond, with the proviso that said tocol or derivative constitutes at least 10% by weight of said formulation.

7. Process according to claim 6, characterized in that said tocol or derivative thereof is selected from the group consisting of tocol, α-tocopherol and γ-tocopherol.

8. The process of claim 6 wherein the hydroxy group of the steroid is esterified.

9. The process of claim 6 comprising further adding at least one fluid carrier selected from the group consisting of vegetable oils, benzyl benzoate, and benzyl alcohol to the formulation with the proviso that said tocol or derivative constitutes at least 10% by weight of said formulation.

10. Process according to claims 6, 7, 8 or 9, characterized in that said tocol or derivative thereof constitutes at least 25% by weight of said formulation.

* * * * *

InnoPharma Exhibit 1046.0212

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,212,863

DATED : July 15, 1980

INVENTOR(S) : Lammert CORNELIUS

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Line 3 of the Abstract, change "comprising" to --containing--.

Column 2, line 51, change "esters" to --ethers--.

Column 6, line 63, in claim 1, change "C_2H_5" to read --OC_2H_5--.

Column 8, line 14, in claim 6, change "or C_2H_5" to read --OCH_3 or C_2H_5--.

Signed and Sealed this

Fourth Day of May 1982

[SEAL]

Attest:

GERALD J. MOSSINGHOFF

Attesting Officer *Commissioner of Patents and Trademarks*

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,212,863

DATED : July 15, 1980

INVENTOR(S) : Lammert CORNELIUS

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 8, line 14, in claim 6, change "OCH_3 or C_2H_5" to read --OCH_3 or OC_2H_5--.

Signed and Sealed this

Twentieth Day of *July 1982*

[SEAL]

Attest:

GERALD J. MOSSINGHOFF

Attesting Officer *Commissioner of Patents and Trademarks*

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ATTACHMENT F - COMPILATION

TAB 2

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European Patent Office
Office européen des brevets

(11) Publication number: **0 346 014 A1**

(12) **EUROPEAN PATENT APPLICATION**

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(54) **Therapeutic product.**

(57) The invention relates to a therapeutic product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions; to a process for the manufacture of said product and to a pharmaceutical composition containing said product. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to a process for the manufacture of said composition.

EP 0 346 014 A1

THERAPEUTIC PRODUCT

This invention relates to a therapeutic product for use in a new method of medical treatment and, more particularly, it relates to a product comprising an oestrogen and a pure antioestrogen for use in a new method for the treatment or prophylaxis of perimenopausal or postmenopausal conditions, particularly perimenopausal or postmenopausal osteoporosis. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to the use thereof in the manufacture of a new medicament for use in the treatment or prophylaxis of perimenopausal or postmenopausal conditions.

When a female animal, particularly a human female, enters the perimenopausal stage the animal's ovaries begin to secrete less of the female sex hormones, particularly oestradiol. Symptoms in women at this stage include the following: vasomotor disturbances (hot flushes), urogenital atrophy (particularly affecting the vagina and distal urethra), psychosomatic complaints, changes in lipid metabolism and osteoporosis. The rate of decline of ovarian function and the severity of the above-mentioned symptoms are highly variable between individual women but in a substantial number of individuals the symptoms are sufficiently severe that treatment is required. Oestrogen replacement therapy has been used in women and it is generally recognised to be effective in combatting the typical perimenopausal and post-menopausal symptoms (British Medical Journal, 1987, 295, 914; American Journal of Obstet. and Gynecol., 1987, 156, 1298 and 1347). However oestrogen replacement therapy can also cause uterine hyperplasia, irregular vaginal menstruation and, in a small proportion of women, endometrial cancer (American Journal of Obstet. and Gynecol., 1987, 156, 1313).

To combat the continuous unopposed stimulation of oestrogen-responsive tissues an oestrogen and a progestogen are normally co-administered for part of each treatment period thereby causing regular vaginal menstruation. (American Journal of Obstet. and Gynecol., 1987, 156, 1304). However the continuation of menstrual periods is unattractive to many postmenopausal women and, in addition, progestogens can cause side effects, for example oedema, premenstrual irritability and breast tenderness.

Alternative therapies are therefore required.

It has recently been shown that compounds demonstrating a mixture of oestrogenic and antioestrogenic properties in warm-blooded animals, including humans, may be of use in the treatment of postmenopausal conditions (European Patent Specification No. 0178862). Particular compounds stated to have such activity include clomiphene and tamoxifen. Comprehensive reviews of the clinical usage of these compounds are available, for example a review of clomiphene by Clark et al. in Pharmacology and Therapeutics, 1982, Volume 15, pages 467 to 519, and a review of tamoxifen by Furr et al. in Pharmacology and Therapeutics, 1984, Volume 25, pages 127-205.

It has also recently been shown that a treatment regime comprising the dosing of a small amount of an oestrogen, for example oestrone sulphate or natural conjugated oestrogens, followed by the dosing of an antioestrogen, for example tamoxifen or clomiphene led to the partial inhibition of the maximum oestrogen-induced stimulation of uterine endometrial tissue (A. Kauppila et al., Gynecol. obstet. Invest., 1988, 25, 58 and Arch. Gynecol., 1983, 234, 49).

It has now been found that administration of an oestrogen and a pure antioestrogen, whether simultaneously, sequentially or separately, results in the oestrogen being selectively effective in some oestrogen-responsive tissues, for example bone, and being selectively opposed in other oestrogen-responsive tissues, for example the endometrium of the uterus, and this is the basis of the present invention.

A pure antioestrogen is a compound which possesses antioestrogenic activity and no oestrogenic activity. This may be demonstrated in rats by the effect of the compound in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when each of a pure antioestrogen and oestradiol benzoate are administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate alone. Unlike the known antioestrogens tamoxifen and clomiphene, when a pure antioestrogen is administered alone to a rat no increase in uterine weight whatsoever is observed.

It is disclosed in European Patent Specification No. 138504 that certain pr ferred steroidal antioestrogens are pure antioestrogens. It is also disclosed in European Patent No. 124369 that certain preferred non-steroidal antioestrogens are pure antioestrogens.

According to the present invention there is provided a product comprising an oestrogen and a pure antioestrogen for simultaneous, s quential or separate use in selective o strogen therapy of perimenopausal or postmenopausal conditions.

11/20/2002, EAST Version: 1.03.0002

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In a particular product of the invention the oestrogen component of a product of the invention is oestradiol, ethinyloestradiol, oestriol, oestron , natural conjugat d oestrogens, piperazine oestrone sulphate, mestranol, chlorotrianisene, dienoestrol, stilboestrol or hexoestrol or a pharmaceutically-acceptable ester thereof.

A pharmaceutically-acceptable ester of the o strogen component of a product of the invention is, for example, an alkyl or aryl ester each of up to 12 carbon atoms. It will be appreciated that an ester of a steroidal oestrogen may be formed at the 3-position, the 17-position or at both of these positions. It will also be appreciated that an ester may be formed at one or both of the phenolic groups in some non-steroidal oestrogens, for example stilboestrol and hexoestrol. A suitable alkyl ester of up to 12 carbon atoms is, for example, an acetate, propionate, butyrate, valerate, hexanoate, heptanoate, octanoate, cyclopentylpropionate, nonanoate, decanoate, undecanoate or dodecanoate. A suitable aryl ester of up to 12 carbon atoms is, for example, a benzoate, toluate or naphthoate. A preferred pharmaceutically-acceptable ester of the oestrogen component of a product of the invention includes, for example, oestradiol benzoate, oestradiol cyclopentylpropionate, oestradiol dipropionate, oestradiol heptanoate, oestradiol undecanoate, oestradiol valerate and stilboestrol dipropionate.

In a further particular product of the invention the pure antioestrogen is
N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl- or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;
N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-triene-7α-yl)butyl]-phenylpropionamide;
7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)triene-3,17β-diol; or
7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

In a further particular product of the invention the pure antioestrogen is a compound of the formula:-
NU-A-X-R^1
wherein NU is 6-hydroxy-2-p-hydroxyphenylnapth-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$ or $-(CH_2)_5-$(1,4-phenylene)$-(CH_2)_2-$;
or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnapth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$ or $-(CH_2)_4-$(1,4-phenylene)$-(CH_2)_2-$;
or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$ or $-(CH_2)_4-$(1,4-phenylene)$-(CH_2)_2-$;
and wherein XR^1 is $-CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $-SR^1$, $-SOR^1$ or $-SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

In a further particular product of the invention the pure antioestrogen is
N-n-butyl-, N-n-butyl-N-methyl-, N-n-pentyl, N-(1H,1H-heptafluorobutyl)-or N-(1H,1H-heptafluorobutyl)-N-methyl-3-p-[5-(6-hydroxy-2-p-hydroxyphenylnaphth-1-yl)pentyl]phenylpropionamide;
N-methyl-N-(1H,1H-heptafluorobutyl)-p-[4-[(1RS,2RS)-6-hydroxy-2-p-hydroxphenyl-2-methyl-1,2,3,4-tetrahydronaphth-1-yl]-butyl]phenylpropionamide;
(1RS,2RS)-1-[4-[p-(2-n-hexylthioethyl)phenyl]butyl]-2-p-hydroxyphenyl-1,2,3,4-tetrahydronaphth-6-ol or the corresponding 4,4,5,5,5-pentafluoropentylthio derivative, or the corresponding hexylsulphinyl, hexylsulphonyl or pentafluoropentylsulphinyl derivatives;
2-p-hydroxyphenyl-1-[5-[p-(2-n-hexylthioethyl)phenyl]pentyl]naphth-6-ol or the corresponding hexylsulphinyl derivative; or
(1RS,2RS)-1-[4[p-(2-n-hexylthioethyl)phentyl]butyl]-2-p-hydroxyphenyl-2-methyl-1,2,3,4-tetrahydronaphth-6-ol or the corresponding 4,4,5,5,5-pentafluoropentylthio derivative, or the corresponding hexylsulphinyl or pentafluoropentylsulphinyl derivative, or the corresponding (1RS,2SR) isomers of both the hexylthio and hexylsulphinyl derivatives.

A preferred product of the invention comprises an oestrogen and a pure antioestrogen for use as stated above wherein the oestrogen is oestradiol or ethinyloestradiol, or a pharmaceutically-acceptable ester thereof, and the pure antioestrogen is 7α-[9-(4,4,5,5,5- pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol or (1RS,2RS)-2-p-hydroxyphenyl-2-methyl-1-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-1,2,3,4-tetrahydronaphth-6-ol.

A particularly preferred product of the invention comprises an oestrogen and a pure antio strogen for use as stated abov wh rein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-

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oestra-1,3,5(10)-triene-3,17β-diol.

According to a further feature of the invention there is provided a process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing together said oestrogen and said pure antioestrogen.

In a further feature of the invention there is provided a process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing into admixture said oestrogen and said pure antioestrogen.

A product of the invention may be administered to a warm-blooded animal, including a human, in the form of a pharmaceutical composition. Thus according to a further feature of the present invention there is provided a pharmaceutical composition which comprises the product of the invention together with a pharmaceutically-acceptable diluent or carrier.

As mentioned above a product of the invention is useful for selective oestrogen therapy of perimenopausal or postmenopausal conditions. It will be understood that there is no absolute requirement that the oestrogen and pure antioestrogen components of the product of the invention must be dosed simultaneously. Sequential or separate use of these components may also provide selective oestrogen therapy and such use is to be understood to fall within the definition of a product of the invention. Thus it will be appreciated that a pharmaceutical composition according to the present invention includes a composition comprising an oestrogen, a pure antioestrogen and a pharmaceutically-acceptable diluent or carrier. Such a composition conveniently provides the product of the invention for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions. A pharmaceutical composition according to the present invention also includes separate compositions comprising a first composition comprising an oestrogen and a pharmaceutically-acceptable diluent or carrier, and a second composition comprising a pure antioestrogen and a pharmaceutically-acceptable diluent or carrier. Such a composition conveniently provides the product of the invention for sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, capsules, aqueous or oily suspensions, emulsions or dispersible powders or granules), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions; for example for use within a transdermal patch), for parenteral administration (for example as a sterile aqueous or oily solution or suspension for intravenous, subcutaneous, intramuscular or intravascular dosing), or as a suppository for rectal dosing or as a pessary for vaginal dosing.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as gelatin or starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylen oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

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Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, castor oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as castor oil, soya bean oil or arachis oil, or a mineral oil, such as, for example, liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

The pharmaceutical compositions may also be in the form of sterile injectable aqueous or oily suspensions, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol, in a vegetable oil (such as arachis oil, castor oil or coconut oil) or in a mineral oil (such as liquid paraffin).

Conveniently the subcutaneous or intramuscular injection of an aqueous suspension or an oily solution or suspension of a pharmaceutical composition of the invention provides a depot of the active ingredients at the injection site from which those ingredients may leach out over a period of time to provide the sustained release thereof.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

According to a further feature of the invention there is provided a process for the manufacture of a pharmaceutical composition as defined above which comprises bringing into admixture a product as defined above together with a pharmaceutically-acceptable diluent or carrier.

The invention also provides a method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering simultaneously, sequentially or separately to a warm-blooded animal an effective amount of a product as defined above. The invention also provides the use of a product as defined above for the manufacture of a new medicament for use simultaneously, sequentially or separately in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

It will be appreciated that the definition of the product of the invention and the pharmaceutical composition of the invention includes only those products or compositions which are useful in a new method for the treatment or prophylaxis of perimenopausal or postmenopausal condition. Pharmaceutical compositions comprising an oestrogen and a pure antioestrogen, together with a pharmaceutically-acceptable diluent or carrier, are novel. In European Patent Sepcifications Nos. 138504 and 124369 it is disclosed that the antioestrogenic activity of the compounds disclosed therein may be demonstrated by the co-administration of a test compound and oestradiol benzoate to an immature female rat. Antioestrogenic activity is demonstrated by antagonism of the increase in weight of the uterus of the rat which is produced when oestradiol benzoate alone is administered to said rat. It is to be noted that, during those tests, the oestradiol benzoate was given by subcutaneous injection whereas the test compound was given separately either orally or subcutaneously.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

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The pharmaceutical compositions of this feature of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the are such as, for example, those disclosed above.

This aspect of the invention also provides a process for the manufacture of a pharmaceutical composition as defined immediately above which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

This aspect of the invention also provides a method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering to a warm-blooded animal an effective amount of a pharmaceutical composition as defined immediately above. The invention also provides the use of a pharmaceutical composition as defined immediately above for the manufacture of a new medicament for use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

As stated above a product of the invention is of use in selective oestrogen therapy of perimenopausal or postmenopausal conditions. Selective oestrogen therapy may be demonstrated using the standard procedure set out below:-

a) an in vivo assay measuring the antioestrogenic activity of a compound and any oestrogenic activity possessed by that compound. This may be demonstrated in rats by the effect of the compound in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when each of a pure antioestrogen and oestradiol benzoate are administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate without the pure antioestrogen. Unlike the known antioestrogens tamoxifen and clomiphene, when a pure antioestrogen is administered alone to a rat no increase in uterine weight whatsoever is observed.

The oestrogenic activity of a compound may be demonstrated in rats by the effect of the compound when it is administered alone to said rat on the uterine weight of the animal.

b) An in vivo assay in mature rats measuring the antioestrogenic activity of a compound by the effect of the compound when dosed during a test period of 28 days in antagonising the protective effect on the animals' bone density of their endogenous oestrogens. The bone density of a group of ovariectomised rats in which endogenous oestrogen levels are much reduced serves as a control for the effect expected to be produced by a fully effective antioestrogen.

The antioestrogenic activity of the compound in mature rats can also be measured in the same assay by measuring the effect of the compound in antagonising the effect of the animals' endogenous oestrogens which serve to increase the weight of their uteri.

A comparison of the potencies of the antioestrogenic effects of a compound as measured by its effects on the animals' bone density and uterine weights allows the selectivity of the antioestrogenic effects of the compound to be measured.

Although the pharmacological properties of a product of the invention vary with the structures of the oestrogenic and antioestrogenic components and with the route of administration, in general a product of the invention comprises:-

(i) an oestrogen which possesses oestrogenic activity in the above test (a) at doses in the range, for example, 0.002-2.0 mg/kg orally or in the range, for example, 0.0001-0.1 mg/kg subcutaneously;

(ii) a pure antioestrogen which possesses antioestrogenic activity in the above tests (a) and (b) at doses in the range, for example, in test (a): ED_{50} 0.05-5 mg/kg orally or ED_{50} 0.01-1.0 mg/kg subcutaneously;

in test (b): antiuterotrophic effect:- ED_{50} < 20 mg/kg/day orally, < 2 mg/kg/day subcutaneously or intramuscularly and < 10 mg/kg/injection when dosed as an intramuscular depot injection; reduction in bone density:- ED_{50} > 20 mg/kg/day orally, > 5 mg/kg/day subcutaneously or intramuscularly and > 10 mg/kg/injection when dosed as an intramuscular depot injection.

A product of the invention is thereby seen to be surprisingly selective as the activity of the pure antioestrogen component is expressed to a high degree within uterine tissue but to a lesser degree on bone.

The size of the dose, for therapeutic or prophylatic purposes, of a product of the invention as defined above will naturally vary according to the nature and severity of the conditions presented, the age and menopausal state of the animal and the route of administration.

In general the minimum quantity of the oestrogenic component of a product of the inv ntion as defined above will be chosen so as to provide a beneficial effect with regard to th nature and severity of the conditions presented. The quantity of the pure antioestrogenic compon nt is then chosen to antagonis to a substantial degree the effect of the oestrogenic component on th uterine tissue. Methods of evaluating the

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condition of uterine tissue are well known to the man skilled in the art, for example, by examination of a specimen of endometrial tissue taken by, for example, suction or, for example, by way of a biopsy.

So far as the oestrogenic component of a product of the invention as defined above is concerned the size of the dose and routes of administration conventionally utilised in oestrogen replacement therapy may be used. Thus, for example, a tablet containing, for example, 0.5 to 2 mg of oestradiol, oestradiol benzoate, natural conjugated oestrogens or oestradiol valerate may be administered daily. Alternatively a tablet containing 10 to 100 μg of ethinyloestradiol may be administered daily. Alternatively the oestrogenic component may be administered by, for example, intramuscular injection utilising, for example, 1 to 10 mg of oestradiol benzoate dissolved in an oil such as ethyl oleate; for example, transdermal means utilising, for example, 10-100 μg of oestradiol contained within a transdermal patch; or, for example, vaginal application utilising, for example, daily application of 0.5 to 2 mg of natural conjugated oestrogens contained within 0.5 to 5 ml of a cream.

So far as the antioestrogenic component of a product of the invention as defined above is concerned the size of the dose is chosen such that the effect of the oestrogenic component on uterine tissue is antagonised to a substantial degree whereas the beneficial effect of the oestrogenic component on bone is substantially unopposed.Thus, for example, the antioestrogenic component may be formulated in like manner to the oestrogenic component, for example as a tablet, an oily solution suitable for intramuscular injection, within a transdermal patch, or within a cream suitable for vaginal application. The daily administration of one or more tablets containing conveniently 50 mg to 5 g, and preferably 50 mg to 500 mg, of a pure antioestrogen may be used. Preferably the pure antioestrogen may be administered by the periodic intramuscular injection of, for example, an aqueous suspension or an oily solution or suspension containing 50 mg to 5 g of the pure antioestrogen. Preferably an oily solution, for example a solution containing arachis or castor oil, an alcohol such as benzyl alcohol and 50 mg to 500 mg of the pure antioestrogen is employed. Such an injection provides a depot of the pure antioestrogen which thereafter leaches out from the injection site to provide a selective antioestrogenic effect for a period of, for example, one to six weeks.

As mentioned above a product of the invention is useful for selective oestrogen therapy of perimenopausal or postmenopausal conditions. As previously mentioned perimenopausal and postmenopausal conditions include, for example, vasomotor disturbances (hot flushes), urogenital atrophy (particularly affecting the vagina and the distal urethra), psychosomatic complaints, changes in the lipid metabolism and oesteoporosis. The selective antioestrogenic effect of the pure antioestrogenic component of a product of the invention, as demonstrated by a greater antioestrogenic effect on the uterus of a rat than on the bone of the rat, allows the beneficial effect of the oestrogenic component of the product of the invention to be selectively applied to the bone and prevents the detrimental effect of an unopposed oestrogenic effect on the uterus. The utero-selective effect of the pure antioestrogenic component of a product of the invention will allow the beneficial effect of the oestrogenic component of a product of the invention to be applied to other oestrogen-responsive tissues, for example those causing vasomotor disturbances, pyschosomatic complaints and changes in lipid metabolism.

The invention will now be illustrated in the following non-limiting Examples.

Example 1

Assay in Mature Rats of the Selective Antioestrogenic Activity of a Pure Antioestrogen

The pure antioestrogen used was (1RS,2RS)-2-p-hydroxyphenyl-2-methyl-1-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-1,2,3,4-tetrahydronaphth-6-ol.

The compound was given subcutaneously as a solution in arachis oil at doses of 2 mg/kg/day and 10 mg/kg/day to two groups of 5 mature rats for a total of 28 days. Further groups of 5 mature rats served as an untreated control group. A further group of 5 mature rats was ovariectomised to serve as another control group. At the end of the treatment period the weights of the uteri of the test and control groups of rats were determined. In addition the femurs were dissected, weighed and their volumes were determined using Archimedes Principle. The femurs were then burned and the residual ash was weighed. From these data, gross femur density and bone mineral density were calculated as follows:-

Gross Femur Density = Femur Weight/Femur Volume

Bon Mineral Density = Femur Ash Weight/Femur Volume

The results shown below in Tables I and II demonstrate that at a dose of 2 mg/kg/day subcutaneously

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the test compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri (90% inhibition of uterine weight) whereas there was no significant inhibition of either bone mineral density or of gross femur density.

TABLE I

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	382 ± 34	
Ovariectomised Controls	111 ± 14	
Test Compound at 2 mg/kg/day s.c.	135 ± 8	91%
Untreated Controls	369 ± 47	
Ovariectomised Controls	99 ± 5	
Test Compound at 10 mg/kg/day s.c.	125 ± 4	90%

TABLE II

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition	Bone Mineral Density (g/ml)	Calculated Inhibition
Untreated Controls	1.612 ± 0.010		0.742 ± 0.009	
Ovariectomised Controls	1.569 ± 0.010		0.685 ± 0.010	
Test Compound at 2 mg/kg/day s.c.	1.604 ± 0.006	19%*	0.730 ± 0.007	21% *
Untreated Controls	1.629 ± 0.014		0.766 ± 0.005	
Ovariectomised Controls	1.571 ± 0.007		0.704 ± 0.005	
Test Compound at 10 mg/kg/day s.c.	1.580 ± 0.004	84%	0.727 ± 0.005	63%

* This level of inhibition was not statistically significant.

Example 2

The experiment described in Example 1 was repeated except that the pure antioestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol. This compound was given at a series of doses as a daily intramuscular injection, the compound having been dissolved in a mixture of propylene glycol: ethanol: water: poloxamer 407. The formulation contained 25 mg of test compound, 100 mg of ethanol (96%), 100 mg of water, 20 mg of poloxamer 407 and sufficient propylene glycol to bring the solution to a volume of 1 ml.

The results shown below in Tables III and IV demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas there was no significant inhibition of gross femur density.

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TABLE III

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	302 ± 36	
Ovariectomised Controls	70 ± 1.3	
Test Compound (mg/kg)		
0.1	208 ± 17	41
0.3	174 ± 16	55
1	94 ± 9	90
3	103 ± 2	86

TABLE IV

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Untreated Controls	1.523 ± 0.008	
Ovariectomised Controls	1.491 ± 0.006	
Test Compound at (mg/kg)		
0.1	1.528 ± 0.005	0%
0.3	1.528 ± 0.008	0%
1	1.532 ± 0.005	0%
3	1.533 ± 0.005	0%

Example 3

The pure antioestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

Each of a series of selected doses of this compound was dissolved in a mixture of castor oil and benzyl alcohol and given by intramuscular injection to a group of 5 mature rats. The formulation contained 50 mg of the test compound, 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. In each case a second dose was administered two weeks after the first dose. Two weeks after the second dose the weights of the uteri of the test groups of rats were determined. In addition the femurs were dissected and analysed for Gross Femur Density as in Example 1.

A further group of rats, given two injections of castor oil separated by a two week period, served as an intact control group. A further group of rats was ovariectomised to serve as another control group.

The results shown below in Tables V and VI demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas at the two higher test doses there was no significant inhibition of gross femur density.

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TABLE V

Treatm nt	Uterine Weight (mg)	Calculated Inhibition
Intact Controls Ovariectomised Controls	318 ± 31 76 ± 4	
Test Compound (mg/rat/dose)		
0.75 1.25 2.5	202 ± 23 180 ± 15 123 ± 12	48 57 81

TABLE VI

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Intact Controls Ovariectomised Controls	1.584 ± 0.007 1.521 ± 0.005	
Test Compound (mg/rat/dose)		
0.75 1.25 2.5	1.562 ± 0.004 1.576 ± 0.004 1.569 ± 0.007	35 13* 23*

* This level of inhibition was not statistically significant.

Claims

1. A product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

2. A product as claimed in claim 1 wherein the pure antioestrogen is
N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl- or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;
N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)butyl]-phenylpropionamide;
7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)-triene-3,17β-diol; or
7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

3. A product as claimed in claim 1 wherein the pure antioestrogen is a compound of the formula:-
NU-A-X-R¹
wherein NU is 6-hydroxy-2-p-hydroxyphenylnaphth-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$ or $-(CH_2)_3-(1,4\text{-phenylene})-(CH_2)_2-$;
or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$or $-(CH_2)_4-(1,4\text{-phenylene})-(CH_2)_2-$;
or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$or$-(CH_2)_4-(1,4\text{-phenylene})-(CH_2)_2-$;

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and wherein XR^1 is $-CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $-SR^1$, SOR^1 or $-SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

4. A product as claimed in claim 1 wherein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)-nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

5. A process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing together said oestrogen and said pure antioestrogen.

6. A pharmaceutical composition comprising a product as claimed in any one of claims 1 to 4 together with a pharmaceutically-acceptable diluent or carrier.

7. The use of a product as claimed in any one of claims 1 to 4 for the manufacture of a new medicament for use simultaneously, sequentially or separately in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

8. A pharmaceutical composition comprising an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

9. A process for the manufacture of a pharmaceutical composition as claimed in claim 8 which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

10. The use of a pharmaceutical composition as claimed in claim 8 for the manufacture of a new medicament for use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

Claims for the following Contracting States: GR, ES.

1. A process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal condition, which process is characterised by bringing together said oestrogen and said pure antioestrogen.

2. A process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process is characterised by bringing into admixture said oestrogen and said pure antioestrogen.

3. A process as claimed in claim 1 or claim 2 wherein the pure antioestrogen is
N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl- or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;
N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)butyl]-phenylpropionamide;
7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)-triene-3,17β-diol; or
7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

4. A process as claimed in claim 1 or 2 wherein the pure antioestrogen is a compound of the formula:-
NU-A-X-R^1
wherein NU is 6-hydroxy-2-p-hydroxyphenylnaphth-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$, or $-(CH_2)_5-(1,4\text{-phenylene})-(CH_2)_2-$;
or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$or $-(CH_2)_4-(1,4\text{-phenylene})-(CH_2)_2-$;
or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$or $-(CH_2)_4-(1,4\text{-phenylene})-(CH_2)_2-$;
and wherein XR^1 is $-CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $-SR^1$, SOR^1 or $-SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

5. A process as claimed in claim 1 or claim 2 wherein th oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

11/20/2002, EAST Version: 1.03.0002

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6. A process for the manufacture of a pharmaceutical composition which comprises bringing into admixture a product as defined in any one of claims 1 to 5 together with a pharmaceutically-acceptable diluent or carrier.

7. A process for the manufacture of a pharmaceutical composition which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

11/20/2002, EAST Version: 1.03.0002

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 30 5563

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,X	EP-A-0 124 369 (IMPERIAL CHEMICAL INDUSTRIES PLC) * Page 15, lines 4-6 *	1-10	A 61 K 31/565// (A 61 K 31/565 A 61 K 31:165)
D,X	EP-A-0 138 504 (IMPERIAL CHEMICAL INDUSTRIES PLC) * Page 14, lines 2-5 *	1-10	
A	CHEMICAL ABSTRACTS, vol. 109, no. 3, 18th July 1988, page 73, abstract no. 17199p, Columbus, Ohio, US; N. FROEHLANDER et al.: "Growth hormone and somatomedin C during post-menopausal replacement therapy with estrogen alone and in combination with an antiestrogen", & MATURITAS 1988, 9(4), 297-302 * Abstract *	1-10	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	20-09-1989	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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ATTACHMENT F - COMPILATION

TAB 3

US005183814A

United States Patent [19]

Dukes

[11] Patent Number: 5,183,814

[45] Date of Patent: Feb. 2, 1993

[54] **SELECTIVE OESTROGEN THERAPY FOR PERIMENOPAUSAL OR POSTMENOPAUSAL CONDITIONS**

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[52] **U.S. Cl.** **514/171**; 514/170; 514/182; 514/622; 514/708; 514/709; 514/710; 514/712; 514/713

[58] **Field of Search** 514/170, 171, 182, 622, 514/708, 709, 710, 712, 713

[56] **References Cited**

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Chemical Abstracts, vol. 109, No. 3, Jul. 18, 1988, p. 73, Abstract No. 17199p.

Primary Examiner—Frederick E. Waddell
Assistant Examiner—Raymond J. Henley, III
Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] **ABSTRACT**

The invention relates to a therapeutic product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions; to a process for the manufacture of said product and to a pharmaceutical composition containing said product. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to a process for the manufacture of said composition.

4 Claims, No Drawings

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SELECTIVE OESTROGEN THERAPY FOR PERIMENOPAUSAL OR POSTMENOPAUSAL CONDITIONS

This invention relates to a therapeutic product for use in a new method of medical treatment and, more particularly, it relates to a product comprising an oestrogen and a pure antioestrogen for use in a new method for the treatment or prophylaxis of perimenopausal or postmenopausal conditions, particularly perimenopausal or postmenopausal osteoporosis. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to the use thereof in the manufacture of a new medicament for use in the treatment or prophylaxis of perimenopausal or postmenopausal conditions.

When a female animal, particularly a human female, enters the perimenopausal stage the animal's ovaries begin to secrete less of the female sex hormones, particularly oestradiol. Symptoms in women at this stage include the following: vasomotor disturbances (hot flushes), urogenital atrophy (particularly affecting the vagina and distal urethra), psychosomatic complaints, changes in lipid metabolism and osteoporosis. The rate of decline of ovarian function and the severity of the above-mentioned symptoms are highly variable between individual women but in a substantial number of individuals the symptoms are sufficiently severe that treatment is required. Oestrogen replacement therapy has been used in women and it is generally recognised to be effective in combatting the typical perimenopausal and post-menopausal symptoms (*British Medical Journal*, 1987, 295, 914; *American Journal of Obstet. and Gynecol.*, 1987, 156, 1298 and 1347). However oestrogen replacement therapy can also cause uterine hyperplasia, irregular vaginal menstruation and, in a small proportion of women, endometrial cancer (*American Journal of Obstet. and Gynecol.*, 1987, 156, 1313).

To combat the continuous unopposed stimulation of oestrogen-responsive tissues an oestrogen and a progestogen are normally co-administered for part of each treatment period thereby causing regular vaginal menstruation. (*American Journal of Obstet. and Gynecol.*, 1987, 156, 1304). However the continuation of menstrual periods is unattractive to many postmenopausal women and, in addition, progestogens can cause side effects, for example oedema, premenstrual irritability and breast tenderness.

Alternative therapies are therefore required.

It has recently been shown that compounds demonstrating a mixture of oestrogenic and antioestrogenic properties in warm-blooded animals, including humans, may be of use in the treatment of postmenopausal conditions (European Patent Specification No. 0178862). Particular compounds stated to have such activity include clomiphene and tamoxifen. Comprehensive reviews of the clinical usage of these compounds are available. for example a review of clomiphene by Clark et al. in *Pharmacology and Therapeutics*, 1982, Volume 15, pages 467 to 519, and a review of tamoxifen by Furr et al. in *Pharmacology and Therapeutics*, 1984, Volume 25, pages 127–205.

It has also recently been shown that a treatment regime comprising the dosing of a small amount of an oestrogen, for example oestrone sulphate or natural conjugated oestrogens, followed by the dosing of an antioestrogen, for example tamoxifen or clomiphene led to the partial inhibition of the maximum oestrogen-induced stimulation of uterine endometrial tissue (A. Kauppila et al., *Gynecol. obstet. Invest.*, 1988, 25, 58 and *Arch. Gynecol.*, 1983, 234, 49).

It has now been found that administration of an oestrogen and a pure antioestrogen, whether simultaneously, sequentially or separately, results in the oestrogen being selectively effective in some oestrogen-responsive tissues, for example bone, and being selectively opposed in other oestrogen-responsive tissues, for example the endometrium of the uterus, and this is the basis of the present invention.

A pure antioestrogen is a compound which possesses antioestrogenic activity and no oestrogenic activity. This may be demonstrated in rats by the effect of the compound in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when each of a pure antioestrogen and oestradiol benzoate are administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate alone. Unlike the known antioestrogens tamoxifen and clomiphene, when a pure antioestrogen is administered alone to a rat no increase in uterine weight whatsoever is observed.

It is disclosed in European Patent Specification No. 138504 that certain preferred steroidal antioestrogens are pure antioestrogens. It is also disclosed in European Patent No. 124369 that certain preferred non-steroidal antioestrogens are pure antioestrogens.

According to the present invention there is provided a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

In a particular product of the invention the oestrogen component of a product of the invention is oestradiol, ethinyloestradiol, oestriol, oestrone, natural conjugated oestrogens, piperazine oestrone sulphate, mestranol, chlorotrianisene, dienoestrol, stilboestrol or hexoestrol or a pharmaceutically-acceptable ester thereof.

A pharmaceutically-acceptable ester of the oestrogen component of a product of the invention is, for example, an alkyl or aryl ester each of up to 12 carbon atoms. It will be appreciated that an ester of a steroidal oestrogen may be formed at the 3-position, the 17-position or at both of these positions. It will also be appreciated that an ester may be formed at one or both of the phenolic groups in some non-steroidal oestrogens, for example stilboestrol and hexoestrol. A suitable alkyl ester of up to 12 carbon atoms is, for example, an acetate, propionate, butyrate, valerate, hexanoate, heptanoate, octanoate, cyclopentylpropionate, nonanoate, decanoate, undecanoate or dodecanoate. A suitable aryl ester of up to 12 carbon atoms is, for example, a benzoate, toluate or naphthoate. A preferred pharmaceutically-acceptable ester of the oestrogen component of a product of the invention includes, for example, oestroadiol benzoate, oestradiol cyclopentylpropionate, oestradiol dipropionate, oestradiol heptanoate, oestradiol undecanoate, oestradiol valerate and stilboestrol dipropionate.

In a further particular product of the invention the pure antioestrogen is

N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl-or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)trien-7α-yl)undecanamide;

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N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-triene-7α-yl)butyl]-phenylpropionamide;

7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]-or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)triene-3,17β-diol; or

7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

In a further particular product of the invention the pure antioestrogen is a compound of the formula:

$$NU—A—X—R^1$$

wherein NU is 6-hydroxy-2-p-hydroxyphenylnapth-1-yl and A is $—(CH_2)_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_5$-(1,4-phenylene)-$(CH_2)_2—$;

or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnapth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $—(CH_2)_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2—$;

or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $—(CH_2)_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2—$; and wherein XR^1 is $—CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $—SR^1$, $—SOR^1$ or $—SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

In a further particular product of the invention the pure antioestrogen is

N-n-butyl-, N-n-butyl-N-methyl-, N-n-pentyl, N-(1H,1H-heptafluorobutyl)-or N-(1H,1H-heptafluorobutyl)-N-methyl-3-p-[5-(6-hydroxy-2-p-hydroxyphenylnaphth-1-yl)pentyl]phenylpropionamide;

N-methyl-N-(1H,1H-heptafluorobutyl)-p-[4-[(1RS,2RS)-6-hydroxy-2-p-hydroxphenyl-2-methyl-1,2,3,4-tetrahydronaphth-1-yl]-butyl]phenylpropionamide; (1RS,2RS)-1-[4-[p-(2-n-hexylthioethyl)phenyl]-butyl]-2-p-hydroxyphenyl-1,2,3,4-tetrahydronaphth-6-ol or the corresponding 4,4,5,5,5-pentafluoropentylthio derivative, or the corresponding hexylsulphinyl, hexylsulphonyl or pentafluoropentylsulphinyl derivatives; 2-p-hydroxyphenyl-1-[5-[p-(2-n-hexylthioethyl)-phenyl]pentyl]naphth-6-ol or the corresponding hexylsulphinyl derivative; or (1RS,2RS)-1-[4[p-(2-n-hexylthioethyl)phentyl]butyl]-2-p-hydroxyphenyl-2-methyl-1,2,3,4-tetrahydronaphth-6-ol or the corresponding 4,4,5,5,5-pentafluoropentylthio derivative, or the corresponding hexylsulphinyl or pentafluoropentylsulphinyl derivative, or the corresponding (1RS,2SR) isomers of both the hexylthio and hexylsulphinyl derivatives.

A preferred product of the invention comprises an oestrogen and a pure antioestrogen for use as stated above wherein the oestrogen is oestradiol or ethinyloestradiol, or a pharmaceutically-acceptable ester thereof, and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol or (1RS,2RS)-2-p-hydroxyphenyl-2-methyl-1-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-1,2,3,4-tetrahydronaphth-6-ol.

A particularly preferred product of the invention comprises an oestrogen and a pure antioestrogen for use as stated above wherein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

According to a further feature of the invention there is provided a process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing together said oestrogen and said pure antioestrogen.

In a further feature of the invention there is provided a process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing into admixture said oestrogen and said pure antioestrogen.

A product of the invention may be administered to a warm-blooded animal, including a human, in the form of a pharmaceutical composition. Thus according to a further feature of the present invention there is provided a pharmaceutical composition which comprises the product of the invention together with a pharmaceutically-acceptable diluent or carrier.

As mentioned above a product of the invention is useful for selective oestrogen therapy of perimenopausal or postmenopausal conditions. It will be understood that there is no absolute requirement that the oestrogen and pure antioestrogen components of the product of the invention must be dosed simultaneously. Sequential or separate use of these components may also provide selective oestrogen therapy and such use is to be understood to fall within the definition of a product of the invention. Thus it will be appreciated that a pharmaceutical composition according to the present invention includes a composition comprising an oestrogen, a pure antioestrogen and a pharmaceutically-acceptable diluent or carrier. Such a composition conveniently provides the product of the invention for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions. A pharmaceutical composition according to the present invention also includes separate compositions comprising a first composition comprising an oestrogen and a pharmaceutically-acceptable diluent or carrier, and a second composition comprising a pure antioestrogen and a pharmaceutically-acceptable diluent or carrier. Such a composition conveniently provides the product of the invention for sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, capsules, aqueous or oily suspensions, emulsions or dispersible powders or granules), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions; for example for use within a transdermal patch), for parenteral administration (for example as a sterile aqueous or oily solution or suspension for intravenous, subcutaneous, intramuscular or intravascular dosing), or as a suppository for rectal dosing or as a pessary for vaginal dosing.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art.

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Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as gelatin or starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, castor oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as castor oil, soya bean oil or arachis oil, or a mineral oil, such as, for example, liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

The pharmaceutical compositions may also be in the form of sterile injectable aqueous or oily suspensions, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol, in a vegetable oil (such as arachis oil, castor oil or coconut oil) or in a mineral oil (such as liquid paraffin).

Conveniently the subcutaneous or intramuscular injection of an aqueous suspension or an oily solution or suspension of a pharmaceutical composition of the invention provides a depot of the active ingredients at the injection site from which those ingredients may leach out over a period of time to provide the sustained release thereof.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

According to a further feature of the invention there is provided a process for the manufacture of a pharmaceutical composition as defined above which comprises bringing into admixture a product as defined above together with a pharmaceutically-acceptable diluent or carrier.

The invention also provides a method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering simultaneously, sequentially or separately to a warm-blooded animal an effective amount of a product as defined above. The invention also provides the use of a product as defined above for the manufacture of a new medicament for use simultaneously, sequentially or separately in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

It will be appreciated that the definition of the product of the invention and the pharmaceutical composition of the invention includes only those products or compositions which are useful in a new method for the treatment or prophylaxis of perimenopausal or postmenopausal condition. Pharmaceutical compositions comprising an oestrogen and a pure antioestrogen, together with a pharmaceutically-acceptable diluent or carrier, are novel. In European Patent Sepcifications Nos. 138504 and 124369 it is disclosed that the antioestrogenic activity of the compounds disclosed therein may be demonstrated by the co-administration of a test compound and oestradiol benzoate to an immature fe-

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male rat. Antioestrogenic activity is demonstrated by antagonism of the increase in weight of the uterus of the rat which is produced when oestradiol benzoate alone is administered to said rat. It is to be noted that, during those tests, the oestradiol benzoate was given by subcutaneous injection whereas the test compound was given separately either orally or subcutaneously.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this feature of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the are such as, for example, those disclosed above.

This aspect of the invention also provides a process for the manufacture of a pharmaceutical composition as defined immediately above which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

This aspect of the invention also provides a method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering to a warm-blooded animal an effective amount of a pharmaceutical composition as defined immediately above. The invention also provides the use of a pharmaceutical composition as defined immediately above for the manufacture of a new medicament for use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

As stated above a product of the invention is of use in selective oestrogen therapy of perimenopausal or postmenopausal conditions. Selective oestrogen therapy may be demonstrated using the standard procedure set out below:

a) an in vivo assay measuring the antioestrogenic activity of a compound and any oestrogenic activity possessed by that compound. This may be demonstrated in rats by the effect of the compound in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when each of a pure antioestrogen and oestradiol benzoate are administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate without the pure antioestrogen. Unlike the known antioestrogens tamoxifen and clomiphene, when a pure antioestrogen is administered alone to a rat no increase in uterine weight whatsoever is observed.

The oestrogenic activity of a compound may be demonstrated in rats by the effect of the compound when it is administered alone to said rat on the uterine weight of the animal.

b) An in vivo assay in mature rats measuring the antioestrogenic activity of a compound by the effect of the compound when dosed during a test period of 28 days in antagonising the protective effect on the animals' bone density of their endogenous oestrogens. The bone density of a group of ovariectomised rats in which endogenous oestrogen levels are much reduced serves as a control for the effect expected to be produced by a fully effective antioestrogen.

The antioestrogenic activity of the compound in mature rats can also be measured in the same assay by measuring the effect of the compound in antagonising the effect of the animals' endogenous oestrogens which serve to increase the weight of their uteri.

A comparison of the potencies of the antioestrogenic effects of a compound as measured by its effects on the animals' bone density and uterine weights allows the selectivity of the antioestrogenic effects of the compound to be measured.

Although the pharmacological properties of a product of the invention vary with the structures of the oestrogenic and antioestrogenic components and with the route of administration, in general a product of the invention comprises:

(i) an oestrogen which possesses oestrogenic activity in the above test (a) at doses in the range, for example, 0.002–2.0 mg/kg orally or in the range, for example, 0.0001–0.1 mg/kg subcutaneously;

(ii) a pure antioestrogen which possesses antioestrogenic activity in the above tests (a) and (b) at doses in the range, for example, in test (a): ED_{50} 0.05–5 mg/kg orally or ED_{50} 0.01–1.0 mg/kg subcutaneously; in test (b): antiuterotrophic effect: $ED_{50} < 20$ mg/kg/day orally, < 2 mg/kg/day subcutaneously or intramuscularly and < 10 mg/kg/injection when dosed as an intramuscular depot injection; reduction in bone density: $ED_{50} > 20$ mg/kg/day orally, > 5 mg/kg/day subcutaneously or intramuscularly and > 10 mg/kg/injection when dosed as an intramuscular depot injection.

A product of the invention is thereby seen to be surprisingly selective as the activity of the pure antioestrogen component is expressed to a high degree within uterine tissue but to a lesser degree on bone.

The size of the dose, for therapeutic or prophylatic purposes, of a product of the invention as defined above will naturally vary according to the nature and severity of the conditions presented, the age and menopausal state of the animal and the route of administration.

In general the minimum quantity of the oestrogenic component of a product of the invention as defined above will be chosen so as to provide a beneficial effect with regard to the nature and severity of the conditions presented. The quantity of the pure antioestrogenic component is then chosen to antagonise to a substantial degree the effect of the oestrogenic component on the uterine tissue. Methods of evaluating the condition of uterine tissue are well known to the man skilled in the art, for example, by examination of a specimen of endometrial tissue taken by, for example, suction or, for example, by way of a biopsy.

So far as the oestrogenic component of a product of the invention as defined above is concerned the size of the dose and routes of administration conventionally utilised in oestrogen replacement therapy may be used. Thus, for example, a tablet containing, for example, 0.5 to 2 mg of oestradiol, oestradiol benzoate, natural conjugated oestrogens or oestradiol valerate may be administered daily. Alternatively a tablet containing 10 to 100 μg of ethinyloestradiol may be administered daily. Alternatively the oestrogenic component may be administered by, for example, intramuscular injection utilising, for example, 1 to 10 mg of oestradiol benzoate dissolved in an oil such as ethyl oleate; for example, transdermal means utilising, for example, 10–100 μg of oestradiol contained within a transdermal patch; or, for example, vaginal application utilising, for example, daily application of 0.5 to 2 mg of natural conjugated oestrogens contained within 0.5 to 5 ml of a cream.

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So far as the antioestrogenic component of a product of the invention as defined above is concerned the size of the dose is chosen such that the effect of the oestrogenic component on uterine tissue is antagonised to a substantial degree whereas the beneficial effect of the oestrogenic component on bone is substantially unopposed. Thus, for example, the antioestrogenic component may be formulated in like manner to the oestrogenic component, for example as a tablet, an oily solution suitable for intramuscular injection, within a transdermal patch, or within a cream suitable for vaginal application. The daily administration of one or more tablets containing conveniently 50 mg to 5 g, and preferably 50 mg to 500 mg, of a pure antioestrogen may be used. Preferably the pure antioestrogen may be administered by the periodic intramuscular injection of, for example, an aqueous suspension or an oily solution or suspension containing 50 mg to 5 g of the pure antioestrogen. Preferably an oily solution, for example a solution containing arachis or castor oil, an alcohol such as benzyl alcohol and 50 mg to 500 mg of the pure antioestrogen is employed. Such an injection provides a depot of the pure antioestrogen which thereafter leaches out from the injection site to provide a selective antioestrogenic effect for a period of, for example, one to six weeks.

As mentioned above a product of the invention is useful for selective oestrogen therapy of perimenopausal or postmenopausal conditions. As previously mentioned perimenopausal and postmenopausal conditions include, for example, vasomotor disturbances (hot flushes), urogenital atrophy (particularly affecting the vagina and the distal urethra), psychosomatic complaints, changes in the lipid metabolism and oesteoporosis. The selective antioestrogenic effect of the pure antioestrogenic component of a product of the invention, as demonstrated by a greater antioestrogenic effect on the uterus of a rat than on the bone of the rat, allows the beneficial effect of the oestrogenic component of the product of the invention to be selectively applied to the bone and prevents the detrimental effect of an unopposed oestrogenic effect on the uterus. The utero-selective effect of the pure antioestrogenic component of a product of the invention will allow the beneficial effect of the oestrogenic component of a product of the invention to be applied to other oestrogen-responsive tissues, for example those causing vasomotor disturbances, pyschosomatic complaints and changes in lipid metabolism.

The invention will now be illustrated in the following nonlimiting Examples.

EXAMPLE 1

Assay in Mature Rats of the Selective Antioestrogenic Activity of a Pure Antioestrogen

The pure antioestrogen used was (1RS,2RS)-2-p-hydroxyphenyl-2-methyl-1-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-1,2,3,4-tetrahydronaphth-6-ol.

The compound was given subcutaneously as a solution in arachis oil at doses of 2 mg/kg/day and 10 mg/kg/day to two groups of 5 mature rats for a total of 28 days. Further groups of 5 mature rats served as an untreated control group. A further group of 5 mature rats was ovariectomised to serve as another control group. At the end of the treatment period the weights of the uteri of the test and control groups of rats were determined. In addition the femurs were dissected, weighed and their volumes were determined using Archimedes Principle. The femurs were then burned and the residual ash was weighed. From these data, gross femur density and bone mineral density were calculated as follows:

Gross Femur Density = Femur Weight/Femur Volume

Bone Mineral Density = Femur Ash Weight/Femur Volume

The results shown below in Tables I and II demonstrate that at a dose of 2 mg/kg/day subcutaneously the test compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri (90% inhibition of uterine weight) whereas there was no significant inhibition of either bone mineral density or of gross femur density.

TABLE I

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	382 ± 34	
Ovariectomised Controls	111 ± 14	
Test Compound at 2 mg/kg/day s.c.	135 ± 8	91%
Untreated Controls	369 ± 47	
Ovariectomised Controls	99 ± 5	
Test Compound at 10 mg/kg/day s.c.	125 ± 4	90%

EXAMPLE 2

The experiment described in Example 1 was repeated except that the pure antioestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol. This compound was given at a series of doses as a daily intramuscular injection, the compound having been dissolved in a mixture of propylene glycol: ethanol: water: poloxamer 407. The formulation contained 25 mg of test compound, 100 mg of ethanol (96%), 100 mg of water, 20 mg of poloxamer 407 and sufficient propylene glycol to bring the solution to a volume of 1 ml.

The results shown below in Tables III and IV demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas there was no significant inhibition of gross femur density.

TABLE III

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	302 ± 36	
Ovariectomised Controls	70 ± 1.3	
Test Compound (mg/kg)		
0.1	208 ± 17	41
0.3	174 ± 16	55
1	94 ± 9	90
3	103 ± 2	86

TABLE IV

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Untreated Controls	1.523 ± 0.008	
Ovariectomised Controls	1.491 ± 0.006	
Test Compound at (mg/kg)		
0.1	1.528 ± 0.005	0%
0.3	1.528 ± 0.008	0%
1	1.532 ± 0.005	0%
3	1.533 ± 0.005	0%

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EXAMPLE 3

The pure antioestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

Each of a series of selected doses of this compound was dissolved in a mixture of castor oil and benzyl alcohol and given by intramuscular injection to a group of 5 mature rats. The formulation contained 50 mg of the test compound, 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. In each case a second dose was administered two weeks after the first dose. Two weeks after the second dose the weights of the uteri of the test groups of rats were determined. In addition the femurs were dissected and analysed for Gross Femur Density as in Example 1.

A further group of rats, given two injections of castor oil separated by a two week period, served as an intact control group. A further group of rats was ovariectomised to serve as another control group.

The results shown below in Tables V and VI demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas at the two higher test doses there was no significant inhibition of gross femur density.

TABLE V

Treatment	Uterine Weight (mg)	Calculated Inhibition
Intact Controls	318 ± 31	
Ovariectomised Controls	76 ± 4	
Test Compound (mg/rat/dose)		
0.75	202 ± 23	48
1.25	180 ± 15	57
2.5	123 ± 12	81

TABLE VI

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Intact Controls	1.584 ± 0.007	
Ovariectomised Controls	1.521 ± 0.005	
Test Compound (mg/rat/dose)		
0.75	1.562 ± 0.004	35
1.25	1.576 ± 0.004	13*
2.5	1.569 ± 0.007	23*

*This level of inhibition was not statistically significant.

What we claim is:

1. A method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering to a warm-blooded animal an oestrogen and a pure antioestrogen, the oestrogen and pure antioestrogen being present in amounts such that the oestrogen is effective only in selected oestrogen-responsive tissues and is selectively opposed in other oestrogen-responsive tissues.

2. The method as claimed in claim 1 wherein the pure antioestrogen is

N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl-or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;

N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)butyl]phenylpropionamide;

7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3-5(10)-triene-3,17β-diol; or 7α-(9-n-heptylsulphinylnonyl-)oestra-1,3,5(10)-triene-3,17β-diol.

3. The method as claimed in claim 1 wherein the pure antioestrogen is a compound of the formula:

$$NU—A—X—R'$$

wherein NU is 6-hydroxy-2-p-hydroxyphenylnaphth-1-yl and A is $—(CH_{12})_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_5$-(1,4-phenylene)-$(CH_2)_2—$;

or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $—(CH_2)_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2—$;

or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $—(CH_2)_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2—$;

and wherein XR^1 is $—CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $-SR^1$, SOR^1 or $-SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H,-heptafluorohexyl.

4. The method as claimed in claim 1, wherein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)-nonyl]oestra-1,3,5(10)triene-3,17β-diol.

* * * * *

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ATTACHMENT F - COMPILATION

TAB 4

Informa Healthcare USA, Inc.
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New York, NY 10017

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INJECTABLE DRUG DEVELOPMENT

TECHNIQUES TO REDUCE PAIN AND IRRITATION

Edited by

Pramod K. Gupta

and

Gayle A. Brazeau

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11

Cosolvent Use in Injectable Formulations

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Formulators today must routinely deal with progressively more water-insoluble compounds. This makes developing solution dosage forms particularly challenging. Identification and utilization of clinically acceptable excipients—as well as scalable methods to formulate solubilized compounds—has been, and continues to be, a subject of great importance to formulation scientists.

One of the most common approaches used in parenteral formulation of water-insoluble compounds is the use of organic cosolvent systems. These systems utilize certain organic solvents combined with physiologically compatible aqueous solutions. These systems are primarily used to provide higher solubility for poorly water-soluble compounds, which allows for these compounds to be administered in solution form. The ability to administer compounds in solution form by the parenteral route eliminates particle size considerations and dissolution barriers, generally providing for complete bioavailability of poorly absorbed and/or highly metabolized compounds by avoiding hepatic first-pass effects. Cosolvents may also be used to improve the chemical stability of compounds prone to hydrolytic or photolytic degradation, or occasionally to decrease the aqueous solubility of a given compound when administered intramuscularly. There are numerous products on the market for parenteral use that utilize cosolvent systems. Table 11.1 lists a number of these products with their cosolvent compositions (Trissel 1996).

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Table 11.1. Cosolvent Composition of Selected Marketed and Investigational Parenteral Products (Trissel 1996)

General Name	Trade Name	Manufacturer	Route	Cosolvent Composition
Digoxin	Lanoxin®	Burroughs Wellcome	IM, IV	40% PG, 10% EtOH, pH 6.8
Trimethoprim-sulfamethoxazole	Septra®	Glaxo Wellcome	IV	40% PG, 10% EtOH, 0.3% diethanolamine, 1% BA
Phenytoin	Dilantin®	Parke-Davis	IV	40% PG, 10% EtOH, pH 12
Diazepam	Valium®	Roche	IM, IV	40% PG, 10% EtOH, 1.5% BA
Lorazepam	Ativan®	Wyeth-Ayerst	IV	41% PG, 9% PEG 400, 2% BA
Pentobarbital	Nembutal®	Abbott	IV	40% PG, 10% EtOH, pH 9.5
Chlordiazepoxide HCl	Librium®	Roche	IM	20% PG, 1.5% BA
Etoposide	VePesid®	Bristol-Myers Squibb	IV	65% PG, 30.5% EtOH, 8% Tween 80®, 3% BA
Miconazole	Monistat®	Janssen	IV	11.5% Cremophor® EL
Secobarbital sodium	Tubex® cartridge	Wyeth-Ayerst	IM, IV	50% PEG, pH 9.5-10.5
Nitroglycerin	Nitro-Bid®	Hoechst Marion Roussel, Abbott	IV	70% EtOH, 4.5% PG
Multivitamins	M.V.I.®-12	Astra	IV	30% PG, 1.6% Tween 80®, 0.028% Tween 20®
Investigational Compounds				
9-Amino-camptothecin			IV	2% DMA, 50% PEG 400
Bryostatin			IV	60% PEG 400, 30% dehydrated alcohol, 10% Tween 80®
Diaziqoune			IV	10% DMA, pH 6.5

Abbreviations: IV: Intravenous; IM: Intramuscular; PG: propylene glycol; PEG: polyethylene glycol; EtOH: ethanol; BA: benzyl alcohol; DMA: dimethylacetamide

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In terms of solubility enhancement, the use of cosolvents is one of the most powerful methods available to formulators. The solubilizing potential of cosolvents compares very favorably to other generally accepted techniques used for solubilization of water-insoluble compounds, including micellar solubilization, complexation, prodrugs, and salt formation. In many instances, cosolvents may be the technique of choice for parenteral applications given that (1) micellarization using surface active agents could likely be problematic from an irritation/toxicity perspective, (2) suitable complexing agents may not be appropriate for the compound of interest, (3) formation of either prodrugs or salt forms may not be possible for a given compound, and (4) appropriate cosolvent vehicle selection may reduce tissue irritation.

Numerous factors must be considered before a cosolvent system is selected. Ideally, the water-miscible organic solvent must be nontoxic; should cause minimal or no hemolysis, irritation, or muscle damage on injection; and should be nonsensitizing. The solvent should also be devoid of any inherent pharmacological activity that may interfere with that of the drug itself. Obviously, the cosolvent formulation should provide the desired pharmaceutical/biopharmaceutical profiles and should allow for a reasonable shelf life following manufacture. These solvents are rarely used undiluted due in part to their inherent properties, for example, viscosity and tonicity. Therefore, the physicochemical properties of the cosolvent system must also be considered (viscosity, pH, lipophilicity), as well as the safety of the various solvents used. A summary of some of the physicochemical properties of common solvents used in parenteral formulations is given in Table 11.2.

Ideally, it is best to select and use solvents that would maximize the solubility of the compound. Maximizing the solubility of a compound in a particular cosolvent system would result in lower total levels of the nonaqueous solvent(s) being administered to the patient, thereby lowering the chance for potential side effects. This will also reduce the chance of precipitation of the solution on administration, which is a major concern when administering doses via the IV route. There are numerous reports in the literature regarding cosolvency theory, and potentially useful methods based on various physicochemical properties for predicting solubilities in various solvents and solvent mixtures, as well as the effects of cosolvent systems on the physicochemical properties of compounds solubilized in them (Hildebrand 1916, 1917, 1919; Hildebrand and Scott 1950; Higuchi et al. 1953; E[illegible]monson and Goyan 1958; Moore 1958; Paruta et al. 1962, 1964; Gorman Hall 1964; Fedors 1974; Martin et al. 1980, 1982; Yalkowsky et al. 1976 tin and Miralles 1982; Yalkowsky and Roseman 1981; Rub[illegible] Yalkowsky 1985, 1987; Yalkowsky and Rubino 1985; Rubino et al bino 1987, 1990; Rubino and Berryhill 1986; Rajagopalan et a[illegible] son et al. 1993; Bendas et al. 1995; Darwish and Bloomfield 1995;

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Table 11.2. Physicochemical Parameters for Commonly Used Organic Solvents (at 25°C)

Solvent	Molecular Weight (g)	Dielectric Constant, ε	Solubility Parameter, δ (cal/cm^3)	Density (g/mL)	Boiling Point (°C)	Interfacial Tension (dyne/cm)
DMF	73	36.7[a]	12.1[a]	0.94[b]	153[b]	6.9[a]
DMA	87	37.8[a]	10.8[a]	0.94[b]	165[b]	4.6[a]
PEG 400	380–420	13.6[a]	11.3[a]	1.13[c]	—	11.7[a]
EtOH	46	24.3[a]	12.7[a]	0.79[b]	78.5[b]	0.5[a]
PG	76	32.0[a](20°)	12.6[a]	1.04[b]	189[b]	12.4[a]
Benzyl alcohol	108	13.1[d]	—	1.04[b]	204.7[b]	—
Glycerin	92	42.5[a]	17.7[a]	1.26[b]	290[b] (dec)	32.7[a]
Water	18	78.5[a]	23.4[a]	1.00[b]	100[b]	45.6[a]
DMSO	78	46.7[a]	—	1.10[a]	189[a]	—

Dec: decomposition
a: Rubino and Yalkowsky (1987)
b: Budavari (1989)
c: Wade and Weller (1994)
d: Weast and Tuve (1967)

al. 1995). Therefore, this chapter focuses more on the conventional solvents and use levels encountered in parenteral dosage forms, safety/toxicity of these cosolvents, and ways in which to minimize cosolvent-related side effects.

Commonly Used Solvents

There are numerous solubilizing agents available to formulators, particularly for use in preclinical work. However, the solubilizers available to formulators for use in humans are considerably more limited, usually on the basis of available safety/toxicity data. The most common organic solvents encountered in cosolvent systems for human clinical/commercial use include PEG 400, PG, glycerol, and ethanol. In general, these solvents are considered to possess a low order of toxicity. This is essential, and obvious, since parenteral administration can result in fairly large amounts of these solvents being placed in the body over a short period of time.

Although the solvents used in cosolvent formulations are generally considered to be of low orders of toxicity, there have been numerous reports of adverse effects related to the vehicles themselves (Carpenter 1947;

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Wang and Kowal 1980; Singh et al. 1982; Smith and Dodd 1982; American Academy of Pediatrics Committee on Drugs 1985; Demey et al. 1988; Golightly et al. 1988; Lolin et al. 1988; Andersen et al. 1989; Napke and Stevens 1990; Doenicke et al. 1992; Rhodes et al. 1993; Windebank et al. 1994; Farooqui et al. 1995). These adverse effects may result from administration of high doses of a single cosolvent formulation or concurrent administration of different formulations that contain similar cosolvent systems. It is important to note that any side effects associated with these usually well-tolerated solvent systems may be much more serious when administered to pediatric patients (Sweet 1958; Martin and Finberg 1970; Brown et al. 1982; Gershanik et al. 1982, Lorch et al. 1985; MacDonald et al. 1987; Huggon et al. 1990). Summaries of single dose LD_{50} values and reported human exposures for organic solvents commonly used in parenteral formulations are presented in Tables 11.3 and 11.4. It has been suggested that these solvents should be used at levels of no more than 25 percent of the LD_{50} value in order to avoid any unwanted pharmacological or toxicological effects, although they may be used at considerably higher concentrations depending on the purpose of the study (Bartsch et al. 1976). Others recommend that certain organic solvents should not be used in pharmacological or toxicological studies at concentrations above 10 percent (Singh et al. 1982). The following discussion addresses the reported safety/toxicity data reported in the literature for many of the solvents used in parenteral formulations.

Polyethylene Glycols

PEGs are polymers of ethylene oxide with the general formula

$$HO\text{-}CH_2\text{-}(CH_2\text{-}O\text{-}CH_2)_n\text{-}CH_2OH$$

where *n* represents the number of oxyethylene groups. The PEGs are designated by a numerical value, which is indicative of the average molecular weight for a given grade. Molecular weights below 600 are liquids, and molecular weights above 1,000 are solids at room temperature. These polymers are readily soluble in water, which make them quite useful for parenteral dosage forms. Only PEG 400 and PEG 300 are utilized in parenteral products, typically at concentrations up to 30 percent (v/v) (Wade and Weller 1994). These polymers are generally regarded as nontoxic and nonirritating. There are numerous reviews regarding the pharmaceutical and toxicological properties of these polyols (Smyth et al. 1950; Rowe and Wolf 1982).

PEGs have been shown to possess marked central nervous system (CNS) effects following IV administration (Lockard and Levy 1978; Lockard et al. 1979). Klugmann and coworkers (1984) found that pretreatment of mice with 15 percent PEG 400 at 20 mL/kg given three hours prior to the

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Table 11.3. Single Dose LD_{50} Values in Rodents for Various Organic Solvents Commonly Encountered in Parenteral Formulations

	Parenteral LD_{50} Values (g/kg) for Various Species						
	Mouse			Rat			References
Solvent	ip	sc	iv	ip	sc	iv	
PEG 300				17		7.1	Rowe and Wolf (1982); Carpenter and Shaffer (1952)
PEG 400	13.2–14.5		8.6	12.3–14.7		4.7–7.3	Budden et al. (1978); Rowe and Wolf (1982); Bartsch et al. (1976)
PG	9.6–11.4	18.5	6.6–8.0	6.7–13.5		6.4–6.8	Davis and Jenner (1959); Bartsch et al. (1976); Latven and Molitor (1939)
EtOH	1.2–3.2	8.3–10.5	2.0–2.5	4.1–5.0		1.4–1.8	Latven and Molitor (1939); Bartsch et al. (1976); Trèmolières and Lowy (1964)
Glycerin	8.7–9.0	0.09–10.0	4.3–6.2	8.7	0.10	5.6	Budden et al. (1978); Latven et al. (1939); Anderson et al. (1950); Bartsch et al (1976); Tao et al. (1983)
DMA	2.3–3.5		2.5–3.0	2.8–4.4	5.3	2.6–4.8	Davis and Jenner (1959); Sherman et al. (1978), Bartsch et al. (1976); Auclair and Hameau (1964); Wiles and Narcisse (1971); Thiersch (1962)
DMF	1.2–5.9		2.8–3.5	4.4–6.1	6.1	2.8–5.7	Davis and Jenner (1959); Bartsch et al. (1976); Auclair and Hameau (1964); Wiles and Narcisse (1964); Theirsch (1962)
Cremophor® EL			2.6-4.2				BASF (1988)
DMSO	2.5–13.9		3.4–7.6	8.2–10.1		5.4–8.1	Bartsch et al (1976); Wiles and Narcisse (1971); Willson et al. (1965)
BA	1.0		< 0.52			0.05–0.08	McCloskey et al. (1986);
0.9%			> 52			> 41.6	Kimura et al (1971)

Table 11.4. Human Exposures to Selected Organic Solvents Commonly Encountered in Parenteral Formulations

Solvent	Dose	Route	Administered As	Clinical Observations	References
DMSO	1 gm/kg	IV	10 to 40% solutions	Hemoglobinuria observed following administration of 20–40% solutions, which cleared within 2–3 h post-	

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Table 11.4. Human Exposures to Selected Organic Solvents Commonly Encountered in Parenteral Formulations

Solvent	Dose	Route	Administered As	Clinical Observations	References
DMSO	1 gm/kg	IV	10 to 40% solutions	Hemoglobinuria observed following administration of 20–40% solutions, which cleared within 2–3 h post-infusion; No indication of short-term nephrotoxicity following evaluation of beta-2-microglobulin.	Bennett and Muther (1981)
DMA	100–610 mg/kg/day for 2–5 days	IV	10% solution administered over 5 to 10 min	Dose-related side effects included nausea and vomiting within 14 h of administration, anorexia; liver toxicity as indicated by increased SGOT levels (5–7 days after start of therapy), returning to normal within 2–5 days after achieving peak levels; altered CNS function—depression, lethargy, confusion, hallucinations—returning to normal within several days after therapy; hypotension and high fever observed at high doses.	Weiss et al. (1962)
Cremophor® EL	2–20 mL	IV	Incremental doses administered every 4 min, each over a 30 sec period	Small transient fall in blood pressure and rise in pulse rate following each dose. No marked changes in respiratory rate and no consistent alterations in central venous pressure observed. Statistically significant effects only observed after the 20 mL dose.	Savege et al. (1973)
PG	5–21 g/day	IV	Administered as an infusion over a 4 h period	No alterations in plasma osmolality, free hemoglobin, or haptoglobin.	Speth et al. (1987)
BA	130–405 mg/kg/day	IV	0.9% BA (bacteriostatic concentration)	*Neonates:* Progressive metabolic acidosis, bradycardia, gasping respirations, seizures, and subsequent death in low birth weight neonates. *Adults:* No clinically significant changes observed in healthy males (hematology, vital signs, electrocardiograms, EEG, laboratory parameters), shown to be as well tolerated as same formulation preserved with parabens.	Brown et al. (1982); Santiero (1989); Evens (1975); Gershanik (1982); Novak et al. (1972)

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administration of adriamycin (a potent antineoplastic agent) resulted in alleviation of some of the toxicity associated with the compound. They also showed that PEG 400 decreased both the acute high-dose and chronic low-dose adriamycin-associated lethality, as well as afforded protection against cardiomyopathy—one of the dose-limiting side effects observed in patients. Additionally, PEG 400 did not interfere with the antitumor activity of the compound. Laine et al. (1995) reported nephrotoxicity due to PEG 400 secondary to chronic high-dose intravenous administration of lorazepam.

PEG 300, PEG 400, and PEG 4000 administered intraperitoneally have been shown to have adverse effects on rat gastrointestinal physiology (Cho et al. 1992). The PEGs caused a decrease in gastric mucosal blood flow (GMBF) as well as gastric secretory function. They also exacerbated ethanol-induced gastric damage in a dose-dependent manner. The gastric damage appeared to be inversely related to molecular weight (PEG 300 > PEG 400 > PEG 4000). Other investigators have shown that the PEGs affect cardiovascular and autonomic systems. PEG 300, PEG 400, and PEG 600 administered intravenously and intra-arterially to dogs produced a dose-dependent enhancement of the blood pressure response to epinephrine and acetylcholine (Heilman et al. 1972). PEG 300 has also been implicated as the causative agent responsible for fatalities and near fatalities due to severe metabolic acidosis in patients (Sweet 1958).

Smith and Cadwallader (1967) evaluated the behavior of erythrocytes in PEG–water solutions. They observed that solutions of PEG 300 in water were hemolytic. They also observed that solutions of water–PEG 400 or water–PEG 600 could afford some protection from hemolysis. They concluded that polyethylene glycols could protect both rabbit and human erythrocytes in the order (MW): 200 < 300 < 400 < 600. The ability of the PEGs to contribute to the tonicity of the resulting solutions was also observed to be inversely related to molecular weight—low molecular weight PEGs contributed to tonicity, and the higher molecular weight species did not. They suggested that this lack of contribution to tonicity was related to decreased membrane permeability of the higher molecular weight species.

Nishio and coworkers (1982) investigated the effects of PEG 300 and PEG 400 on erythrocytes. They showed that incubation of erythrocyte suspensions in the presence of PEG–saline solutions resulted in the release of potassium ions and hemoglobin. They found that hemolysis and potassium ion loss decreased with increasing concentrations of PEGs, and that no loss was observed in iso-osmotic and hyperosmotic concentrations following a 2 min incubation time. However, longer incubation times (through 2 h) resulted in potassium loss and hemolysis in iso-osmotic and hyperosmotic solutions (PEG 300 > PEG 400).

Fort and coworkers (1984) evaluated the hemolytic potentials of mixtures of ethanol and water or saline with PEG 400 by both in vitro and in vivo methods. They showed that a PEG 400:ethanol:water mixture of 3:2:5 resulted in no hematuria in vivo in rats, while partial hemolysis was

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observed in vitro using dog blood. All other mixtures resulted in hematuria and hemolysis. Reed and Yalkowsky (1985) reported that the in vitro hemolytic LD_{50} value (total volume percent cosolvent required to produce 50 percent hemolysis of healthy erythrocytes) for PEG 400 was 30.0 (total volume percent). This indicated that red blood cells were relatively tolerant of PEG 400.

Propylene Glycol

PG, a dihydroxy alcohol, is one of the more common solvents encountered in pharmaceutical cosolvent formulations, for both parenteral and nonparenteral dosage forms. PG is generally regarded as nontoxic. It is more hygroscopic than glycerin and has excellent solubilizing power for a wide variety of compounds. In addition, it has excellent bacteriocidal and preservative properties (Heine et al. 1950).

PG is metabolized to carbon dioxide and water via lactic and pyruvic acid intermediates; therefore, it is not prone to the severe toxicities associated with the use of other glycols, such as ethylene glycol (Huff 1961; Lehman and Newman 1937a, b). It is approximately one-third as intoxicating as ethanol (Seidenfeld and Hanzlik 1932). It is a generally recognized as safe (GRAS) listed material (*Federal Register* 1982). The World Health Organization (WHO) has established an acceptable daily intake (ADI) at 25 mg/kg body weight (FAO/WHO 1974).

When used in large concentrations, PG has been associated with marked hyperosmolality (Bekeris et al. 1979; Glasgow et al. 1983; Flinger et al. 1985); metabolic acidosis due to the formation of lactic acid (Kelner and Bailey 1985; Pesola et al. 1990); CNS depression (Arulanatham and Genel 1978; Lolin et al. 1988); intoxication (Cate and Hendrick 1980; Demey et al. 1984); augmentation of muscle twitch induced by benzodiazepines (Driessen et al. 1985); contact dermatitis in sensitive individuals (Fisher 1995); cerebral ischemia (Drummond et al. 1995); renal compromise (Levy et al. 1995); and cardiovascular side effects, including hypotension, bradycardia, atrial and ventricular conduction abnormalities (Gross et al. 1979), as well as allergic reactions leading to hypersensitivity myocardltis. These complications can be particularly serious in infants. Other investigators have suggested that the main toxic effect of PG is depression of the CNS (Martin and Finberg 1970; Zarolinski et al. 1971). Additionally, there have been numerous reported side effects following nitroglycerin (Hill et al. 1981; Col et al. 1985; Demey et al. 1988) and etomidate therapies (Morgan et al. 1977; Doenicke et al. 1982; Fellows et al. 1983; Bedichek and Kirschbaum 1991; Doenicke et al 1994; Moon 1994; Levy et al. 1995; Van de Wiele et al. 1995).

There are numerous reports regarding the use of PG based on safety/toxicity data (Seidenfeld and Hanzlik 1932; Braun and Cartland 1936;

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Weatherby and Haag 1938; Morris et al. 1942; Dominguez-Gil and Cadorniga 1971a, b; Zarolinski et al. 1971; Ruddick 1972). Seidenfeld and Hanzlik (1932) reported single fatal doses of PG administered intramuscularly and intravenously to rats and rabbits. No symptoms were reported in rats and rabbits until IM doses exceeded 6.3 to 7.4 g/kg. Increased respiratory rate, loss of equilibrium, depression, and subsequent coma and death were observed. IM fatal doses were 14 g/kg and 7 g/kg in rats and rabbits, respectively. IV fatal doses were 16 g/kg and 5 g/kg in rats and rabbits, respectively. Braun and Cartland (1936) indicated that the minimum fatal IV dose to rats was 18.9 g/kg. They also noted that administration of undiluted PG destroyed the veins, making subsequent administration very difficult, and that PG was better tolerated than glycerol by IM and subcutaneous (SC) routes. There are numerous reports of convulsions following intraperitoneal (IP) administration in mice (Lampe and Easterday 1953; Braun and Cartland 1936).

The hemolytic potential of PG has been well documented by numerous investigators (Weatherby and Haag 1938; Randolph and Mallery 1944; Potter 1958; Brittain and D'Arcy 1962). Weatherby and Haag (1938) evaluated hemolysis of various PG–saline mixtures using an in vitro method. They observed hemolysis in cases where the PG concentration was greater than or equal to 0.14 M. They believed that PG permeated the erythrocytes so rapidly that it did not exert an appreciable osmotic effect on the cell. Brittain and D'Arcy (1962) later evaluated hematologic effects following IV administration of PG to rabbits. The rabbits were given a single dose of 4 mL/kg of either 12.5, 25, or 50 percent PG in normal saline via the marginal vein. They observed no effect on red blood cell count, total white cell count, or hemoglobin concentration. However, they observed a marked decrease in clotting times with an associated increase in platelet count. They also reported no effect of the PG concentrations on fragility of the red blood cell membranes. Fort and coworkers (1984) evaluated hemolysis due to PG–containing formulations by both in vitro (using dog blood) and in vivo (rats) methods. The compositions evaluated ranged from 10 to 60 percent PG, 0 to 40 percent ethanol diluted with either water or 0.9 percent NaCl. All of these formulations caused hemolysis in vitro. However, only the 1:3:6 PG:ethanol:saline mixture resulted in no hematuria when administered to rats, while all other compositions caused hematuria. Reed and Yalkowsky (1985) determined the in vitro red blood cell hemolytic LD_{50} for PG to be 5.7, which indicated that it was fairly hemolytic relative to the other solvents tested. Only glycerin and DMSO were found to be more hemolytic than PG by this method.

There has been some work conducted in humans evaluating hemolysis following administration of PG–containing solutions. In the work by Speth and coworkers (1987) evaluating the pharmacokinetics of PG in humans, they reported no alterations in plasma osmolality, free hemoglobin or haptoglobin following IV infusion (4 hour) of total PG levels ranging

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from 5.1 to 21.0 g/day, with C_{max} values up to 425 μg/mL. They found that PG exhibited nonlinear pharmacokinetics and that clearance was dose and concentration dependent (saturable) in the dose range of 3 to 15 g/m^2, with a mean elimination half-life of 2.3 hours. There were no signs of metabolic acidosis or changes in osmolality in these patients, even though the plasma levels were in the range where these effects had been previously reported. The absence of effects could have been due to the slow rate of administration, or to the presence of additional excipients in the formulation (soybean lecithin, 0.5 mg/mL; PEG 300, 75 mg/mL; and PG, 25 mg/mL).

Ethanol

Ethanol (EtOH) is typically used as a solvent in pharmaceutical applications; however, it also possesses some antimicrobial properties. Parenteral products typically use 95 percent or 96 percent rather than absolute alcohol at use levels up to 50 percent. However, these levels typically are associated with pain on injection. EtOH is a component of commercial parenteral formulations for such compounds as diazepam, phenytoin, and digoxin. However, parenteral administration of EtOH-containing formulations has been associated with various complications. Such cases have been reported with IV administration of nitroglycerin (Shook et al. 1984). Intoxication was observed in several elderly patients receiving high doses of IV nitroglycerin. These patients received up to 20.7 mL EtOH/h during their course of therapy, which exceeded the average adult rate of EtOH metabolism of 10 mL/h (Hill et al. 1981). These effects would likely be more pronounced in patients with compromised hepatic function and myocardial ischemia or low cardiac output. Others reported that rapid infusion of EtOH may be cardiotoxic, in that it possesses both atrial and ventricular arrhythmogenic properties, as well as negative inotropic effects (Ahmed et al. 1973; Delgado et al. 1975; Child et al. 1979).

The toxicity of EtOH has been well documented (Lehman 1937b; MacGregor et al. 1964; Maling 1970; Wiberg et al. 1970). It is fairly toxic when administered intraperitoneally. Heistand (1952) reported that mortality increased with increasing concentrations of ethanol injected intraperitoneally when the amount of alcohol was held constant. Wiberg et al. (1970) showed that high concentrations of EtOH (20 percent w/v) produced a fatal chemical peritonitis. Maling (1970) determined the IV LD_{50} to be 2.0 g/kg and 4.2 g/kg in mice and rats, respectively. The LD_{50} following subcutaneous administration to mice was determined to be 8.3 g/kg. Lethal doses in dogs following subcutaneous and IV administration were found to be 6.0 to 8.0 g/kg and 5.4 g/kg, respectively. A comprehensive list of effects of EtOH as a function of blood level in humans is also listed.

EtOH is a well-known CNS depressant. The result of ingestion is intoxication, with associated loss of muscle coordination, slurred speech, or

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more severe effects including lethargy, stupor, coma, respiratory depression, and possibly death. These same effects have been observed following IV administration. There are also reports of fatalities in neonates and children following IV administration of ethanol (Gettler and St. George 1935; Jung et al. 1980).

Fort et al. (1984) evaluated hemolysis due to various EtOH–containing concentrations ranging from 30 to 40 percent diluted in either water or 0.9 percent NaCl. They found that all mixtures caused hemolysis in vitro; however, the 3:7 EtOH:0.9 percent NaCl caused no hematuria in vivo. Reed and Yalkowsky (1985) determined the in vitro hemolytic LD_{50} to be 21.2 (total volume percent) for EtOH, indicating that it was fairly well tolerated by erythrocytes.

Glycerin

Glycerin (glycerol) is one of the oldest and most widely used excipients in pharmaceutical products. It is a clear, colorless liquid that is miscible with water and alcohol. Glycerol is hygroscopic, stable to mild acidic and basic environments, and can be sterilized at temperatures up to 150°C. It is well known as both a taste masking and cryoprotective agent, and as an antimicrobial agent. It has good solubilizing power and is a commonly used solvent in parenteral formulations. It is considered to be one of the safest excipients used since it is metabolized to glucose or to substances that are involved with triglyceride synthesis or glycolysis (Frank et al. 1981). It is a GRAS–listed excipient and is typically used at levels of up to 50 percent in parenteral formulations (Wade and Weller 1994).

Glycerol is a naturally existing sugar alcohol that is endogenous to humans. It is broken down to triglycerides, glucose by the gluconeogenesis pathways or to pyruvate by the glycolytic pathway. It has also been used in parenteral formulations as an energy source (Fairfull-Smith et al. 1982; Jones 1982; Tao et al. 1983). Glycerol has been used clinically to treat Reye's syndrome (Mickell et al. 1977), traumatic intracranial hypertension (Wald and McLaurin 1982), brain edema in stroke patients (Tourellotte et al. 1972; Macdonald and Uden 1982), reduce intraocular pressure in cataract surgery (Guindon et al. 1981), and improve hearing loss associated with Meniere's disease (Angleborg et al. 1982; Lunsford 1982).

Somewhat surprisingly, there are numerous reports of adverse effects following administration of this endogenous substance, including hemolysis, hemoglobinuria, renal damage, hyperglycemia, hyperosmolality, and convulsions. A fairly extensive review of adverse reactions resulting from IV administration of glycerol is given by Frank et al. (1981). There are reports that glycerol is approximately 20 times more toxic when administered intraperitoneally or subcutaneously, as compared to the IV route (Tao et al. 1983). However, some of this sensitivity to IP administration may be related to strain differences (Uche et al. 1987).

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Patients with acute cerebral infarction received 10 percent glycerol solutions administered daily for 7 to 10 days over a 6 h period (Welch et al. 1974). In these reports, there were no reported side effects even with prolonged administration, with the exception of "transient hemoglobinuria" in cases where the glycerol content of the solutions was 30 percent or greater. However, side effects, including hematuria, hemoglobinuria, and hemolysis have been reported by other physicians (Cameron and Finchk 1956; Potter 1958; MacCannel 1969; Hagnevik et al. 1974). Hagnevik and coworkers (1974) reported that administration of 20 percent glycerol in normal saline to three patients during intracranial surgery resulted in either (1) no effect; (2) massive hemolysis and hemoglobinuria that dissipated quickly; or (3) severe hemolysis and hemoglobinuria, as well as serious renal damage. However, the rates of administration that resulted in these side effects were more rapid—60 g/15 min, 70 g/30 min, and 80 g/60 min—than those used previously (wherein the dose was infused over 6 h). The resulting hemolytic side effects were most likely due to the rapid rate of administration.

Early studies by Smith (1950) reported that glycerol did not have a direct toxic effect on erythrocytes, which seems reasonable since it is used as a cryoprotectant to prevent hemolysis during freeze-thaw studies. These studies showed that no hemolysis resulted from diluting blood with 30 percent glycerol in Ringer's solution (1:1 ratio), followed by freezing at -70°C. No hemolysis was reported for up to 8 weeks. The same results were obtained when the glycerol solution was prepared in normal saline. It should be noted that the absence of hemolysis could have been in part due to the presence of the various salt solutions.

However, glycerol is known to permeate red blood cells rapidly, causing fluid influx and subsequent hemolysis (Tourtellotte et al. 1972). Early work by Husa and Adams (1944) showed that glycerol was hemolytic even at iso-osmotic concentrations, and that the addition of NaCl reduced its hemolytic potential. Similar findings were observed by other investigators (Hammarlund and Pedersen-Bjergaard 1961; Zanowiak and Husa 1959). Cadwallader and coworkers (1963, 1964) calculated the isotonic coefficients for glycerin solutions and showed that the addition of increasing amounts of NaCl afforded some protection from hemolysis, again indicating that the degree of hemolysis resulting from IV administration was dependent on the tonicity of the glycerol-saline solutions. Reed and Yalkowsky (1985) reported that glycerol was the most hemolytic of the 15 organic solvents evaluated, with a hemolytic LD_{50} value of 3.7 (total volume percent).

Cremophors

The cremophors are water soluble polyoxyethylene derivatives of castor oil that are nonionic surface-active agents. Several grades are used in pharmaceutical formulations, particularly Cremophor® EL (Polyoxyl 35 castor oil) and Cremophor® RH40 (Polyoxyl 40 hydrogenated castor oil).

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However, Cremophor® EL is the grade used for parenteral applications in humans. These substances are mixtures of hydrophilic and hydrophobic components, composed primarily of ricinoleic acid esters and fatty acid esters of glycerol/polyglycol and polyglycols. The main component of Cremophor® EL is glycerol–polyethylene glycol ricinoleate. Cremophor® EL is a pale yellow, oily liquid that forms clear solutions when mixed with water. It is also readily soluble in water-alcohol mixtures. It can be heat sterilized at a temperature of 120°C for 30 min, but it may be prone to hydrolysis if heated in the presence of strong acid or basic substances (BASF 1988).

The most common adverse effect reported following administration of cremophor-containing formulations are severe reactions related to histamine release. The cremophors have been implicated in anaphylactoid reactions, typically following rapid IV injections (Dye and Watkins 1980; Hopkins 1988; Reynolds and Aronson 1992; Dorr 1994). Hopkins (1988) and Reynolds and Aronson (1992) reported anaphylactoid responses following IV administration of vitamin K in a cremophor solution. However, Havel et al. (1987) reported that this formulation was well tolerated in patients. Patients treated with miconazole preparations containing cremophors have also presented unusual serum lipoprotein patterns, hypercholesterolemia, and hypertriglyceridemia (Golightly et al. 1988). There are numerous reports in the literature relating to anaphylactic reactions following administration of althesin and propanidid (Watkins 1979; Watkins et al. 1976, 1978; Forrest et al. 1977; Dye and Watkins 1980). Windebank and coworkers (1994) reported that cremophor was a potential neurotoxic agent since a total dose 0.1 percent (v/v) produced axonal swelling and degeneration of dorsal root ganglion neurons, and 0.001% (v/v) produced demyelination in vitro.

Earlier studies in dogs showed that Cremophor® EL caused histamine-like responses accompanied by marked hypotension in dogs. Studies were subsequently conducted to evaluate whether these cardiorespiratory effects occurred in normal human volunteers following IV administration of Cremophor® EL (Savege et al. 1973). Subjects were given incremental dose volumes ranging from 2 to 20 mL (administered every 4 min, each over a 30 sec period). Following administration of each dose of Cremophor® EL, there was a small, transient reduction in blood pressure and a rise in pulse rate. However, none of these changes were statistically significant, with the exception of the high dose (20 mL). These studies showed no marked change in respiratory rate or pattern and no consistent alterations in central venous pressure.

Benzyl Alcohol

Benzyl alcohol (BA) is a bacteriostatic agent used against gram-positive bacteria, yeasts, molds and fungi, and it is commonly used as a preservative in parenteral products. It also has anesthetic properties at levels of

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approximately 1 percent. The bacteriostatic activity is reduced in the presence of nonionic surface-active agents. It also has good solubilizing power, and is typically used in concentrations up to 2 percent as a preservative and up to 5 percent as a solvent. BA is commonly found as a preservative in intravascular flush solutions at a level of 0.9 percent. The WHO has established an ADI of 5 mg/kg (FAO/WHO 1980).

BA is metabolized in the body to benzaldehyde via alcohol dehydrogenase and subsequently to benzoic acid via aldehyde dehydrogenase. However, the reported toxicities, particularly acute toxicity, appeared to be associated with the parent compound and not the metabolite. Studies using the enzyme inhibitors pyrazole (alcohol dehydrogenase inhibitor) and disulfiram (aldehyde dehydrogenase inhibitor) showed that marked lethality was observed with increased plasma levels of BA, and not with benzaldehyde levels (McCloskey et al. 1986). These elimination pathways are saturable, indicating that additional amounts of BA would likely result in significantly higher plasma levels once the metabolic capacity has been exceeded.

Toxicity studies in adult and neonatal mice were conducted following IP administration of single doses of BA ranging from 500 to 1500 mg/kg administered in maximum dose volumes of 0.28 mL and 0.07 mL for adult and neonates, respectively (McCloskey et al. 1986). The data showed that the acute LD_{50} for BA was 1,000 mg/kg for both adult and neonatal groups after 4 h. However, deaths were observed in the adult group at day seven, resulting in a revised LD_{50} value of 650 mg/kg.

Macht (1920) reported on the toxicity of intravenously administered alcohols to cats. He reported that BA was approximately 8 times more toxic than ethanol, with lethal doses of 5.0 mL/kg and 0.6 mL/kg, respectively. Kimura et al. (1971) investigated the parenteral toxicity data for BA, finding that a 0.9 percent solution was quite safe following administration of 1 mL/kg to dogs and monkeys. They found no changes in complete blood counts or blood chemistry values. They also reported that rapid IV injections of 0.9 percent BA could be safely given to mice to a maximum volume of 50 mL/kg. Kimura et al. (1971) reported that BA was significantly more toxic than ethanol when administered at the same doses to mice, rats, and dogs.

Most of the early studies evaluating the toxicity of BA indicated that it was a relatively harmless substance with regard to humans. However, numerous incidences of BA toxicity following parenteral administration of solutions containing levels of only 0.9 percent have subsequently been reported in the literature. Reported toxicities of BA include hypersensitivity reactions, hemolysis, sedation, dyspnea, loss of motor function, and possible death. Toxicity has been reported following exposure to catheter flush solutions containing very low levels of BA (0.9 percent). However, the most severe toxic effects, including death, have occurred in neonates (Gershanik et al. 1982; Jarvis et al. 1983; Benda et al. 1986; Wilson et al. 1986; Hiller et

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al. 1986; González de la Riva Lamana 1987; and Santeiro 1989). Its use has been implicated as the causative agent in "gasping syndrome" in neonates (Gershanik et al. 1982). This syndrome is characterized by a progression of symptoms from gradual neurological deterioration, severe metabolic acidosis, gasping respiration, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, to cardiovascular collapse.

Several investigators have reported that BA caused hemolysis of erythrocytes (Kimura et al. 1971; Ohmiya and Nakai 1978; McOrmond et al. 1980). Ohmiya and Nakai (1978) later reported that the hemolytic potential of BA was time, dose, and temperature dependent. They also showed that the concentration of erythrocytes had a profound effect on the amount of hemolysis observed. They determined that the hemolytic in vitro LD_{50} using their method was 100 mM following incubation for 60 min at 37°C. Kimura and coworkers (1971) evaluated blood chemistry profiles following administration of 0.9 percent solutions of BA to rats, mice, and dogs, and determined that these concentrations were completely nonhemolytic in dogs and monkeys at a dose level of 1 ml/kg. They determined that the lethal IV dose of 0.9 percent BA in dogs was 0.83 to 1.06 g/kg. Additionally, they showed that slow IV administration of up to 40 mL/kg 0.9 percent BA to rats resulted in no fatalities.

Amide Solvents

N,N-Dimethylacetamide

N,N-dimethylacetamide (DMA) is a clear liquid that is used as a solvent for poorly water-soluble compounds in the pharmaceutical industry. It is miscible with water and alcohols and very soluble in organic solvents and mineral oil. It is mildly hygroscopic, stable to heat and hydrolysis, and has a low vapor pressure. DMA is sequentially metabolized to monomethylacetamide, and subsequently to acetamide (Kim 1988).

Caujolle et al. (1970) reported "maximum doses never fatal" (MDNF) and "minimum doses always fatal" (MDAF), for DMA as 2.5 g/kg and 6.0 g/kg for mice, and 2.5 g/kg and 3.7 g/kg for rats, respectively. They also reported 24 h LD_{50} values for DMA as 4.19 g/kg and 3.84 g/kg for mice and rats, respectively. Testicular injury was reported following a single IP dose of up to 3 g/kg DMA. However, subchronic administration of 36 IP injections at low doses did not show any toxicity or histopathology.

Wiles and Narcisse (1971) evaluated the parenteral toxicity of DMA by IV and IP administration to mice and rabbits. They observed the same signs of toxicity by both routes of administration, which included decreased activity, weakness, anesthesia, analgesia, labored breathing, cyanosis, collapse, and convulsions accompanied by hemorrhage prior to death. They found that toxicity was dose related, with faster onset of toxic signs

following administration of higher doses. IV administration of 708 to 1,480 mg/kg DMA to rats resulted in a rapid period of hypotension, followed by a long-lasting hypertensive period. IV administration of DMA to dogs and cats at a dose of 95 mg/kg caused no changes in blood pressure. At 236 mg/kg, mild hypotension was observed over a 5 min period. A dose of 472 mg/kg was lethal to cats (Auclair and Hameau 1964).

DMA has been used as a solvent for numerous pharmaceutical preparations, including oxytetracycline, chloramphenicol, and reserpine (Spiegel and Noseworthy 1963). DMA has also been used as a solvent for certain anticancer compounds, including amsacrine. In vehicle studies conducted in mice, the single IV dose LD_{50} was found to be 2,341 mg/kg.

DMA was believed to possess some inherent antitumor activity and was subsequently taken into Phase I clinical trials in 17 patients as a potential antitumor agent (Weiss et al. 1962). DMA was administered at doses ranging from 100 mg/kg/day to 610 mg/kg/day from a 10 percent solution over 5 to 10 min for 3 to 5 days. Toxicity—specifically gastrointestinal, hepatic, and CNS—was observed at the high doses. However, all signs of toxicity appeared to be reversible, returning to normal following completion of the therapy. Gastrointestinal signs of toxicity included nausea, vomiting, and anorexia. Hepatic toxicity was manifested by elevated serum glutamic-oxaloacetic acid transaminase (SGOT) levels up to several days after the completion of therapy, which returned to normal 2 to 5 days after reaching peak levels. No evidence of hepatic toxicity was observed on biopsy 3 weeks after therapy was completed. CNS effects (including depression, lethargy, occasional confusion and disorientation) were observed after the second or third day of therapy. The degree of lethargy and confusion ranged from mild to severe. Some patients developed hallucinations, perceptual distortions, and, at times, became delusional at high doses of DMA (above 400 mg/kg). CNS symptoms preceded more severe side effects, including hypotension and high fever, in 3 patients. However, typical use levels for parenteral applications are approximately 30 mg/kg, and would not be expected to cause these side effects (Spiegel and Noseworthy 1963).

Reed and Yalkowsky (1985) determined that DMA was very nonhemolytic with an in vitro hemolytic LD_{50} value of 37.0 (total volume percent). Only dimethylisosorbide was found to be less hemolytic (39.5).

N,N-Dimethylformamide

N,N-dimethylformamide (DMF) is a widely used organic solvent with excellent solubilizing capacity. It has been referred to as the "universal organic solvent" due to its small size, electron-donating properties, and high dielectric constant (Budavari 1989). It is a colorless liquid that is miscible with water and other organic solvents.

Following parenteral administration, DMF is metabolized in vivo to either monomethylformamide or N-(hydroxymethyl)-N-methylformamide. It

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is primarily excreted in the urine as either of the metabolites, with relatively small amounts excreted as intact parent compound (Kennedy and Short 1986).

Generally, the formamides possess a relatively low order of toxicity following single-dose administration. Kutzsche (1965) determined the acute toxicity (LD_{50} values) of DMF following IV administration in dogs, guinea pigs, and rabbits to be 0.47 g/kg, 1.0 g/kg, and 1.8 g/kg, respectively. However, liver damage has been reported in rats following single IP doses of 0.6, 0.9, or 1.2 g/kg DMF. Davis and Jenner (1959) reported the LD_{50} values following IP administration to mice to be 1.1 g/kg. Reported IP LD_{50} values in rats are 1.3 g/kg (Massmann 1956) and 2.5 g/kg (Thiersch 1962).

Montaguti et al. (1994) evaluated the relative hemolytic potentials of several organic solvents, including DMF, dimethylsulfoxide (DMSO), EtOH, PEG 400, and BA, in several different mouse strains. They found that DMF was well tolerated in terms of hemolytic and precipitation potentials (in vitro tests). Hemolytic potential was evaluated following incubation of the solvent with blood at 37°C for 45 min. In general, DMF was the best tolerated of the solvents evaluated in both of these studies. DMF has been reported to be hemolytic when incubated with human erythrocytes for 45 min at 37°C (Cadwallader and Phillips 1969). These amides have been shown to readily penetrate the red blood cell membrane and afford little to no protection from hemolysis.

Dimethylsulfoxide

DMSO is a colorless, aprotic solvent that has a relatively high dielectric constant. It is miscible with water and many common organic solvents, including glycerol, acetone, and EtOH, in all proportions. DMSO is also very hygroscopic, capable of absorbing over 70 percent of its own weight at 20°C/65 percent relative humidity (RH) (Willson et al. 1965). Additionally, it has excellent solubilizing properties. Pharmacological evaluations showed that drugs administered systemically in DMSO did not significantly alter their lethality or cellular penetration (Dixon et al. 1965).

Toxicity studies have shown that DMSO possesses a relatively low order of toxicity. Willson et al. (1965) evaluated both acute and multiple dose toxicity from IV and IP injections in mice, rats, and dogs. Anemia and peritoneal inflammation were observed following 24 daily injections of DMSO to rats. No fatalities were observed in dogs receiving 1.2 g/kg or less daily by IV injection for 24 days. They observed perivascular inflammation and intravascular thrombosis, which was attributed to repeated administration of undiluted DMSO. However, dilution of DMSO prior to administration eliminated these unwanted effects. Additionally, hemolytic anemia, which was found to be reversible, was observed in rats and dogs following repeated IV injections of DMSO.

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Studies conducted in humans at doses of 1 gm/kg administered intravenously from 10 to 40 percent solutions resulted in transient hemoglobinuria, which resolved within 2 to 3 hours (Bennet and Muther 1981). These studies also showed no short-term nephrotoxicity.

DMSO has been shown to exert cryoprotective effects in the preservation of red blood cells, platelets, bone marrow, and tissue culture cells (Lovelock and Bishop 1959; Pyle and Boyer 1962; Porterfield and Ashwood-Smith 1962). Additionally, DMSO in concentrations up to approximately 20 percent has been shown to reduce the hemolytic activity of various antimicrobial preservatives, including phenols, BA, thimerosal, and benzalkonium chloride (Ansel and Leake 1966; Ansel and Cabre 1970).

However, there are numerous in vitro and in vivo reports of the hemolytic nature of DMSO. Cadwallader and Drinkard (1967) evaluated the behavior of human erythrocytes in the presence of water–DMSO cosolvent systems ranging from 5 to 40 percent DMSO. They found that hemolysis occurred in all DMSO-containing solutions, and those with compositions greater than 35 percent DMSO resulted in discoloration and precipitation. Norred et al. (1970) speculated that DMSO was capable of removing fatty acids from the erythrocyte membrane in a concentration-dependent manner. The leaching of fatty acids led to the formation of lesions, which subsequently disrupted the integrity of the membrane. Reed and Yalkowsky (1985) determined the in vitro hemolytic LD_{50} value for DMSO to be 5.1 (total volume percent). Only glycerin was found to be more hemolytic than DMSO of the 15 solvents tested in the study. Montaguti and coworkers (1994) reported marked hemolytic activity of DMSO, tested in dose ranges from 1.0 to 5.66 mL/kg in 3 inbred mouse strains. These reports were consistent with previous reports indicating high hemolytic potential in mice, rats, cats, and dogs (Rosenkrantz et al. 1963; DiStefano and Klahn 1965; Willson et al. 1965). These effects have been reported to be markedly reduced when the DMSO solutions were diluted with saline.

Hemolytic Potential of Solvents/Cosolvents

It is preferable to utilize injectables that are totally biocompatible with body fluids. However, the incorporation of cosolvents into parenteral formulations has long been recognized as having the potential to destroy red blood cells, as does the addition of water alone. These solvents have the ability to hemolyze cells via either membrane disruption/interaction or by osmotic action. Early investigators have shown that the composition of parenteral dosage forms directly influenced the hemolysis of erythrocytes (Husa and Rossi 1942; Easterly and Husa 1954; Grosicki and Husa 1954; Hartman and Husa 1957; Cadwallader and Husa 1958; Thomasson and Husa 1958; Ansel and Husa 1959; Marcus and Husa 1959; Winters and Husa 1960; Schnell

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and Husa 1962; Cadwallader 1963; Ansel 1964, 1965; Ku and Cadwallader 1975). These authors have also shown that the effect on the erythrocytes depends not only on the concentration of the organic in the cosolvent but also its ability to penetrate or disrupt the cell membrane. Therefore, there have been numerous investigations as to which vehicles are more tolerated for parenteral applications. Tables 11.5a and 11.5b summarize the in vitro hemolytic LD_{50} values for several common organic solvents encountered in parenteral formulations and the effects of increasing concentrations of NaCl on the observed hemolytic potentials (Reed and Yalkowsky 1985, 1986).

Table 11.5a. LD_{50} Values Expressed as Total Volume Percents of Various Cosolvents for Lysis of Erythrocytes (Reed and Yalkowsky 1985)

Cosolvent	LD_{50}
Glycerin	3.7
DMSO	5.1
PG	5.7
10% EtOH, 40% PG	10.3
EtOH	21.2
PEG 400	30.0
DMA	37.0
DMI	39.5

Table 11.5b. Effect of Increasing Sodium Chloride Concentrations on LD_{50} Values Expressed as Total Volume Percents of Various Cosolvents for Lysis of Erythrocytes (Reed and Yalkowsky 1986)

	Aqueous NaCl Concentration			
Cosolvent	**0.9%**	**1.8%**	**2.7%**	**3.6%**
Glycerin	3.3	8.3	12.7	11.9
PG	6.2	14.7	20.0	19.3
PEG 200	10.2	22.4	26.6	27.9
DMA	36.6	40.4	39.3	36.9
PEG 400	29.6	33.5	27.6	23.9
DMI	17.9	16.6	15.9	9.6
EtOH	20.5	20.0	20.5	19.7

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There is a great deal of information available in the literature regarding the hemolytic potential of various solvents/cosolvents. However, much of this information is contradictory as to whether a particular cosolvent system is hemolytic or nonhemolytic. The discrepancies regarding hemolytic potential of a particular solvent system apparently result from the differences in the test methods used to evaluate the degree of hemolysis, particularly relating to volume ratios of blood to cosolvent, incubation/contact times, and whether the systems are static or dynamic (Banziger 1967; Wickliffe et al. 1968; Fort et al. 1984; Obeng and Cadwallader 1989; Krzyzaniak et al. 1997a, b, c). The temperature at which samples are maintained has also been shown to have a direct effect on the observed degree of hemolysis, with lower temperatures resulting in lesser extents of hemolysis (Cadwallader et al. 1964; Kimura et al. 1971). Additionally, it is also important to note that there may also be some species and/or strain differences relating to how susceptible blood cells might be to hemolysis (Montaguti et al. 1994).

Reed and Yalkowsky (1985, 1986) performed numerous studies addressing the effect of various cosolvents on hemolysis using an improved hemolytic method that would be suitable for use in the presence of cosolvent systems. They used terminology that expressed the ratio of blood to cosolvent volume as a concentration (i.e., total volume percent of cosolvent). A blood to cosolvent ratio of 9:1 would be expressed as a 10 percent cosolvent. They determined the LD_{50} values for various cosolvent systems. They found that EtOH, PEG 400, DMA, and dimethyl isosorbide (DMI) were considerably less hemolytic than DMSO and PG (Table 11.5a). The 10 percent EtOH–40 percent PG vehicle commonly used in marketed products (and well accepted as a parenteral vehicle) had an LD_{50} value approximately twofold greater than the very hemolytic solvents DMSO and PG.

Reed and Yalkowsky (1985, 1986) investigated the hemolysis resulting from increasing amounts of various cosolvents in water, as well as the importance of the ratios of blood to test solution. They showed that hemolysis was clearly a function of the concentration of the organic component present in the cosolvent mixture. DMSO and PG cosolvent mixtures were found to be quite hemolytic, even at relatively low cosolvent fractions. Surprisingly, some solvents were well tolerated even when tested undiluted (DMA, DMI, PEG 400) at blood:test solution ratios of 9:1. Reed and Yalkowsky (1987) continued to investigate cosolvent-induced hemolysis in an attempt to determine the relationship between structure and hemolytic potential for the above cosolvents. They concluded that the simple alcohols became more hemolytic with increasing chain length, consistent with other reports for simple alcohols (Ku and Cadwallader 1984) and both anionic and cationic detergents (Ross and Silverstein 1954). They also observed that decreasing steric bulk attached to the hydroxyl groups, and decreasing the number of hydroxyl groups resulted in a decreased hemolytic potential.

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Although they were unable to determine a relationship between LD_{50} values and physicochemical properties for all of the solvents tested, they did observe a good correlation between LD_{50} values and log partition coefficient (PC) values when only the simple alcohols were included in the regression analysis. Similar attempts to correlate physical parameters with hemolytic potential have been made for drug molecules using dielectric constants, pH values, hydrogen bonding numbers, van der Waals volume, pK_a, octanol-water partition coefficients, and lipid spin labeling. However, no clear association has been made between any single parameter and resulting damage to the erythrocytes.

Ward and Yalkowsky (1992) later proposed that the hemolytic potential of a cosolvent was most accurately described by a single parameter, the effective concentration (EC), which could be used to generate dose-response hemolysis curves. They used the data obtained by Obeng and Cadwallader (1989) for PG cosolvent systems as the basis for their work. They defined the EC as the concentration in the final mixture of aqueous PG cosolvent solution and blood:

$$EC = \frac{\text{PG concentration} \times \left(\dfrac{\text{solution volume}}{\text{injection time}}\right)}{\text{blood flow rate}}$$

They proposed that use of this term essentially condensed several parameters (including vessel diameter, blood flow rate, injection volume, concentration and rate of administration) into a single parameter. They demonstrated with the PG system that there was a relationship between hemolytic potential and effective concentration, and that these kinetic factors must be considered in order to evaluate hemolysis in an in vitro system accurately.

Krzyzaniak et al. (1997a, b) showed that the degree of solvent-induced hemolysis was not only dependent on the ratio of formulation to blood but also to the amount of time in which the formulation was in contact with blood. Their in vitro method of determining hemolysis incorporated factors relating to the dynamics of an IV injection. The fundamental basis for this was that once a cosolvent formulation is injected into a vein, it is immediately mixed (and subsequently diluted) with blood, resulting in a decreased concentration of cosolvent formulation to which the erythrocytes will be exposed. Initially, the effect of contact time and volume of water and various concentrations of salt solutions were evaluated (Krzyzaniak et al. 1997a). Research showed that longer contact times resulted in greater degrees of hemolysis, with more hemolysis observed for systems where the ratio of test solvent to blood was increased. Subsequent evaluations were focused on various cosolvent systems, using EtOH, glycerol, PG, and PEGs (Krzyzaniak et al. 1997b). They determined a hemolytic potential rank order

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for these tested solvents to be: glycerin > PG > PEG 300 > EtOH, although there was no difference between PEG 300 and EtOH at short contact times. For all cosolvent systems tested the observed extent of hemolysis increased as a function of cosolvent composition as well as contact time.

Krzyzaniak and coworkers (1997c) pointed out the range of conditions utilized in the most common in vitro methods, and the differences as to whether hemolysis occurred in the presence of a given cosolvent. The conditions used in the various models were so different, it is not surprising that there were inconsistencies with regard to hemolysis caused by cosolvents. The amount of hemolysis resulting from an IV injection of any given cosolvent depends on the initial concentration of the cosolvent, the concentration of the formulation after initial mixing with blood, and the amount of time to be completely diluted by the total blood volume.

In Vitro/In Vivo Hemolysis Comparisons

Fort and coworkers (1984) investigated the hemolysis of aqueous PEG 400, PG, and EtOH combinations in vivo and in vitro. Hemolysis was evaluated following a 2-week period of IV administration of a PG:EtOH:water solution (5:1:4) to rats and dogs. After 2 weeks, observations included decreases in hematocrit, hemoglobin, and number of erythrocytes, as well as marked hematuria. Further evaluation of urine samples showed that they were positive for occult blood, bilirubin, ketones, and protein. Several cosolvents (PG, PEG 400, and EtOH) of varying compositions were also evaluated in vivo in rats and in vitro in dog blood. It was found that any combination of EtOH and water with PG (10–30 percent) resulted in hematuria and complete in vitro hemolysis in all tested ratios. The same results were obtained when 0.9 percent NaCl was substituted for water with the exception of 10:30:60 (PG:EtOH:saline), which did not cause hematuria in vivo, but caused complete hemolysis in vitro. They also found that 40 percent EtOH in the presence or absence of normal saline caused hemolysis. Lower concentrations of EtOH (30 percent or less) in solutions containing normal saline did not cause hematuria even though some hemolysis in vitro was observed. The solution containing PEG:EtOH:water (3:2:5) was found to be nonhemolytic. Fort et al. (1984) concluded that intravenously administered PEG solutions were less hemolytic than similar solutions containing PG.

Krzyzaniak and coworkers (1997c) compared hemolysis using nine different in vitro methods, including a dynamic method which represented a more realistic picture of what happens to the formulation in vivo following an injection. They found that the hemolysis data generated by their dynamic model was much more representative of what was observed in vivo as compared to data generated by the other in vitro methods (Table 11.6). Excellent agreement was observed when comparing hemolysis data obtained from their dynamic in vitro method to that observed in vivo. Several

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Table 11.6. Detection of Hemolysis by In Vivo and In Vitro Methods (Krzyzaniak 1997a)

Number	Formulation Composition	Hemolysis Observed in vivo	In Vitro Method (% Hemolysis Detected)			
			Husa and Adams (1944)	Fort et al. (1984)	Reed and Yalkowsky (1985)	Krzyzaniak et al. (1997c)
1	Normal saline (NS)	no[a,b,c]	0.0	0.0	0.0	0.0
2	10% EtOH in NS	no[c]	1.7	1.7	0.0	0.7
3	30% EtOH in NS	no[a]	92.4	89.2	0.0	0.5
4	40% PG in NS	yes[c]	50.7	23.3	61.0	5.6
5	60% PG in water	yes[a]	87.3	100.0	100.0	9.5
6	10% PG + 30% EtOH in NS	no[a]	82.3	85.3	0.0	1.2
7	10% EtOH + 20% PG in water	no[b]	89.5	81.3	8.8	2.0
8	10% EtOH + 40% PG in water	yes[a,b]	63.0	78.9	69.2	10.3
9	20% EtOH + 30% PEG 400 in water	no[a]	44.1	37.4	0.0	0.3

a: Fort et al. (1984)

b: Gerald (1988)

c: Turitto (1996)

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of the vehicles tested by the static in vitro methods gave false-positive results when compared to results obtained from in vivo hemolysis studies (due to the high ratio of formulation to blood and the long incubation times). Although these static in vitro methods were not accurate in assessing the degree of hemolysis in vivo, they can be useful in assessing potential cellular damage resulting from IM injections, where there is a prolonged contact time between the vehicles and the tissues.

Methods to Reduce Hemolysis

Use of Additives. Numerous investigators have reported that the addition of various salts, including NaCl and sodium sulfate (Na_2SO_4), affords partial to full protection from hemolysis. It is well known that solutions of various therapeutic compounds (such as ammonium chloride, urea, boric acid, EtOH, and glycerin) fail to prevent hemolysis even when used at isotonic levels, indicating marked differences between iso-osmotic and isotonic values for compounds that can affect the red blood cell membrane (Husa and Rossi 1942; Husa and Adams 1944; Easterly and Husa 1954; Grosicki and Husa 1954; Hartman and Husa 1957; Cadwallader and Husa 1958; Thomasson and Husa 1958; Ansel and Husa 1959; Marcus and Husa 1959; Zanowiak and Husa 1959; Winters and Husa 1960; Hammarlund and Pedersen-Bjergaard 1961; Schnell and Husa 1962; Cadwallader 1963; Ansel 1964; Cadwallader et al. 1964). This is due to the fact that some of these additives may permeate the red blood cell membrane, causing an influx of water, resulting in hemolysis. Therefore, whether an additive has protective effects on erythrocytes will depend on its ability to penetrate the cell membrane. Such cosolvent compositions that are iso-osmotic with blood (0.9 percent or 0.15 M NaCl isotonic comparators) include 2.6 percent glycerin in water, 2.0 percent PG in water, 8.7 percent PEG 300, and 11.6 percent PEG 400.

Over the years, Husa and coworkers found that hemolysis occurred in solutions containing less than 0.45 percent NaCl, and that it was prevented with the use of concentrations from 0.45 to 0.9 percent. Hemolysis also resulted from solutions containing 1 to 2 percent dextrose, partial hemolysis at 3 percent dextrose, and solutions containing 4 to 5 percent dextrose resulted in no hemolysis. They showed that the 9 substances tested fell into 3 categories: prevents hemolysis (NaCl, dextrose), induces hemolysis (ammonium chloride, boric acid, carbitol) and those of moderate hemolytic potential (EtOH, PG, glycerin, diethylene glycol). Ammonium chloride, boric acid, and carbitol appear to cause hemolysis by a mechanism other than osmotic effects, probably by changing the permeability of the erythrocyte membrane.

Hammarlund and Pedersen-Bjergaard (1958, 1961) evaluated the effect of iso-osmotic solutions on erythrocyte hemolysis. They evaluated various salts for their potential for protecting erythrocytes from hemolysis.

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They showed that monovalent amine salts typically resulted in hemolysis, whereas divalent and trivalent amine salts usually protected from hemolysis. They also showed that the addition of either NaCl or Na_2SO_4 was able to prevent hemolysis of erythrocytes exposed to various iso-osmotic solutions of ephedrine. They found that an iso-osmotic solution of EtOH (1.39 percent) required 0.5 percent NaCl to prevent hemolysis. Cadwallader and Drinkard (1967) also showed that the addition of isotonic amounts of various compounds (NaCl, calcium chloride, dextrose, lactose, potassium bromide, sodium citrate, sodium bromide, sodium iodide, and sodium salicylate) prevented hemolysis in aqueous solutions containing 5 to 40 percent DMSO. These studies again illustrate the difference between iso-osmotic concentrations and isotonic concentrations.

Cadwallader (1963) calculated "hemolytic" isotonic coefficients for several polyhydric alcohol-water solutions (PG, glycerol). These data showed that water-glycerin and water–PG mixtures should not be assumed to be hypertonic with respect to blood. In fact, all mixtures studied were found to be hypotonic with respect to rabbit and human erythrocyte membranes. Therefore, isotonicity calculations were not valid for these applications. They also showed that PG was more hemolytic than glycerin, consistent with Jacobs and coworkers' (1935) observation that each additional hydroxyl group added to the propane molecule decreased the rate of penetration into erythrocytes.

Reed and Yalkowsky (1986) showed the effect of increasing amounts of NaCl on the hemolytic LD_{50} values of the common organic solvents found in parenteral formulations (Table 11.5b). They showed differences in the degrees of protection afforded by NaCl between the various solvents. For example, the presence of NaCl had essentially no effect on the LD_{50} value for EtOH, whereas it decreased the LD_{50} value for glycerol by almost fourfold.

Fu et al. (1987) investigated several parenteral vehicles for hemolytic potential both in vitro and in vivo following IV administration to rats. The animals were dosed daily with a single bolus dose of 2.5 mL/kg through the tail vein for 2 weeks. They reported a high degree of hemolysis for a 15 percent PG solution, which was significantly reduced by the addition of either 1.8 percent NaCl or 20 percent sorbitol (concentrations higher than those yielding isotonic solutions). They also showed that PEG 400 had the ability to reduce the hemolytic potential of a 15 percent PG solution from approximately 80 percent hemolysis (with no added PEG 400) to approximately 20 percent hemolysis with addition of 20–45 percent PEG 400. This is useful to formulators in that it makes the vehicle more biocompatible, as well as provides increased solubilization power for the cosolvent system.

Use of Slow Infusion Rates. One of the easiest ways to minimize hemolytic consequences of administration of parenteral products containing cosolvents is to administer these doses as slow infusions, as opposed to bolus

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injections. This results in lower effective concentrations of cosolvent in the plasma. Slow administration of the dose also reduces the chance of precipitation of the drug in the vascular compartment by allowing for gradual dilution with the plasma components.

Welch et al. (1974) reported that glycerol has been used successfully in the treatment of more than 500 patients with acute cerebral infarctions when administered daily for 7 to 10 days infusing 500 mL of 10 percent glycerol in normal saline over 6 h with none of these adverse effects. This study did report that hemolysis was seen when the solution was administered as a rapid infusion. However, Hagnevik et al. (1974) reported hemolytic changes ranging from hemolysis and mild to marked hemoglobinuria following administration of 20 percent glycerol at rates of 60 g/15 min, 70 g/30 min and 80 g/60 min to 3 patients undergoing intracranial surgery. As one can see, there were enormous differences in the rates of administration of the glycerol solutions between these reports. The side effects were associated with much faster infusions than those used by others to treat stroke patients (Meyer et al. 1971). Therefore, one can observe that the rate of administration has a tremendous effect on the glycerol-related hemolysis observed following IV administration. These data from Welch and coworkers suggest that it would be entirely possible to greatly reduce or eliminate the hemolysis when administering such solutions slowly.

Obeng and Cadwallader (1989) evaluated the effect of various parameters on the observed degree of hemolysis. These included flow rate of red blood cells at the site of injection, internal diameter, distance downstream from the site of injection, injection volume, rate of administration, and cosolvent composition. This method was a more realistic model for hemolysis, since it allowed for mixing of the cosolvent with blood at the site of injection and a relatively short contact time between the test solution and the blood. These studies clearly showed that the kinetic factors (rate of administration, blood flow rate) affected the degree of hemolysis associated with various cosolvents and recommended that solutions having known hemolytic potentials be administered slowly via large veins.

The *Physicians Desk Reference* (PDR 1994) recommends slow administration for many cosolvent-containing compounds that have been associated with various complications following IV administration. Such compounds include phenytoin, digoxin, diazepam, pentobarbital, lorazepam, and etoposide. Typically, the recommendations are to administer these doses slowly as infusions, with rates not to exceed 2 to 50 mg/min, depending on the compound. When administering doses to neonates or children, the rates of administration may need to be even slower, as is the case with phenytoin (not to exceed 1 to 3 mg/kg/min for neonates, compared to 50 mg/kg for adults). Slow administration allows for adequate mixing with blood and minimizes the risk of precipitation of the dose.

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Muscle Damage

Administration of formulations by the IM and SC routes is somewhat more flexible than formulations administered by the IV route because solutions or suspensions, either aqueous or oily, can be given. Use of these formulations tends to result in a more controlled release of drug. Cosolvents are frequently used to reduce the aqueous solubility of a given compound, such that it precipitates upon administration into tissues. The precipitation is followed by a resolubilization of the compound over time as the compound is slowly absorbed. The rate of solubilization is dependent on the properties of the tissues, such as pH and blood flow (Evans et al. 1973), and the vehicles used to administer the compound. Local muscle damage may result from direct damage to the sarcolemma membrane of the muscle fibers, or by some toxic effect of either the drug or the vehicle on myofibril intracellular organelles and membranes. Muscle damage may also contribute to the pain at the site of injection.

Hem and coworkers (1974–1975) evaluated the tissue irritation (muscle damage) and injectability of 23 potential nonaqueous parenteral vehicles. They found that several vehicles caused very little irritation (benzyl benzoate, 1,3-butylene glycol, ethyl oleate, glyceryl triacetate, sesame oil: benzyl benzoate [1:1], sesame oil) and were well absorbed; several caused moderate irritation (butyl lactate, castor oil, glyceryl monoricinoleate) and were not absorbed; and a number that caused necrosis (ethyl formate, isoamyl formate, octyl alcohol, polyoxyethylene oleyl ether, n-propyl alcohol, propylene carbonate, sorbitan trioleate). They included DMA in the study, finding that it was very well absorbed from the site of injection but caused moderate irritation that was found to dissipate within 7 days postinjection. Oshida and coworkers (1979) evaluated the physicochemical properties and local toxic effects of 335 parenteral formulations. They evaluated pH, osmotic ratio, hemolytic potential, cytotoxic effects on cultured cells, and muscle lesions following IM administration of 0.5 mL to the vastus lateralis or sarcospinalis muscle of rats. They showed there was a close correlation between the hemolytic potential of the formulation and the severity of muscle damage observed.

Svendson (1983) and Svendson and coworkers (1985) evaluated the muscle damage resulting from IM injections of several neuroleptic drugs in aqueous and oil vehicles, including Viscoleo®, sesame oil, methyl oleate, and squalane. They observed the injection site three days after IM administration of 2 mL of the various formulations. The most damage was observed with cis-(Z)-clopenthixol, regardless of formulation. Postmortem findings showed well-defined, relatively large areas of muscle necrosis in all of the animals administered aqueous formulations. These areas were considerably larger than those observed in the oil-treated animals. Generally, Viscoleo® (a triglyceride vegetable oil composed of short chain and saturated fatty acids, caprylic acid, capric acid, and lauric acid) resulted in

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much less damage than the aqueous solutions. Formulation of haloperidol, cis-(Z)-clopenthixol, or chlorpromazine in any of the oil vehicles essentially eliminated the observed muscle damage that resulted from administration of the aqueous solutions—necrotic areas were reduced from 5- to 34-fold when the oily vehicles were used instead of the aqueous formulations.

It has been observed that one of the consequences of IM injections is release of the enzyme creatine kinase (CK) into plasma, which is found in large amounts in skeletal muscle. This enzyme has been used as a marker of muscle damage (Attar and Matta 1971; Anderson and Damsgaard 1976; Greenblatt et al. 1976; Steiness et al. 1974, 1978; Svendson et al. 1979; Diness 1985). Steiness et al. (1974) reported that the size of the resulting necrotic area following IM administration of digoxin or the vehicle control to pigs was related to the injection volume (ranging from 1.5 to 4.0 mL). The necrotic areas resulting were, however, much smaller for the vehicle groups than those receiving the digoxin formulation, indicating that the drug itself contributed greatly to the necrosis.

Several investigators evaluated the effects of PG and glycerol formal vehicles on muscle necrosis (Rasmussen and Svendson 1976; Svendson et al. 1979). Svendsen et al. (1979) evaluated the effects of different dilutions of PG or glycerol formal in distilled water or 0.9 percent saline on the measured CK activity in muscle taken from the injection area and the contralateral uninjected site for up to 72 h postinjection. They showed that CK depletion from the muscle, which subsequently appeared in the plasma, was dependent on the PG or glycerol formal content of the vehicle—higher cosolvent compositions led to higher plasma CK levels, with PG causing greater CK release than glycerol formal. They also showed that local muscle damage (as indicated by weight of the isolated damaged muscle tissue) correlated with relative CK activity depletion in the muscle.

Brazeau and Fung (1989a, c) also evaluated PEG 400, PG, and EtOH cosolvent mixtures for their myotoxic potential using an in vitro model that they developed. This model measures cumulative release of CK as a marker of muscle damage, and the values can be compared to positive and negative control values. The specific details of this model are discussed in other chapters in this volume. They showed that at moderate cosolvent concentrations (20–40 percent, v/v), PG was considerably more myotoxic than PEG 400 or EtOH (PG > EtOH > PEG 400). This seemed to correlate with hemolytic potentials of the cosolvent mixtures as reported by Reed and Yalkowsky (1985). These results were compared to those obtained in vivo in rabbits, evaluating serum CK levels following IM administration of 40 percent PG, 40 percent PEG 400, or normal saline. They showed that in all cases serum CK levels increased following the injection. However, the levels were much higher for the cosolvent formulations (PG >> PEG 400 > saline). They observed that it took 3 days to return to normal serum CK levels.

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In more recent studies, we have investigated the in vitro myotoxicity of DMA, Cremophor® EL, polysorbate 80, safflower oil, and Labrafil® using the isolated muscle model as above. The results from these studies are shown in Table 11.7 and are compared to our historical positive and negative control values (Dilantin® injection and normal saline, respectively). The toxicity of all these solvents, with the exception of safflower oil and 30% Cremophor® EL (very close to the negative saline control value), was intermediate between the positive and negative control values. This would be consistent with an oily vehicle being less toxic to tissues versus an aqueous vehicle. It is unclear as to why there was no concentration-myotoxicity response between the concentrations of Cremophor® EL. Of all these solvents, DMA and polysorbate 80 were found to be the most toxic. This could be attributed to their ability to solubilize the muscle membrane leading to release of CK.

In an attempt to elucidate the factors responsible for muscle damage, Brazeau and Fung (1989c) evaluated how physicochemical properties of the vehicle composition affected muscle damage following IM administration of various cosolvents, including PG–water, EtOH–water and PEG 400–water mixtures. The properties that were evaluated were dielectric constant, apparent pH, surface tension, and viscosity. They made several notable observations, including (1) as the hydrophilicity of the cosolvent mixtures increased, myotoxicity decreased; (2) there was no defined pH range where muscle damage could be minimized; and (3) that, unlike hemolysis, the addition of NaCl had no protective effect on muscle damage produced. They concluded that myotoxicity was not exclusively related to a single parameter or a combination of the four parameters evaluated.

Table 11.7. Myotoxicity of Selected Solvent Vehicles

Vehicle	Myotoxicity – Cumulative CK Release over 2 h Mean CK (× 100) and (SEM); $n = 4–6$
20% DMA	9.50 (2.60)
30% DMA	13.4 (2.10)
20% Cremophor® EL	6.87 (1.69)
30% Cremophor® EL	4.94 (0.83)
5% Tween 80®	20.1 (3.21)
Safflower oil	2.89 (1.47)
20% Labrafil®	7.90 (1.65)
30% Labrafil®	8.94 (1.69)
Positive control Dilantin® injection	70.1 (4.71)
Negative control normal saline injection	5.06 (0.50)

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Chu and Brazeau (1994) also showed that PG and PEG 400 had different effects on skeletal muscle sarcoplasmic reticulum calcium uptake and release. They showed that 10.5 percent PEG 400 stimulated calcium uptake without significantly altering the adenosine triphosphatase (ATPase) activity of the calcium pump. However, at 10.5 percent PG, there was no significant effect on either calcium uptake or ATPase activity of the pump. These findings further supported the role of calcium in mediating cosolvent-induced muscle damage, as suggested earlier (Brazeau and Fung 1990b). They also provided a possible explanation for the differences in the two cosolvents in their potentials to cause muscle damage, based on increased myoplasmic calcium removal and reduced calcium release.

Cosolvent-Related Pain on Injection

The use of parenteral routes of administration may result in pain and irritation at the site of injection. This may be related to the injection itself or the properties of the drug substance. However, the pain and irritation many times appears to be associated with the formulation vehicle, particularly those that contain high fractions of cosolvents or those that have high osmolalities. In general, comparisons between solutions containing lower or different cosolvent compositions or lower osmolalities have shown fewer incidences of pain on injection, as well as reduced local toxicity (Bjork et al. 1969; Almèn and Tragardh 1973; Almèn et al. 1977; Tillman et al. 1979).

There have been numerous methods and guidelines published relating to the assessment of pain (Beecher 1957; Woodforde and Merskey 1972; Ohnhaus and Adler 1975; Celozzi et al. 1980; Vierck and Cooper 1984; Comerski et al. 1986; Marcek et al. 1992; Gupta et al. 1994). These methods can be characterized as reflexive (tail-flick, paw-lick, hot plate, or pinch test), conscious escape (flinch-jump test), prolonged protective activity (fleeing/fighting), and retreat/withdrawal responses. These models vary in the degree of subjectivity of the pain assessment and are discussed elsewhere in this book.

Cosolvents Known to Cause Pain

Glycerin has been recognized as an irritating agent that caused pain and inflammation at the site of injection. Van Metre et al. (1996) reported pain and dermal reactions caused by the administration of glycerin in immunotherapy solutions. Such solutions come prepared in 50 percent glycerin to preserve potency for 2 to 3 years. The solutions are supposed to be diluted prior to administration to levels between 10 to 30 percent glycerin and administered in volumes ranging from 0.1 to 1.0 mL. Their results showed that

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pain scores of subjects given glycerin increased significantly as both glycerin concentration and dose volume increased.

When used undiluted, PG can cause considerable pain and irritation at the site of injection. These effects have been reported for parenteral administration of nitroglycerin (Demey et al. 1984; Shook et al. 1984; Col et al. 1985; Demey et al. 1984,1988); etomidate (Bedichek and Kirschbaum 1991; Levy et al 1995), multivitamins (Glasgow et al. 1983), and phenytoin (Hitotsumatsu et al. 1995). Other investigators have shown that altered formulations of various cosolvent-containing preparations, containing either reduced organic fractions or using a mixture of different organic solvents to minimize the load of a particular solvent, were less painful than when administered in the traditional formulation (Burton et al. 1974). Many of these studies have shown that pain on injection was associated with the formulation vehicle, particularly when containing relatively high amounts of PG.

Diazepam, which contains 40 percent PG, has been associated with many incidences of pain on injection, which has been related to the composition of the formulation vehicle. Pain on injection has been reported in up to 22 percent of patients, with subsequent development of venous sequelae (phlebitis, thrombosis, or thrombophlebitis) appearing in up to 30 percent of patients (McClish 1966; Brown and Dundee 1968). It is suspected that precipitation of the poorly water-soluble drug on administration is at least partially responsible for these side effects. Langdon et al. (1973), however, did not observe any correlation between pain on injection and development of venous sequelae.

While evaluating pain and irritation following injection of various parenteral formulations using the rat paw-lick model, Gupta and coworkers (1994) suggested that there was a pain "threshold limit" in terms of observed number of paw licks related to the concentration of a pain-inducing component, at least in the case of PG–containing formulations. In these studies, concentrations above this "threshold limit" did not result in increases in the pain responses, making predictions using this model somewhat problematic. These data showed that administration of formulations containing 50 percent PG caused less pain than formulations containing 40 percent PG, in both the presence and absence of 5 percent EtOH. The same observation was made for PG solutions containing 15 percent EtOH, whereby more pain was observed at 35 percent PG, as compared to preparations containing 40 or 50 percent PG. Analysis of CK levels following these injections showed that they increased (indicative of muscle damage) as a function of the cosolvent composition. Therefore, one must be cautious when interpreting data from these pain models, since pain may not correlate with damage resulting from the injection of the formulation.

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Methods to Minimize Pain

There have been numerous investigations as to how to reduce the pain following parenteral administration of various formulations. In many cases, these methods are similar to those used to minimize hemolysis. The most common methods used to minimize pain on injection are (1) administration of the dose via a large vessel; (2) dilution of the formulation in some manner that does not result in precipitation, or similarly, administration of the dose as a slow infusion to reduce the effective concentration of cosolvent in the system at a given period of time; (3) formulation of the compound using solvents that are less irritating; or (4) prior or coadministration of an anesthetic or analgesic agent, such as lidocaine or morphine, to reduce the pain.

Administration Via Large Vessels

Kawar and Dundee (1982) investigated the effect of choice of injection site, including the variables of vein size and location. They observed that the greatest incidence of pain occurred when administering various formulations via small to medium sized veins, and that using the hand and wrist veins caused more pain than those in the antecubital space (Table 11.8). The use of large veins rather than small veins, and selecting the antecubital space rather than the back of the hand or wrist consistently showed better tolerability, regardless of whether the formulation contained 0.9 percent saline or various cosolvents.

Similarly, Langdon et al. (1973) reported that venous sequelae occurred less frequently when administering IV doses of diazepam through larger veins. They noticed that phlebitis almost always resulted when administering the doses through small veins. The incidence of pain resulting from administration of propofol, an anesthetic agent, has been reported to range from 25 to 100 percent if given via a vein on the dorsal side of the hand (Hynynen et al. 1985; Stark et al. 1986; Sebel 1989; Stokes et al. 1989; Johnson et al. 1990), and only 3 to 36 percent if injected into larger, proximal veins in the antecubital fossa (McCulloch and Lees 1985; Scott et al. 1988; Gehan et al. 1991).

Dilution of the Formulation

Dilution of cosolvent formulations has been shown to reduce the incidences of both pain and venous sequelae. However, precipitation of a poorly water-soluble drug is likely to result if diluted into an aqueous medium (water, saline, or even plasma). Precipitation may be immediate or may develop over time. Van Metre and coworkers (1996) showed that pain resulting from subcutaneous injections of glycerol solutions (0, 10, 20, and 30 percent glycerol with dose volumes ranging from 0.1 to 1.0 mL) to

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Table 11.8. Frequency of Pain on Injection and Venous Sequelae Following Administration of Various Test Formulations (Total Number of Patients Evaluated in Parenthesis) (Kawar and Dundee 1982)

Drug/Formulation	Primary Solvent	% Frequency of Pain on Injection	% Frequency of Venous Sequelae	% Sequelae Related to Vein Size		% Sequelae Related to Vein Site	
				Large	Small + Medium	Antecubital Fossa	Back of Hand + Wrist
0.9% Saline	Water	0 (50)	2 (50)	0 (18)	3 (32)	0 (23)	4 (27)
2.5% Thiopentone	Water	9 (100)	4 (50)	5 (20)	3 (30)	17 (12)	0 (38)
1.0% Methohexitone	Water	12 (100)	10 (50)	12 (24)	8 (26)	12 (33)	6 (17)
1.0% ICI 35868 (Disoprofol)	Cremophor® EL	4 (50)	10 (50)	12 (24)	8 (26)	8 (48)	50 (2)
0.5% Diazepam Valium®	Propylene glycol	37 (100)	40 (50)	18 (28)	32 (22)	17 (30)	50 (20)
Diazemuls®	Soya bean oil	0 (50)	2 (50)	0 (31)	5 (19)	0 (32)	6 (18)
0.5% Midazolam	Water	1 (400)	8 (100)	11 (65)	3 (35)	11 (70)	0 (30)

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15 subjects increased significantly as a function of both injection volume and glycerol concentration.

Alteration of the Vehicle Composition

In efforts to minimize both pain and venous sequelae, alternative formulation vehicles have been used for administering diazepam to patients. Burton and coworkers (1974) used a solution of 1 percent Cremophor® EL in saline to dilute diazepam to a final concentration of 1 mg/mL. Following administration of this formulation to over 400 patients, it was reported that incidences of pain on injection were essentially eliminated, even when injected into small veins, and incidences of venous sequelae in these patients were reduced to less than 1 percent. This eliminated precipitation of the solution, which was observed in the traditional formulation (Jusko et al. 1973). They also observed that if pain was observed following IV administration, flushing the vein with 5 mL saline or 10 mg of heparin sodium through the same needle diminished the incidence of venous sequelae.

Kortilla et al. (1976) evaluated the effects of PG following IM injection in humans, comparing pain, muscle damage and precipitation for the following diazepam formulations: Valium® (Roche), Diapam® (Orion) and an experimental formulation 301-K 2/74 (Orion). The 301-K 2/74 formulation contained a lower concentration of PG (20 percent) with 60 percent PEG 300. The Valium® and Diapam® formulations contained the same cosolvent composition (41 percent PG, 8.5 percent EtOH). These formulations provided no statistical differences in plasma levels following IM administration, although the levels for Valium® tended to be lower than for the other formulations. At doses of 0.15 mg/kg, they found that pain was significantly greater in the Valium® and Diapam® formulations than in the 301-K 2/74 or placebo (301-K 2/74 with no drug) in double blind crossover studies. This is consistent with earlier rat studies showing a lack of irritation after IM injections of the PG/PEG vehicle. They also showed that the PG/PEG formulation was less likely to precipitate as compared to the Diapam® formulation. Addition of 10 mg (2 mL) of Diapam® to 100 mL of 5 percent glucose caused precipitation, whereas up to 25 mg (5 mL) of the PG/PEG formulation could be added before precipitation was observed.

Kawar and Dundee (1982) evaluated the pain on injection of several preparations that were formulated in different solvent systems in a patient population. They evaluated factors such as composition, size of the vessel through which the dose was administered, and the frequency of venous sequelae. They found that the formulation causing the most irritation was the Valium® formulation containing 40 percent PG and 10 percent EtOH. The same compound formulated in an oil-based system caused no pain on administration. The other formulations composed of either water or Cremophor® EL caused less pain. Additionally, the PG formulation caused the

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highest percentage of venous sequelae as compared to the other vehicles. Diazepam formulated in the oil-based vehicle was essentially the same as the saline controls, suggesting that these sequelae were the result of the cosolvent.

Administration of Anesthetic/Analgesic Agents

The use of anesthetic/analgesic agents to minimize pain following injection of various parenteral formulations has been studied using agents ranging from aspirin to morphine (Comerski et al. 1986; King et al. 1992; Marcek et al. 1992; Doenicke et al. 1996). Comereski et al. (1986) observed that coadministration of lidocaine (0.5 to 1 percent) offered protection from pain but not from the associated muscle damage resulting from the injection. Marcek and coworkers (1992) reported the effect of morphine administered 15 min prior to being given an infusion of an irritating solution (0.05 M potassium chloride). They found that administration of morphine (ranging from 2 to 4 mg/kg) virtually eliminated the pain associated with the test solution alone. Celozzi and coworkers (1982) also showed that coadministration of a local anesthetic (lidocaine) reduced the pain associated with subplantar administration of antibiotic solutions. They showed that the administration of the anesthetic reduced the pain to approximately the same level as the control water injections. It is typically thought that pain on injection is related to muscle damage caused by the administration of the dose.

Propofol (Diprivan®) has a very high incidence of pain on IV injection. Several investigators showed that the use of various anesthetic/analgesic agents resulted in abatement of pain caused by the administration of propofol (Bahar et al. 1982; Brooker et al. 1985; Helbro-Hansen et al. 1988; Gehan et al. 1991; King et al. 1992). King and coworkers (1992) showed that coadministration of lidocaine (ranging from 5 to 20 mg doses) resulted in the reduction of both the incidence of pain and its severity. In this study of 368 patients, the incidence of pain following administration of lidocaine was 32 percent, relative to 73 percent following saline injection. The degree to which the pain was alleviated was found to be dose responsive. However, 6 percent of patients treated with 20 mg lidocaine still reported unpleasant pain.

CONCLUSIONS

The use of cosolvents as solubilization enhancers in parenteral formulations has been, and continues to be, a valuable tool for the formulation scientist. However, it becomes crucial for the formulator to understand prior to the selection or use of these cosolvent systems that they differ widely in

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their physicochemical properties, which in turn can result in varying degrees of adverse effects such as hemolysis, muscle damage, and pain at the injection site. The most commonly used cosolvents in parenteral formulations—including the polyethylene glycols, propylene glycol, ethanol, glycerin, cremophors, benzyl alcohol, dimethylacetamide, and dimethylsulfoxide—have been highlighted in this chapter. Furthermore, cosolvent-related factors, mechanisms, and approaches to offset the hemolysis, muscle damage, or pain following injection have been generally presented so that the formulator can rationally select and incorporate these agents into the design of injectables.

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17

Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parenteral Products

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Parenteral products significantly contribute to global health by providing effective and immediate therapy through direct delivery of therapeutic compounds to the patient. However, as with most routes of delivery, parenteral drug administration has both real and perceived disadvantages. The two potential disadvantages that are typically associated with parenteral therapy are tissue damage and injection pain. Whether this pain is real or imagined makes little difference to the patient, and there exists a significant literature that both highlights the pain caused by injectable drug products and offers methods to reduce these effects.

The first section of this chapter provides a strategy that can be used to develop a parenteral product. Emphasis is placed on the two formulation parameters, pH and tonicity, that are usually associated with tissue damage and injection pain. It is through the adjustment of these parameters that the product formulator can minimize adverse effects. The second section of this chapter describes administration techniques used by

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healthcare professionals to reduce tissue damage or pain caused by commercial parenteral products. By recognizing the potential risks these alterations may confer to commercial formulations (such as decreased product stability or modified efficacy), the formulator will be better prepared to support the "real-world" use of the product.

FORMULATION DEVELOPMENT

The development strategy for parenteral products is similar for all products. The challenge is in the details of solving the physical/chemical difficulties encountered with a specific molecule within the timeline allowed for development. This section provides a parenteral product development outline with an emphasis on two formulation parameters, pH and tonicity, which may be modified to minimize tissue damage and pain caused by a parenteral product.

The activities necessary to develop a parenteral product can be placed into the following three broad areas: preformulation, formulation, and scale-up. While there are alternative development perspectives, all development ultimately needs to accomplish the same activities. Preformulation includes the characterization of the bulk drug plus initial screening for excipient compatibility with the drug. Formulation activities include the identification and selection of a suitable vehicle (aqueous, nonaqueous, or cosolvent system), necessary excipients with appropriate concentrations (buffers, antioxidants, antimicrobials, chelating agents, and tonicity contributors), and the container/closure system. Scale-up activities aid in moving the product to a manufacturing site (although not discussed here, references are available to provide guidance).

Preformulation

Preformulation studies provide fundamental data and the experience necessary to develop formulations for a specific compound. Activities are initiated and experiments performed for the purpose of characterizing specific and pharmaceutically significant physicochemical properties of the drug substance. These properties include interactions of the drug with excipients, solvents, packaging materials, and, specifically relating to the subject of this book, biological systems. These investigations also evaluate the drug under standard stress conditions of temperature, light, humidity, and oxygen. Many of these factors should be considered critically prior to animal testing, since these data will influence activities such as samples prepared for toxicology and animal testing, solubilization techniques, and design of subsequent studies.

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Areas of specific interest during preformulation are provided in outline form below, along with an outline of additional characterization information needed to formulate a protein drug substance. Since analytical methods are usually developed concurrently with the preformulation data and then refined during formulation activities, the team must effectively communicate and collaborate to ensure appropriate assays are used to obtain data having sufficient accuracy and precision.

Preformulation Physicochemical Properties

1. Molecular weight
2. Color
3. Odor
4. Particle size, shape, and crystallinity
5. Thermal characteristics
   - 5.1. Melting profile
   - 5.2. Thermal profile
6. Hygroscopicity
7. Absorbance spectra
8. Solubility
   - 8.1. Selected solvents (water, ethanol, propylene glycol, polyethylene glycol 400, plus others as necessary)
   - 8.2. pH profile
   - 8.3. Temperature effects
   - 8.4. Partition coefficient
9. Stability
   - 9.1. Selected solvents
   - 9.2. pH profile
10. Ionization constant (pK or pI)
11. Optical activity

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Additional Characterization for Protein Drugs

1. Physical stability
   - 1.1. Aggregation
2. Solubility
3. Chemical stability
   - 3.1. Beta-elimination
   - 3.2. Deamidation
   - 3.3. Isomerization/cyclization
   - 3.4. Oxidation
   - 3.5. Thiol disulfide exchange
4. Analytical methods
   - 4.1. Fluorescence spectroscopy
   - 4.2. Electrophoresis
   - 4.3. Calorimetry
   - 4.4. Size exclusion chromatography
   - 4.5. Reverse phase high performance liquid chromatography (HPLC)
   - 4.6. Circular dichroism
   - 4.7. Mass spectrometry
   - 4.8. Light scattering

Formulation

Formulation activities include the identification and selection of a suitable vehicle (aqueous, nonaqueous, or cosolvent system), necessary excipients with appropriate concentrations (buffers, antioxidants, antimicrobials, chelating agents, and tonicity contributors), and the container/closure system. The formulator is interested in the same list of activities given for preformulation; however, the activities are focused on specific excipients and characterization of the formulation. The principles of formulating a parenteral product have been outlined by several authors, although most do not specifically include the evaluation of tissue damage or pain caused by injection of the final product. This is likely due to the assumption that

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deviation of pH or tonicity from physiological conditions causes these effects. It is, however, important to consider that a product may cause tissue damage with little associated pain, pain with little tissue damage, or both pain and tissue damage. Therefore, the models utilized to assess either the pain or tissue damage associated with a product need to be selected carefully. Several complementary methods may be needed, and these models are provided throughout this book.

Significant formulation activities begin with initial preformulation data and knowledge of the specific route of administration. These data provide the formulator with the requirements and limitations for the final formulation. Due to the location of human pain receptors, formulation approaches to reduce pain are more critical for subcutaneous (SC) and intradermal injections and less critical for intramuscular (IM) and intravenous (IV) administration.

Injection volume is one of the most important considerations in the formulation development of a commercial product. This volume is selected based on the proposed injection route. Since veins have a relatively large volume and blood flow rate, a product administered by the IV route can have a volume greater than 10 mL; as the volume increases, the delivery rate may need to be controlled. This is in contrast to IM injections, which are normally limited to 3 mL, SC injections to 1 mL, and intradermal injections to 0.2 mL. Recommended maximum injection volumes are author dependent but not radically different.

Thus, the factors that need to be considered in evaluating the hemolysis caused by a product include both the quantity and proportions of the substances and how rapidly the blood dilutes the product. The data in Table 17.1 provide some perspective on the vascular system's capability of diluting an injected IV product, in terms of both volume and rate. The choice of solvent is dependent both on the route of administration, which

Table 17.1. Physical Characteristics of the Arteriovenous System

Anatomical Section	Volume (cm^3)	Velocity (cm/sec)
Aorta	100	40
Arteries	325	40–100
Arterioles	50	10–0.1
Capillaries	250	0.1
Venules	300	0.3
Veins	2,200	0.3–5
Vena cava	300	5–30

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as noted above imparts volume limitations, and on drug solubility in the selected solvent. IV injections are typically restricted to dilute aqueous solutions to ensure compatibility with the blood; however, IM or SC injections allow for oily solutions, cosolvent systems, suspensions, or emulsions. Pain, soreness, and inflammation of tissues are frequently observed in the administration of parenteral suspensions, particularly with products having a high solid content.

A third important consideration in the development of a parenteral product is compatibility of the formulation with the tissue. An isotonic solution is less irritating, causes less toxicity and pain, and minimizes hemolysis. An isotonic product, however, is not always the goal since for SC or IM injections a hypertonic solution may facilitate drug absorption. Having an isotonic product is, however, very important for intraspinal injections, where the fluid circulation is slow and abrupt changes in osmotic pressure can contribute to unwanted and potentially severe side effects.

The choice of acceptable excipients in parenteral product development remains limited compared to other dosage forms, due to concerns of injection safety and feasibility of sterilization. In order to avoid uncertainty and reduce development time, most formulators select excipients successfully used in marketed products. A short list of commonly used additives, their functions, and typical concentrations is given in Tables 17.2 and 17.3. As the number of biotechnology products increases, excipients such as human serum albumin (HSA), amino acids, and sucrose are finding increasing utility. In Europe, the use of animal-derived excipients such as HSA and some polysorbate surfactants has become problematic due to the increasing concern with bovine spongiform encephalitis (BSE). This concern is expanding to the rest of the world and has impact on the selection of excipients.

An excipient selected for a parenteral product may serve one or more purposes. For example, benzyl alcohol is primarily a preservative; however, it has a transient local anesthetic property. Dual roles may help in the goal to minimize both the number of product ingredients and their quantity. The justification for each selection will become a part of the formulation development report.

Antimicrobials

Preservatives are always included in a product when multiple doses will be drawn from a single vial unless the drug itself is bacteriostatic. The addition of an antimicrobial is not a substitute for good manufacturing practices; however, many times they are added to single-use containers. They are specifically excluded from large-volume products intended for infusion. In some cases, as with benzyl alcohol, the excipient may have multiple functions. Therefore, the decision whether or not to include a preservative in a single-use product may be product specific. The rationale

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Table 17.2. Additives Commonly Used in Parenteral Products

Substance	Concentration (percent)
Antimicrobial	
Benzalkonium chloride	0.01
Benzethonium chloride	0.01
Benzyl alcohol	1–2
Chlorobutanol	0.25–0.5
Chlorocresol	0.1–0.3
Metacresol	0.1–0.3
Phenol	0.5
Methyl p-hydroxybenzoate	0.18
Propyl p-hydroxybenzoate	0.02
Butyl p-hydroxybenzoate	0.015
Antioxidants	
Acetone sodium bisulfite	0.2
Ascorbic acid	0.1
Ascorbic acid esters	0.015
Butylhydroxyanisole (BHA)	0.02
Butylhydroxytoluene (BHT)	0.02
Cysteine	0.5
Monothioglycerol	0.5
Sodium bisulfite	0.15
Sodium metabisulfite	0.2
Tocopherols	0.5
Glutathione	0.1
Surfactants	
Polyoxethylene sorbitan monooleate	0.1–0.5
Sorbitan monooleate	0.05–0.5

for any preservative addition should be a part of the product development report.

Common antimicrobial agents are given in Table 17.2. These agents are grouped into five chemical classes: quaternary ammonium compounds, alcohols, esters, mercurials, and acids. The alcohols and esters are commonly used in parenteral products. The quaternary compounds, which are commonly used in ophthalmic products, are not compatible with negatively charged ions or molecules.

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Table 17.3. Common Buffers Used in Parenteral Formulations

Buffer	pK_a	Usual Buffering Range
Acetic acid	4.8	3.5–5.7
Citric acid	3.14, 4.8, 5.2	2.1–6.2
Glutamic acid	2.2, 4.3, 9.7	8.2–10.2
Phosphoric acid	2.1, 7.2, 12.7	2–3.1, 6.2–8.2
Benzoic acid	4.2	3.2–5.2
Lactic acid	3.1	2.1–4.1
Ascorbic acid	4.2, 11.6	3.2–5.2
Tartaric acid	3.0, 4.3	2.0–5.3
Succinic acid	4.2, 5.6	3.2–6.6
Adipic acid	4.4, 5.28	3.4–6.3
Glycine	2.34, 9.6	1.5–3.5, 8.8–10.8
Malic acid	3.4, 5.1	2.4–6.1
Triethanolamine	8.0	7–9
Diethanolamine	9.0	8.0–10.0
Tromethamine	8.1	7.1–9.1

The literature reports interactions of the parabens with surfactants and formation of molecular complexes with gelatin, methylcellulose, polyvinyl pyrrolidone, and polyethylene glycol. These interactions may decrease preservative efficacy. Some antimicrobial compounds, such as benzyl alcohol, may be adsorbed by the container closure. Thus, microbial preservation must be demonstrated for the final formulated product.

Buffers

The buffer system establishes and maintains the product pH. A specific buffer system is selected such that the pK_a of the system is within one pH unit of the pH desired for the product. A list of common buffers is provided in Table 17.3. The selection of the product pH is based on the stability of the active drug. When alternative buffers are available, a comparison of their respective effects on stability will usually aid in the final choice. The acetate buffer system is not a good choice for a lyophilized product due to the volatility of acetic acid. Loss of acetic acid results in a pH shift when the product is reconstituted. The pH of solutions containing a phosphate buffer system have been shown to shift during cooling due to precipitation of sodium phosphate species. These pH shifts during freezing may cause

damage to a protein. Since the specific buffer and the buffer capacity can contribute to injection pain, these effects should be evaluated in the selection of the buffer. Each species of the buffer system affects the tonicity of the final product; this influence must be considered during product development. For example, as the pH of a formulation containing monosodium phosphate is adjusted, the disodium salt is formed and contributes to product tonicity.

Antioxidants

Preformulation data will identify compounds sensitive to oxidation. Free radicals or molecular oxygen mediates oxidation, and several alternative stabilization approaches are available. In many cases, several approaches are utilized concurrently. One approach is lowering the product pH, which, according to the Nernst equation, increases the oxidation potential of the drug and thus increases stability. When oxygen contributes to degradation, it can be displaced during the filling operation by "bubbling" an inert gas such a nitrogen or argon gas through the solution prior to filling the vials. Additionally, the container headspace can be overlaid with the inert gas. An antioxidant may be useful if further protection is necessary. The specific antioxidant selected should have a lower oxidation potential than the drug. Several antioxidants and concentrations should be evaluated because, in many cases, a single agent is not sufficient. Sulfites are associated with allergic reactions in some patients. This reaction has a rapid onset and is not always confirmed by an oral challenge. Despite this reaction potential, sulfites may be used in a formulation if necessary to stabilize a life-saving product.

Examples of antioxidants include sodium bisulfite, ascorbic acid, glutathione, and propyl gallate. Sodium bisulfite tends to react irreversibly with the double bonds found in aldehydes and some ketones, and frequently results in a significant loss of biological activity. Epinephrine forms a bisulfite addition product, as do other sympathomimetic drugs having ortho- or para-hydroxybenzyl alcohol derivatives. The meta-hydroxy alcohol does not react with sodium bisulfite. Sulfites are converted to sulfates in the oxidation reaction, and if small amounts of barium are present, a precipitate will form.

Chelating Agents

Chelating agents are used to increase the solubility of a drug or to impart some product stability. Compounds such as ascorbic acid, citric acid, and ethylenendiaminetetraacetic acid chelate metals, which would otherwise catalyze oxidation reactions, and provide measurable benefits for some products.

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Surfactants

Surfactants are used to solubilize a drug and, for protein products, to minimize adsorption of the protein on surfaces. Most polysorbates are derived from animal sources, and their use in Europe is becoming problematic due to the increasing concerns with BSE. This concern is expanding to the rest of the world and will impact in the selection of excipients. Several suppliers are beginning to offer polysorbates from vegetable sources. Polysorbates can contain peroxides that may adversely affect product stability and, as for all excipients, specifications will need to be established.

Tonicity Agents

The active drug and each excipient contribute to the tonicity of the formulation. When the tonic contribution of these combined ingredients is not sufficient to provide an isotonic solution, then tonicity agents, such as dextrose, sodium chloride (NaCl), sodium sulfate, or mannitol can be added. Additional details are provided in the osmolality section below.

In summary, formulation activities focus on the selection of the solvent, the necessary excipients (buffers, antimicrobials, antioxidants, chelating agents, surfactants, and tonicity agents) with corresponding concentrations, the container/closure system, and on demonstrating adequate stability.

Focus on Osmolality, Cosolvents, Oils, and pH

The contribution of isotonicity in reducing injection pain is not always clear but, at a minimum, it may reduce tissue irritation. Injection pain may occur during and immediately following product administration but may be delayed or prolonged, with an increase in severity with subsequent injections. Pain can be difficult to assess because significant patient variation exists, and there are few preclinical methods for evaluation.

Literature describing pain associated with parenteral products has focused on three areas: osmolality, cosolvents, and pH. This is a pragmatic focus since osmolality and pH are easy to measure. Unfortunately, the adjustment of pH and osmolality may not be possible for some formulations due to physical or chemical stability of the product. In other products, the drug molecule may be inherently painful when injected. In both of these cases, formulations must be delivered at a low drug concentration or in complex formulations (such as emulsions or liposomes), in an attempt to "hide" the drug from pain receptors. Due to volume constraints, these are not always a viable alternative for IM or SC injections, leaving the formulator to design the best possible product and otherwise relying on the health professional to further minimize the injection pain at the time of administration. Since these formulations pose significant development

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issues, most formulators optimize the pH and isotonicity and provide information on appropriate dilution for administration.

Osmolality

The primary purpose for adjusting product osmolality is to minimize red blood cell lysis, tissue damage, and pain when the product is administered. An isotonic solution provides an electrolyte environment that allows human erythrocytes to maintain "tone." If cells are placed into a hypertonic solution, the cells may lose water and shrink (crenation). If placed in a hypotonic solution, the water moves into the cells, which can then swell to the point of breaking. Thus, the formulator's goal is to develop a product that, when administered, will be as close to isotonic as possible. In fact, the British Pharmacopoeia states that aqueous solutions for SC, intradermal, or IM injections should be made isotonic if possible. Unfortunately, there is no formulation solution for a product that is hypertonic. The necessity for administration in a diluted form or by slow infusion is appropriately noted in the product package insert.

Common agents used to adjust tonicity of a product include dextrose, NaCl, mannitol, and sodium sulfate. Care must be taken if sodium sulfate is selected for a product packaged in barium-containing glass, because even extremely small amounts of leached barium can lead to the precipitation of barium. Since all ingredients contribute to the tonicity of the product, it is necessary to measure or calculate the contribution of each and then, if necessary, adjust the product tonicity with additional agents.

Measuring Osmolality. Determination of osmolality is performed by measuring one of the four colligative properties, which depend only on the number of "particles" in the solution: (1) osmotic pressure elevation, (2) boiling point elevation, (3) freezing point depression, and (4) vapor pressure elevation. Of these methods, freezing point depression and vapor pressure elevation are most commonly utilized. These methods are relatively easy to perform and reasonably accurate. Commercial instruments are readily available.

Iso-osmolality, as determined by physical methods such as freezing point depression or vapor pressure reduction, is different from isotonicity determined by biological methods such as erythrocyte hemolysis. This difference is important since cells do not always behave as semipermeable membranes, and measuring biological compatibility by direct methods will identify problematic molecules that can cause lysis or tissue damage. Urea is the most frequently cited example of such a molecule; a 1.8 percent solution of urea has the same osmotic pressure as NaCl at 0.9 percent, but causes cell lysis. Other compounds that have specific cellular effects include glycerin, propylene glycol, and boric acid.

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Although physical methods such as freezing point depression and vapor pressure are valuable tools in formulation development and quality control of the product, it is imperative to have direct methods to measure the effect of the product on red blood cells and tissue. Methods to evaluate cellular effects are given below, and methods to evaluate tissue effects are provided in other chapters of this book. The references provide additional information, and formulators are encouraged to include them in their library.

Determining Tonicity (Hemolysis). A common in vitro method to evaluate a product is by measuring erythocyte hemolysis. Typically the release of hemoglobin from the damaged cells is measured spectrophotometrically; however, a more sensitive method is to directly observe the changes in cell volume. An aqueous isotonic NaCl solution is used as the standard. Several protocols are available that describe incubating the product with erythrocytes suspended in defibrinated blood for a specified time, centrifuging to separate the erythrocytes and ghost cells, and then using a spectrophotometer to determine the absorbance of the supernatant versus a standard at 520 nm. Solution to blood ratios of 100:1 have been used. Concerns that this ratio is not realistic and can often give misleading results has lead investigators to use dilutions of 1:10—a complete reversal of proportions—with no hemolysis found.

Others have evaluated product effects by directly observing variations of red blood cell volume when suspended in solution. This method is more sensitive to small tonicity differences than the hemolysis method.

An alternative method to determine the compatibility of a product with blood is proposed by Ito et al. (1966). The coil planet centrifuge (CPC) method was originally developed to examine dynamic membrane properties of erythrocytes. The system comprises three instruments: the CPC itself, gradients for preparing the solution having an osmotic gradient in a coil, and a scanning spectrophotometer for recording a hemolytic pattern of the sample coil. The CPC is a specific centrifuge that rotates at 1,600 rpm around the main axis at a constant temperature of 37°C, while the coil holder fitted with coils rotates at 16 rpm. The design of this equipment ensures that the centrifugal force is constant irrespective of the distance from the main axis. It has been found that measuring the hemolysis of oil injections and those of high concentration or viscosity by this method is difficult, if not impossible.

The "osmogram" output shows red blood cell hemolysis as a function of the osmotic gradient. The hemolytic pattern of injections are divided into the following four patterns:

1. Hemolysis is remarkable, or erythrocyte is coagulated and does not move.

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2. Hemolysis takes place gradually and then continues or is shifted to the side of high osmotic pressure.
3. No change is observed.
4. Pattern is shifted to low osmotic pressure, indicating stabilization of the erythrocyte membrane.

This method may provide valuable information for the evaluation of parenteral products; however, the full potential of the method is unknown since there is little information available.

Calculating Tonicity. Several methods used to calculate tonicity are summarized below.

(1) The method of NaCl equivalents expresses tonicity in terms of the amount of drug equivalent to NaCl since, in most cases, when an aqueous solution is iso-osmotic with 0.9 percent NaCl, it will be isotonic with physiologic systems. The NaCl equivalent value, E, is defined as the weight of NaCl having the same osmotic effect as 1 g of the drug. A 1 percent NaCl solution has an equilibrium freezing temperature of -0.58°C and is given a NaCl E value of 1.00. The freezing temperature of serum is -0.52°C, equivalent to the freezing temperature of a 0.9 percent NaCl solution. Therefore, if a 1 percent solution of a specific compound has a freezing temperature of -0.058°C, then it has an E value of 0.1. Thus, 1.0 g of this compound will have the same tonic value as 0.1 g of NaCl; to prepare 100 mL of an isotonic solution containing 1 g of this substance, 0.8 g of NaCl must be added. *Remington's* (Gennaro 1995) has an extensive list of NaCl equivalents for specific excipients and drugs.

Different compounds can be used to adjust solution tonicity. For example, in the above calculation, 0.8 g of NaCl was needed to render the solution isotonic. If, however, dextrose is desired to adjust tonicity, then the amount of dextrose would be

$$(1 \text{ g dextrose}/0.16 \text{ g NaCl}) \times 0.8 \text{ g NaCl} = 5 \text{ g dextrose}$$

A comparison of measured osmolality to calculated values using the NaCl equivalent method shows agreement within 10 percent; for most systems this is sufficiently accurate.

(2) The freezing point depression method uses "D" values having units of °C per x percent of drug. The D values for some drug compounds can be obtained in the literature.

(3) The V value of a drug is the volume of water used to dissolve a specific weight of drug to prepare an isotonic solution. The purpose of this method is to prepare an isotonic solution of the drug and then to dilute this to the desired final concentration with a suitable isotonic vehicle. This method is most commonly used for ophthalmic preparations. Values for commonly used drugs are available in the literature.

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(4) Other calculations such as the L_{iso} method can be used for estimations when values for a specific compound are not available. The mathematical relationship of L_{iso} to the NaCl equivalent, E, is:

$$E = 17 (L_{iso}/M)$$

where M is the molecular weight of the compound. Average L_{iso} values for different types of compounds are given in Table 17.4.

Cosolvents and Oils

Cosolvents are commonly used to enhance drug solubility and stability. Cosolvents may include ethanol, propylene glycol, polyethylene glycols, and glycerin. These components have intrinsic effects on biologic tissue and can alter the properties of other excipients, thus influencing the tissue damage or pain caused by the product. There is a dearth of literature on the pain caused by cosolvents, but there is also a growing body of knowledge on the tissue damage that they can cause. It is not certain that tissue damage is always directly correlated with injection pain, but minimization of both pain on injection and potential for tissue damage should be included in the product development plan.

In studies by Brazeau and Fung (1989a, b), moderate concentrations of organic cosolvents (20 to 40 percent v/v) show the following relative myotoxicity ranking: propylene glycol > ethanol > polyethylene glycol 400. These investigators also discovered that total myotoxicity equaled the sum of the individual myotoxicity of each component, with the exception of preparations containing polyethylene glycol 400, which apparently has a protective effect.

Table 17.4. Average L_{iso} Values for Different Types of Compounds

Compound Type	L_{iso}	Example
Nonelectrolyte	1.9	Sucrose
Weak electrolyte	2.0	Phenobarbital, boric acid
Di-divalent electrolyte	2.0	Zinc sulfate
Uni-univalent electrolyte	3.4	Sodium chloride
Uni-divalent electrolyte	4.3	Sodium sulfate, atropine sulfate
Di-univalent electrolyte	4.8	Calcium chloride
Uni-trivalent electrolyte	5.2	Sodium phosphate
Tri-univalent electrolyte	6.0	Aluminum chloride
Tetraborates	7.6	Sodium borate

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Consideration must also be given to cosolvent effects on other product excipients. Since most buffers are conjugates of a weak acid or base, the polarity shift caused by cosolvents may shift the pK_a of the buffer species. It is best to evaluate biological compatibility using direct biological methods, because cosolvents may have both specific cellular effects and indirect excipient effects.

Another class of nonaqueous vehicles used in parenteral formulations are the fixed oils, including corn, cottonseed, olive, peanut, sesame, and soybean. Oils of vegetable origin are selected because they can be metabolized, are liquid at room temperature, and will not rapidly become rancid. To remain liquid at room temperature, a fixed oil must contain unsaturated fatty acids, which, when present in excessive amounts, can cause tissue irritation. The U.S. Pharmacopeia (USP) includes specifications for rancidity, solidification range of fatty acids, and free-fatty acids. The formulator may include antioxidants, such as tocopherol (a natural component of many fixed oils) to prevent the product from becoming rancid.

pH

A product buffer system is selected to help maintain an environment in which the drug is stable throughout the commercial shelf life of the product. These systems are composed of a weak acid or base and a corresponding salt. The ratio of these species determines the pH, and the concentration provides a buffer capacity to resist pH changes due to product degradation or container-closure interactions. A buffer system is most efficient at its pK_a, thus, buffers are generally chosen within one pH unit of the desired product pH.

The buffer concentrations typically chosen for a product range from 1 to 2 percent, although higher concentrations of up to 5 percent have been used with citrate buffers. The more a pH deviates from physiological conditions and the higher the buffer capacity, the more likely the product will contribute to tissue damage or injection pain. Table 17.3 provides a list of acceptable buffers with pK_a values and usual pH buffer ranges.

Buffer systems are in an equilibrium that is sensitive to temperature and the concentration of each species. Each species in this equilibrium may contribute differently to product osmolality. There may be an error in estimating the contribution to osmolality of each species at room temperature, since the most common method to measure osmolality is by freezing point depression. Cutie and Sciarrone (1969) demonstrated for boric acid, Sorensen, and Palitzsch buffers that if formulated to be isotonic as measured by freezing point depression, the solutions may be slightly hypertonic at 37°C. Sodium tetraborate has, in fact, been demonstrated to have a NaCl equivalent (E value) of 0.45 at 37°C but 0.35 at 0°C, a 23 percent change. For most formulations, this is not of physiological significance;

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however, it should not be discounted for those formulations where close tolerance to isotonicity is necessary.

A vapor pressure osmometer provides an alternative to the freezing point method and may be particularly useful when the data for temperature and concentration effects on ionization constants are not available. A limitation of the vapor pressure method includes interference by volatile substances such as ethanol.

Post-Formulation Procedures

Despite efforts to minimize or eliminate pain through formulation optimization, some products remain painful when injected. The literature is replete with suggestions on how to reduce pain during the administration of a product. Unfortunately, much of these data are incomplete or seemingly contradictory. Deficiencies in the research conducted on children's pain have been noted, and the point is frequently made that children are shortchanged with respect to pain management. Post-formulation efforts to alleviate pain which are discussed in this chapter are included in the following categories: pH, additives or solvent adjustments; devices or physical manipulations, and psychological.

pH, Additives, and Solvents

Drugs stable only in acidic conditions are purposefully formulated to ensure an adequate commercial shelf life. Because these acidic products are associated with injection pain, sodium bicarbonate is extemporaneously added prior to administration to more closely match physiological pH (pH 7.3). This approach appears to successfully reduce the pain caused by local anesthetics; however, studies with other products have been equivocal. For anesthetics, this increased pH will alter the stability of the product and may result in the precipitation of the less soluble, nonionized species. The amount of sodium bicarbonate that can be safely added is variable given the range of anesthetic products (pH of 3.5 to 5.5), the concentration of sodium bicarbonate, and other variables.

The reduction in pain for anesthetic products does not appear to be entirely due to the increased pH of the solution. The indirect effect of increasing product pH is to shift the equilibrium of anesthetics to the uncharged species that may diffuse more rapidly and consequently inhibit pain perceptions. Individual drugs or drug species (charged or uncharged) may have different intrinsic pain induction potential, independent of pH. The study design and product ingredients must be considered when evaluating data, because some excipients such as benzyl alcohol have local anesthetic properties.

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Another extemporaneous technique is to add lipids to the commercial formulation. This method shifts more of the drug from the aqueous phase and has been successful in reducing injection pain for methohexital and propofol. Such additions need to be supported by studies to verify product stability, similar pharmacokinetics, and efficacy.

Clinicians also minimize or eliminate injection pain by topical administration of local anesthetics, which decrease pain sensation, or nitroglycerin ointment, which dilates local blood vessels and promotes absorption of the irritating substance. Although of interest to the formulator, these topical approaches do not pose formulation issues.

Devices and Physical Manipulations

Parenteral administration techniques will affect the magnitude of the pain. These include the practical training received by healthcare professionals; proper selection of administration equipment; and manipulation of the injection rate, injection site, and temperature. The formulator should note how health professionals may use the product and consider the need for pertinent data during product development.

Parenteral administration techniques are part of a nurse's education. This practical training is aimed at increasing the comfort of the patient and efficiency of the nurse. The references given at the end of this chapter provide additional detail and information on less common parenteral routes of administration.

Subcutaneous Injection

Drugs recommended for SC injection include nonirritating aqueous solutions and suspensions contained in 0.5 to 2.0 mL (target 1 mL or less) of fluid. The needle sizes are 25 gauge 5/8 in. length for an average adult and 25 gauge 1/2 in. length for an infant, child, elderly, or thin patient. After cleaning the area with an alcohol sponge, allow the skin to dry before skin penetration to avoid the stinging sensation caused by the alcohol entering the subcutaneous tissue.

With the nondominant hand, grasp the skin around the injection site firmly to elevate the subcutaneous tissue, forming a 1 in. fat fold. This provides rigidity for needle entry. Tell the patient "you will feel a prick as the needle is inserted." Holding the syringe in the dominant hand with the needle bevel up, insert the needle quickly in one motion. Release the patient's skin to avoid injecting the drug into compressed tissue to minimize irritation of nerve fibers, confirm the needle is in the tissue, and inject slowly. After the injection, remove the needle quickly. Cover the skin and massage the site gently (unless contraindicated as with heparin or insulin) to help distribute the drug and reduce pain.

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Intradermal Injection

Intradermal injections are typically used only for local effects or diagnostic purposes in volumes of 0.5 mL or less. Needles of 26 or 27 gauge and 1/2 to 5/8 in. in length are used. The injection is given at a 15° angle about 1/8 in. below the epidermis at sites 2 in. apart. Stop when the needle bevel tip is under the skin and inject slowly; some resistance should be felt. A wheal should form; if it does not, the injection is too deep. Withdraw the needle at the same angle as the entry. Do not massage the site, as this may cause irritation.

Intramuscular Injection

IM injections deliver medication into highly vascularized deep muscle tissue. Because there are few sensory nerves in these tissues, pain is minimized when injecting irritating drugs. The volume for IM injection can be up to 5 mL, although it is typically less than 3 mL. A 20 to 25 gauge needle of 1 to 3 in. in length is used. Once the appropriate injection site has been selected and properly prepared, gently tap it to stimulate nerve endings and minimize pain when the needle is inserted. The gluteal muscles should not be used for a child under the age of 3, nor for someone who has not been walking for the prior year. Never inject into sensitive muscles, especially those that twitch or tremble when you assess site landmarks. Injections in these trigger areas may cause sharp or referred pain, such as pain caused by nerve trauma.

Intravenous Bolus Injection

Bolus drug administration is used when immediate drug effects are necessary, when the drugs cannot be diluted (diazepam, digoxin, phenytoin), or for drugs that are too toxic or irritating for other routes of administration. A 20 gauge needle is typically used. Bolus injections are given through the largest vein suitable, since the larger the vein, the more dilute the drug becomes, thus minimizing vascular irritation. An in-depth discussion of specific routes of administration, techniques, equipment, and cautions is readily available in the literature referenced at the end of this chapter.

Devices

Devices offer significant opportunities to reduce the fear and increase the consistency of parenteral injections. Some of these devices are needle free, with the product propelled through the skin under pressure. Some studies have demonstrated reduced pain during administration. These devices may affect the quality of a shear-sensitive macromolecule or alter drug

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pharmacokinetics (PK) due to the pattern of drug deposition. For a given product, additional product or PK characterization may be necessary. These devices deliver subcutaneous injections; however, controversy remains on whether they can deliver an IM injection.

Other devices use "hidden" needles with guides that facilitate insertion of the needle and subsequent injection of the medication. These allow for reproducible injections. Their utility is dependent on the perception of the patient, the cost of the device, and the ease of use. These devices have been shown to be less painful and improve compliance for chronic administration of SC injections.

Temperature

Healthcare providers continually explore methods to increase the comfort of the patient by altering the temperature of the product or skin. Numbing the skin surface with ice or other means has successfully been used to reduce injection pain; in one case, injecting a cool solution before infusing the drug appeared to be successful in reducing pain. Changing the product temperature is more significant to the product formulator. Warming propofol to 37°C has been demonstrated to decrease the incidence of pain by 37 percent. Since both cooling and warming have been shown to reduce injection discomfort, it may be that some relief is provided by the quick, but transient temperature effects on the nociceptor receptors or pain mediators. The formulator should be aware that products might be either cooled or warmed by healthcare professionals and, therefore, consider the impact of temperature changes on the formulation during product development.

Psychological

The contribution of psychological factors to injection pain is substantial and has been considered in the design of the new devices mentioned previously. Psychology is used in the clinic to minimize injection pain, particularly in children. These are interesting and provided here for completeness.

The pain experience is influenced by age, physical, emotional, cultural, and, social factors as are the preferred control methods. A Gallup Poll stated that 58 percent of children rely on their own coping skills, such as thinking about something else to make shots bearable, and 47 percent said they specifically disliked needles. Perhaps we as healthcare providers can provide more assistance.

Several articles provide lists and examples of proactive psychological techniques shown to minimize injection pain, including distraction, honesty, and a demonstration of caring. Distraction asks the patient to focus on an image and and to use breathing techniques. The person giving the injection should be honest yet supportive while making general sympathetic statements that indicate the child can control pain. The child should

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be involved in discussions, and all actions should be described before or as they are being performed.

The psychology and perception of pain are important factors in pain management and both the healthcare provider and formulator can effectively utilize the techniques mentioned above in the development, support, and administration of therapeutic products.

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ATTACHMENT F - COMPILATION

TAB 5

United States Patent Office

3,164,520

Patented Jan. 5, 1965

3,164,520

INJECTABLE STEROID COMPOSITIONS CONTAINING AT LEAST 75% BENZYL BENZOATE

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No Drawing. Filed Oct. 29, 1962, Ser. No. 233,931

4 Claims. (Cl. 167—58)

This invention relates to compositions of matter and more particularly to new parenterally administrable pharmaceutical compositions comprising one or more active medicaments and a physiologically acceptable non-toxic pharmaceutical vehicle, comprised essentially of benzyl benzoate.

The active medicament which may be incorporated in the novel compositions of this invention may be any one which is administered for use in comparatively large unit dosages, for example, 10 mg./ml. to 500 mg./ml. and which is soluble in benzyl benzoate. Examples of the medicaments which may be employed in this invention include inter alia, steroid hormones, especially those steroid hormones which exhibit anabolic, estrogenic, androgenic and progestational activity, for example, 17-hydroxyprogesterone and the esters thereof, testosterone, estradiol and the acid esters thereof, progesterone and its derivatives and Δ^1-testololactone and its derivatives. In the most preferable embodiment of this invention the active medicament is a steroid hormone although other pharmaceutically active compounds may also be employed, with satisfactory results.

Heretofore it has been well recognized in the preparation of parenterally administrable pharmaceutical compositions that a suitable solvent must be employed to render the composition injectable. However, as the science of medicine has progressed it has been found that increasingly higher dosages of certain medicaments must be employed in the treatment of certain ailments in order to achieve several advantages. Among these advantages can be numbered the prolongation of activity of the medicaments involved and the lessening of the total number of individual injections which are needed to obtain the same results.

Additionally, it has been found that new chemical modifications of medicaments are continually being discovered and the solubility of these modified medicaments in the solvents commonly employed, appears to be more and more limited and it has therefore become increasingly difficult to dissolve these new modified medicaments in parenterally acceptable vehicles. It is well-known that certain pharmaceutical vehicles yield satisfactory results at low level medicament concentrations when employed in compositions for parenteral administration. Such vehicles are the vegetable oils such as cotton seed oil, peanut oil, sesame oil, or corn oil, in combination with small amounts of benzyl benzoate. However, when an increased dosage level of the medicaments is employed, along with a correspondingly necessary increased amount of pharmaceutical vehicle it has been found that certain undesirable disadvantages exist.

The undesirable disadvantages which are present when the prior art vehicles are employed with a high dosage level of medicaments, are many. In addition to the prior art vehicles being incapable of solubilizing any great quantities of the medicaments, it has been found that the compositions heretofore employed produce an undue amount of irritation at the site of injection, when parenterally administered into the animal being treated.

It has now been found that the disadvantages encountered in the parenteral administration of high dosage levels of the medicaments of this invention can be avoided by employing the novel pharmaceutical compositions of

this invention. It has been found that these disadvantages can be overcome by employing benzyl benzoate as the essential component of the pharmaceutical vehicle of parenterally administrable compositions. The benzyl benzoate has been found to be capable of dissolving great quantities of the medicaments of this invention and the resulting parenterally administrable composition employing this vehicle does not produce undue irritation when injected into the animals being treated.

The amount of benzyl benzoate which may be employed in the compositions of this invention while still yielding satisfactory results has been found to range from about 75% to 100% by volume of the pharmaceutical vehicle employed. Thus the ratio of benzyl benzoate present in the pharmaceutical vehicle as compared to any other ingredients therein must be at least 3 to 1. In the most preferable embodiment of this invention it has been found that a pharmaceutical vehicle consisting essentially of pure benzyl benzoate yields the best results although at lower levels satisfactory results are also obtained.

As is common in the art of preparing parenterally administrable pharmaceutical compositions other additives such as preservatives, antioxidants or anesthetics, such as benzyl alcohol and the other like well known additives may also be included in the pharmaceutical compositions of this invention. However, their use herein is permissive and not mandatory as their incorporation or omission in the final product of this invention does not substantially affect the results herein obtained.

The compositions of this invention are easily prepared by merely taking the desired amount of medicament and dissolving it in the pharmaceutical vehicle of this invention by any means known in the art, for example, by mere stirring.

The final compositions of this invention are parenterally administrable to the animal being treated. The administration of the composition may be accomplished intramuscularly, subcutaneously or in any other manner known to the art as may be determined in the individual cases wherein this invention is employed. It has been generally found that the most preferable results are obtained when an intramuscular route of administration is employed, although other methods of administration will also give satisfactory results.

The invention is more particularly illustrated by the following examples:

Example 1

Two g. of the acetophenone derivative of 16,17-dihydroxyprogesterone are dissolved in 10 ml. of benzyl benzoate with stirring and warming. The resultant solution is then filled in vials of 5 ml. each and sterilized by autoclaving at 121° C. for two hours.

0.25 ml. of the resulting solution is then injected into the vastus lateralis muscle of a rabbit producing a lesion at the site of the injection having the size of about 640 cubic millimeters after two days.

When 2 g. of the acetophenone derivative of 16,17-dihydroxyprogesterone are dissolved in 4.5 ml. of benzyl benzoate and 5.5 ml. of castor oil in accordance with the procedure of Example 1 and 0.25 ml. of the resultant solution is injected intramuscularly into the rabbit a lesion at the site of injection having a size of 967 cubic millimeters after two days.

Example 2

The procedure of Example 1 is followed except that 2 g. of testosterone palmitate are substituted for the acetophenone derivative of 16,17-dihydroxyprogesterone of Example 1.

0.25 ml. of the resultant solution is injected intramus-

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cularly into a rabbit producing a lesion at the site of injection having the size of about 420 cubic millimeters after two days. When 2 g. of testosterone palmitate are dissolved in a vehicle consisting of 40% castor oil and 60% benzyl benzoate and the resultant solution is injected intramuscularly into the rabbit, a lesion at the site of injection having a size of 610 cubic millimeters is produced after two days.

Example 3

A 25% solution of progesterone is prepared by dissolving 2.5 g. of progesterone in benzyl benzoate to make 10 ml. Sterilization is obtained by autoclaving the solution at 121° C. for 2 hours. When 0.25 mg. of this solution is injected into the vastus lateralis muscle of the rabbit, a lesion is produced which, after 2 days, measures 672 cubic millimeters.

When 2.5 g. of progesterone are dissolved to make 10 ml. in a mixture of 50% benzyl benzoate and 50% castor oil as the vehicle, and 0.25 ml. of this solution is injected into the rabbit muscle, a lesion size of 898 cubic millimeters is produced after two days.

Example 4

A 50% solution of hormones is prepared by dissolving 2.5 g. of progesterone and 2.5 g. of 17-hydroxyprogesterone caproate in benzyl benzoate to make 10 ml. of final product. After autoclaving at 121° C. for 2 hours to sterilize, 0.25 ml. of the solution is injected into a rabbit muscle and the lesion size is measured after 2 days. A lesion consisting of 572 cubic millimeters was produced. When this same hormone combination in the same proportions was dissolved in a vehicle consisting of 46% benzyl benzoate and 54% castor oil, a rabbit muscle lesion size of 1047 cubic millimeters is produced 2 days after injection of 0.25 ml. of test material.

Example 5

A 40% solution of testosterone enanthate is prepared by dissolving 4.0 g. in benzyl benzoate to make 10 ml. of final volume. After autoclaving at 121° C. for 2 hours to sterilize, 0.25 ml. of the solution is injected into the vastus lateralis muscle of the rabbit and the lesion size is measured after 2 days. A lesion consisting of 847 cubic millimeters is produced.

When this same quantity of hormone is dissolved in a vehicle consisting of 20% benzyl benzoate and 80% sesame oil and 0.25 ml. is injected a lesion size of 1441 cubic millimeters is produced.

Example 6

A 5% solution of Δ^1-testololactone is prepared by dissolving 50 mg./ml. in benzyl benzoate and after autoclaving to sterilize, 0.25 ml. of the solution is injected into a rabbit muscle. After 2 days a lesion size of only 483 cubic millimeters is produced.

Example 7

15 mg. of Δ^1-testololactone is dissolved in a solution comprised of 7.5 ml. of benzyl benzoate and 2.5 ml. of castor oil. The resultant solution is sterilized, then filled in vials of 5 ml. each and sterilized by autoclaving at 121° C. for 2 hours. The injectable solution may then be administered to the patient being treated.

This invention may be variously otherwise embodied within the scope of the appended claims.

What is claimed is:

1. A parenterally administrable pharmaceutical composition comprising the acetophenonide of 16,17-dihydroxyprogesterone and a physiologically acceptable non-toxic pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

2. A parenterally administrable pharmaceutical composition comprising testosterone palmitate and a physiologically acceptable non-toxis pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

3. A parenterally administrable pharmaceutical composition comprising testosterone enanthate and a physiologically acceptable non-toxic pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

4. A method of administering a large single dosage of a steroid which comprises parenterally administering to the patient being treated a composition comprising a steroid selected from the group consisting of 17-hydroxyprogesterone, the caproate ester of 17-hydroxyprogesterone, testosterone, the enanthate ester of testosterone, the palmitate ester of testosterone, estradiol, progesterone, and Δ^1-testololactone, and a pharmaceutical carrier, said carrier being at least 75% by volume of benzyl benzoate.

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ATTACHMENT F - COMPILATION

TAB 6

USE OF NONAQUEOUS SOLVENTS TO PREPARE INJECTION SOLUTIONS

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UDC. 615.456.2.014.24

Until now a rather considerable number of solvents which are used to prepare injection solutions has been described in the literature. These can be divided into three basic classes: aqueous, nonaqueous, and mixed solvents.

To the class of aqueous solvents we can assign those in which water is the main component. This can be water for injections, solutions of various inorganic salts in water, cosolvents used to accelerate the solution of the active materials, and the like.

To the class of nonaqueous solvents we may assign those in which the main component is some organic compound which permits one to obtain solutions of medicinal agents that are suitable for injections – vegetable oils, polyethylene oxides, or the like.

And finally, to the class of mixed solvents we may assign solvent mixtures which enable one to prepare injection solutions when it is not possible to prepare stable solutions by using the individual solvents, or when one wishes to make sure of obtaining a number of fixed solution characteristics, for example, a given dwelling time of the active substance in the blood system, or the like.

The present review is devoted to the use of nonaqueous solvents to prepare injection solutions.

Solvents which belong to the nonaqueous class present special interest, since using them permits one to prepare injection solutions of substances which are unstable in water or do not dissolve in it, to obtain solutions with an increased suitability time, and also to solve a number of other technological and pharmacological problems.

The following requirements are imposed on these solvents:

1. Pharmacological harmlessness: a) limited acute toxicity; b) limited chronic toxicity (on repeated introduction); c) absence of local (irritating) action in the doses employed.

2. Absence of an effect of increasing toxicity at an adequate therapeutic action of the solution and medicinal agent.

3. Chemical compatibility.

4. Technological suitability: a) high dissolving power; b) possibility of sterilization; c) low viscosity; d) absence of reaction with apparatus; e) absence of fire hazard.

5. Availability.

From the point of view of therapeutic effect, an important property of a solvent is its solubility in water or miscibility with it. On this may depend the rate of action of the medicine, the rate of solvent reabsorption, and local transferability.

In a number of cases, when the active substance is insoluble or poorly soluble in water, contact with tissues causes precipitation of the active substance at once after subcutaneous or intramuscular introduction;

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TABLE 1. Most Important Characteristics of Vegetable Oils Used to Prepare Injection Solutions

Oil	Saponification No.	Iodine number	Acid No.	Refractive index	Density
Almond oil	190—195	93—102	<2,5	1,470—1,472	0,913—0,918
Peanut oil	185—197	85—105	<2,0	1,468—1,47250 (40°)	0,910—0,920
Cottonseed oil	190—198	109—116	<0,4	1,4645—1,4655 (40°)	0,915—0,921
Sunflower oil	188—194	125—136	<0,5	—	0,917—0,924
Corn oil	187—193	102—128	<0,4	—	0,914—0,921
Olive oil	190—195	79—88	<0,2	—	0,910—0,915
Peach oil	187—195	96—103	<2,5	1,470—1,473	0,914—0,920
Sesame oil	188—195	103—116	<2	1,472—1,476	0,916—0,921

this is regulated by the rate of diffusion and resorption of the solvent by the organism. Thus, in this case the solvent has the function of a carrier, which permits one to make the injection.

In other words, a substance which is insoluble in water has a different "fate," depending on where it was introduced – under the skin or into a muscle, and whether it was dissolved in a nonaqueous solvent which mixes or does not mix with water. In the first case the medicine is precipitated more or less rapidly, and naturally is resorbed more or less rapidly by the organism. In the second case it remains in a solution which diffuses slowly around the site of injection. When the solution is resorbed, the medicine manifests its activity. Therefore, in each separate case of preparing an injection solution in an nonaqueous solvent it is necessary to take into account the properties of the solvent and the therapeutic effect which one wishes to attain.

Of all the nonaqueous solvents, the following have the greatest practical value: vegetable oils, ethyl oleate, propylene glycol, and polyethylene glycols with molecular weights of 300 and 400.

Together with water, vegetable oils are most frequently used as solvents. This is explained not only the appropriate properties of the oils, which determine their use for injections, but also by the fact that they came first into pharmaceutical practice as solvents. The long time of use of vegetable oils as solvents for injection has made it possible to find rather effective and reliable methods for purifying them, for storing and sterilizing them, and for studying their pharmacological properties.

It should be noted that oils are used mainly for intramuscular injections; only rarely for subcutaneous ones. In recent years a number of authors have proposed ultra-emulsions of vegetable oils (cottonseed, soya, sesame, or sunflower) for parenteral feeding.

In Table 1 we give the most important characteristics of the oils which are used as solvents, according to data from various pharmacopoeias. And, still, fatty oils have limited use; first, they have a high viscosity, in connection with which oil injections are painful; second, only a small number of medicines dissolve in oils. Finally, oil injections can cause granuloma formation. Attempts are being made to reduce the significance of these defects of oil solutions. For example, in individual cases ethyl ether or an ethylene glycol ether is added to reduce viscosity. The solubility of some materials is increased by adding "cosolvents" (benzyl benzoate, benzyl alcohol, or the like). In those cases where the substance dissolves only in an oil or the oil is a stabilizing agent for the medicine, the use of oil is quite justified.

In recent years, synthetic and semisynthetic preparations have been acquiring ever-increasing importance as solvents for injection; these make up a very numerous group of the nonaqueous solvents and belong to various classes of chemical compounds. Here belong the alcohols (ethyl, benzyl, phenylethyl, propylene glycol, butylene glycol, trichloro-t-butyl, etc.), ethers and esters (polyoxyethylene glycol, ethyl ether, phenoxyethanol, ethyl acetate, ethyl oleate, benzyl benzoate, etc.), amides (N-methylacetamide and N,N-dimethylacetamide), sulfoxides, and the like.

In Table 2 we give the basic characteristics of solvents of the ester or ether group. The solvents of this group belong to the esters and ethers formed by various alcohols and acids. Some of them are used as replacements for oils. The esters used as solvents are less viscous media. To these belong the esters of organic acid with 8 to 23 carbon atoms: those of oleic and butyric acids, octyl levulinate, etc. Ethyl oleate has received very wide circulation at present; its characteristics are given in more detail below.

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TABLE 2. Basic Characteristics of Solvents of the Ether–Ester Type

Name, formula	Mol. wt.	d	Bp (in deg)	Solubility	Toxicity
Diethyl ether $C_2H_5OC_2H_5$	74,12	0,713	35,6	Solubility in water – 6.5%; dissolves in alcohol, readily soluble in chloroform or benzene	Toxic
Ethyl acetate $CH_3COOC_2H_5$	88,10	0,901	77,15	Soluble in water, alcohol, or ether	Toxic
Phenoxyethanol $C_6H_5OCH_2CH_2OH$	138,17	1,1094	237, 245 134—135 [18]	Solubility in water, 2.6 g per 100 ml; readily soluble in alcohol or ether	—
Ethyl lactate $CH_3CH(OH)COOC_2H_5$	118,14	1,031	150—152, 154	Readily miscible with water. Used as a cosolvent in preparing oil solutions of steroid hormones	LD_{50} subcutaneously, 2.5 ml/kg; intravenously, 0.6 ml/kg (mice)
Isopropyl myristate $CH_3(CH_2)_{12}CH_2COOCH(CH_3)_2$	978,0	0,852	—		
Diethyl carbonate $C_2H_5OCOOC_2H_5$	118,14	0,9751(20) 4	125,8	Immiscible with water; miscible with oils	LD_{50} intraperitoneally, 100 ml/kg (mice)
				Immiscible with water; miscible with alcohol or ether.	LD_{50} (60% in olive oil) 28 ml or 15 mg per kg of weight (rats)

ETHYL OLEATE

$C_6H_5COOCH_2C_6H_5$

This is a light yellow, oily liquid with a strong disagreeable odor. It is insoluble in water, but mixes with fatty oils, alcohol, or ether. Its specific gravity is 0.869–0.870 (at 20°). Its acid number is 0.3–0.5 mg KOH/g; peroxide number, 0.07% iodine (not more); iodine number, 73–82.

According to the recommendation of the International Pharmacopoeia, it should be used as the solvent for desoxycorticosterone acetate, menadiol, estradiol monobenzoate, progesterone, and testosterone propionate. Ethyl oleate is described also in the pharmaceutical codes of England (1963) and the U. S. A. (volume XXV), as well as in the pharmacopeias of France (1958) and England (1958, 1963).

In distinction from vegetable oils, ethyl oleate has a greater dissolving power and a constant chemical composition. Like the fatty oils, it is well tolerated by the ill, with this sole difference – it is less viscous and is absorbed more rapidly into the tissue. A greater intensity and duration of action of testosterone phenylpropionate or testosterone propionate in ethyl oleate has been noted, as compared with preparations in corn oil [4]. A greater activity of hormones in ethyl oleate solution has also been reported more recently [5].

Ethyl oleate is sterilized by heating at 150° for 1 h. The coefficient of thermal expansion is rather large (over 10% on heating to 150°). It is recommended to sterilize solutions in closed vessels, which are filled with an inert gas (nitrogen). If the substances to be dissolved in it do not withstand sterilization, then the ethyl oleate is sterilized separately. It is recommended to add 2 or 3% of benzyl alcohol [6]. Ethyl oleate reacts with rubber to a greater extent than fatty oils.

BENZYL BENZOATE

$CH_3(CH_2)_7CH = CH(CH_2)_7COOC_2H_5$

This is the ester of benzyl alcohol with benzoic acid. It is a transparent, colorless, oily liquid with an agreeable aromatic odor; its taste is sharp and stinging. It hardly dissolves at all in water or glycerine, but it mixes with alcohol, chloroform, ether, or fatty oils. Its specific gravity is 1.118; bp, 323°.

According to the literature [5], the toxicity of this ester is slight; however, it exerts its own pharmacological action (a depressive action on the operation of the heart and respiratory organs), which should apparently limit its use. In the USSR it was authorized for medicinal use by order No. 182 of the Ministry of Public Health of the USSR, March 30, 1970. As a medicinal preparation it is used in dermatological practice for treating all forms of rashes. By the state pharmacopoeia of the USSR, edition 10, it is authorized for use in injections of a 2.5% solution of progesterone in peach oil: progesterone, 10 or 25 g; benzyl benzoate, 200 ml; peach oil, to 1 liter.

A "pure" benzyl benzoate manufactured in the USSR is offered by the S. Ordzhonikidze Scientific-Research Institute of Ord-

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TABLE 3. Basic Properties of Solvents of the Monohydric Alcohol Group

Name, formula	Mol. wt.	d	Bp (in deg)	Solubility	Toxicity, LD_{50}
Ethyl alcohol C_2H_5OH	4607	0.789	78.32	Readily soluble in water, ether, chloroform, or methanol	Intravenous, 1973 mg/kg (mice); subcutaneously, 8285 mg/kg.
Benzyl alcohol $C_6H_5CH_2OH$	108.14	1.050 (15/15) 1.0427 (19)	205.2	Solubility in 100 ml of water, 4 g of preparation; in 100 ml of alcohol 66.7 g. Very readily soluble in ether, acetone, methanol, or chloroform.	Toxic. Used in concentrations of not over 3%. Has irritant action in concentration of 5%.
1-Phenylethanol $C_6H_5CH(OH)CH_3$	122.17	1.013	205	Insoluble in water. Readily soluble in alcohol or ether.	
2-Phenylethanol $C_6H_5CH_2CH_2OH$	122.17	1.0235 (25/4)	219-227	Solubility in 100 ml of water, 1.6 g of preparation. Soluble in alcohol or ether.	

zhonikidze, and it complies with the requirements of foreign pharmacopoeias (U.S. Pharmacopoeia, 17th edition, and British pharmacopoeia, 1968). Benzyl benzoate is used extensively abroad. It is included in the Polish Pharmacopoeia, 4th edition, 1965, the British pharmacopoeia for 1968, the Yugoslavian pharmacopoeia for 1951, the Czechoslovakian for 1970, and several others.

According to the British pharmacopoeia for 1968, benzyl benzoate is used in oil injection solutions of dimercaprol. The composition of the prescription is: dimercaprol, 5.0 g; benzyl benzoate, 9.6 ml; peanut oil, to 100 ml. It is also used in hydroxyprogesterone preparations which have been admitted to sale, where the benzyl benzoate enters in a 30% concentration in sesame oil or 46% in castor oil. Benzyl benzoate has been investigated in the USSR [7] with the objective of using it for injections of hormone preparation solutions. The experience of many years in use of oil solutions of some preparations, mainly of the steroid class, has shown that they are either very difficultly soluble in oil, or gradually crystallize out of the solutions during the storage process, forming rather coarse crystals which do not dissolve again even on heating.

Benzyl benzoate has been used as a cosolvent to obtain stable oil solutions of hormone preparations. Solutions of 5% androstenediol dipropionate containing 30% benzyl benzoate, 12.5% hydroxyprogesterone carbonate containing 30% benzyl benzoate, or 5% testosterone propionate containing 20% benzyl benzoate have withstood a year of storage at 26°. During the storage period, crystals of the preparations did not separate from the solutions. It was also established that mixtures of benzyl benzoate with peach oil in concentrations from 10 to 50% are completely nontoxic. The amount of benzyl benzoate was established experimentally in each individual case.

In Tables 3 and 4 we give the basic characteristics of solvents of the alcohol group. Polyhydric alcohols are good solvents for many substances widely used in pharmaceutical practice (alkaloids, sulfanilamides, antibiotics, barbiturates, and anesthetics), and the solutions obtained are more stable than the corresponding aqueous solutions. Of these, propylene glycol (1,2-propanediol) presents the greatest interest. It is a transparent, colorless, and viscous liquid with a specific gravity of 1.036, which absorbs moisture from the air; it has a freezing point of −59° and a bp of 188°. It is miscible with water, acetone, and chloroform, but does not mix with fatty oils. Under normal conditions it is stable, but at high temperatures it is oxidized to propionaldehyde and lactic, pyruvic, and acetic acids. The toxicity of this solvent is very low. According to the literature [8], the minimum lethal dose on intravenous injection to rats is 1.68 g/kg,

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TABLE 4. Basic Characteristics of Solvents of the Polyhydric Alcohol Group

Name, formula	Mol. wt.	d	Bp (in deg)	Solubility	Toxicity, LD_{50}
Ethylene glycol CH_2OHCH_2OH	62.07	1.1155 (20/4)	198-200	Soluble in water, ethanol, or ether (7.89 g/100 ml).	Toxic
Propylene glycol $CH_3CH(OH)CH_2OH$	76.10	1.0364	188	Miscible with water, acetone, or chloroform; immiscible with fatty oils.	Intraperitoneally, 9.7 g/kg; intravenously, 8.0 g/kg; subcutaneously, 18.5 g/kg (mice).
1,3-Butanediol $CH_3-CH(OH)-CH_2CH_2OH$ / $CH_3CH(OH)CH_2CH_2OH$	90.12	1.0053	204	Soluble in water, or alcohol; insoluble in ether.	Subcutaneously, 16.5 ml/kg (mice); subcutaneously, 20.06 ml/kg (rats).
Diethylene glycol $CH_2OHCH_2OCH_2CH_2OH$	106.0	1.118	244.33	Miscible with water, alcohol, or glycols; insoluble in hydrocarbons.	By mouth, 23-25 ml/kg (mice).
Polyethylene glycols (polyethylene oxides) with various molecular weights	200 300 400*	1.11 1.14		Soluble in water, alcohol, or ketones; not hydrolyzed.	Intraperitoneally, 7.75, 9.25, 11.75 ml/kg (mice); 32.5, 35.6, 49.0 g/kg (rats).
Glycerin† $CH_2OHCHOHCH_2OH$	92.10	1.261	290	Miscible with water or alcohol.	Subcutaneously, 10 ml/kg; intravenously, 6 ml/kg; subcutaneously, 12 ml/kg; intravenously, 7 ml/kg.

*Freezing point, 2-6°.
†17.9, 20°.

and to rabbits is 5.25 g/kg. The minimum lethal dose on intramuscular injection is 14.7 g/kg for rats, and for rabbits is 7.5 g/kg. The LD_{50} for mice on intraperitoneal injection is 9.7 g/kg; subcutaneously, 18.5 g/kg; and intraveneously, 8.0 g/kg. Some investigators [9] do not confirm the toxicity of propylene glycol after it has been sterilized with a bactericidal lamp at a dose of 2.5 Mrad. The action of propylene glycol on the nervous system is like that of ethyl alcohol, but is three times as weak. When propylene glycol injections were made in physiological solution in concentrations up to 50%, it did not cause changes in the amount of erythrocytes, hemoglobin, or leucocytes in rabbits [10]. An increase in the number of polymorphic corpuscles was noted, plus a decrease in the number of lymphocytes, as well as a considerable shortening of the blood coagulation time. Propylene glycol is a good solvent for sulfanilamides, barbiturates, vitamins A and D, antibiotics (tetracycline, chlorotetracycline, oxytetracycline, or chloramphenicol), anesthesine, procaine, alkaloid bases, and many other medicinal substances [5].

Undilute propylene glycol causes a burning sensation at the site of injection; diluted solutions do not cause this effect. Solutions of propylene glycol should be injected deeply into the muscular tissue. The solutions used most often are 60%. The solution prepared for barbiturates may serve as an example: benzyl alcohol, 2 ml; propylene glycol, 60 ml; water to 100 ml [6]. The Hungarian pharmacopoeia (1967) recommends using propylene glycol to inject quinidine sulfate. Here it is emphasized that alkaloid bases in propylene glycol solutions do not separate out as precipitates on considerable dilution with water. According to the literature [11], a solution of quinidine hydrochloride consisting of 10.0 g of the preparation and 75.0 g of propylene glycol did not give any color changes or crystallize over a six-month period. The quinidine action is displayed in children already after 15 min, and is retained for 2 h on intramuscular injec-

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TABLE 5. Basic Characteristics of Polyethylene Glycols

Type of PEG	Av. mol. wt.	Viscosity at 25° (cP)	Hydroxyls (in mg KOH/g)	Toxicity, LD_{50}: mice, intraperitoneally (in ml/kg)	Toxicity, LD_{50}: rats (in g/kg)	Time required for filtration: through filter No. 3, 20°	through filter No. 4, 20°	through filter No. 4, 40°	through filter No. 4, 60°
200	190—210	45—55	533—589	7,75	32,5	1 min 30 sec	30 min	12 min	7 min
300	285—315	60—85	356—392	9,25	35,6	2 min 50 sec	32 »	12 min 30 sec	7 min 30 sec
400*	380—420	85—115	271—299	11,75	49,0	2 min	35 »	10 min 30 sec	9 min

*Congealing point, 2-6°.

tion. In the literature [12], the use of propylene glycol is described as a solvent for the intravenous injection of desoxycorticosterone in a concentration of 10 mg/ml. The authors recommend injecting this solution slowly, at a rate of 2.5 ml/min, since the preparation crystallizes out at the moment of dilution with water. Good results were obtained on adding digoxin in a solution of 40% propylene glycol and 10% ethanol [13]. Intramuscular introduction of oxytetracycline in propylene glycol makes it possible to increase considerably the circulation time of the preparation in the blood. Such a solution is stable on storage for 2 years at room temperature; in the absence of propylene glycol, it is stable for only 2 days. Phenobarbital and amobarbital are made up in solutions which contain 60% propylene glycol and 2% benzyl alcohol. Pure propylene glycol dissolves phenobarbital better, and in larger amounts than pure alcohol; however, upon gradual addition of water the solubility of the preparation in propylene glycol is reduced more rapidly than that in alcohol [5].

Propylene glycol stabilizes ascorbic acid well. According to the literature, it is less toxic (LD_{50} on intraperitoneal injection, 9.7 g/kg; intravenously, 8 g/kg; subcutaneously, 18.5 g/kg) than ethylene glycol or glycerin (LD_{50} on subcutaneous injection, 10 ml/kg; intravenously, 6 ml/kg). Sterilization of propylene glycol is effected by heating to 140° for 3 h [14]. This solvent is included in many foreign pharmacopoeias. According to the British pharmacopoeia (1968), a digoxin solution for injection is official which contains 0.025 mg of the preparation in 1 ml, melarsoprol and sodium phenobarbital in a mixture of 90 parts propylene glycol and 10 parts water. According to the Czechoslovakian pharmacopoeia for 1970, the digoxin solution for injection which is official is made up in a mixture of glycerin, propylene glycol, and water. Propylene glycol also is found in the French (1965) and International pharmacopoeias, and in the pharmacopoeia of the U. S. A. (1970).

Polyethylene Glycols (PEG). These represent a promising group of nonaqueous solvents. They are products of the polymerization of ethylene oxide, and have the general formula:

$$H-[OCH_2CH_2]_n-OH,$$

where n is in the range from 4 to 455, which corresponds to a molecular weight range from 200 to 20,000. Some synonyms are polyethylene oxide (PEO) polyoxyethylene, polyglycol, carbowax, skurol, postonal, macrogolyum, and macrogol.

Depending on the degree of polymerization, PEG can have a consistency from a viscous liquid to a solid material (Tables 4 and 5). The PEG with molecular weights of 200, 300, 400, and 600 are practically colorless, hygroscopic, and viscous liquids. The viscosity increases with increase in molecular weight, and the hygroscopicity decreases. PEG dissolve in water, aliphatic alcohols (methyl, ethyl, propyl, isopropyl, butyl, etc.), esters (methyl acetate, ethyl acetate, butyl acetate, amyl acetate, etc.), acetone, cyclohexanol, chloroform, carbon tetrachloride, benzene, toluene, xylene, etc. They are insoluble in ether, vaseline oil, turpentine, or fatty oils. The PEG do not have acute or chronic toxicity; they are stable to the action of light, heat, and moisture; they are inert; they accept coloring well; they dissolve easily in the digestive tract; they have no flavor; and they mix well with one another [15].

PEG esters are also used, for example PEG stearate, Tweens, polyglycol 1000 VRS monocetyl ether, glycofurol, and some others; this offers the possibility of obtaining solutions of substances which are difficultly soluble in water, plus stable emulsions and suspensions.

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TABLE 6. Basic Properties of Solvents of the Amide Group

Name, formula	Mol. wt.	Solubility	Toxicity, LD_{50}
N-Methylacetamide* $CH_3CONHCH_3$	73.0	Soluble in water	Intravenously, 4.2 g/kg (mice)
N,N-Dimethylacetamide $CH_3CON(CH_3)_2$	87.12	Miscible with water, soluble in organic solvents and mineral oils	Intraperitoneally, 3236 mg/kg (mice); intraperitoneally, 5012 mg/kg (mice)
N-β-Hydroxyethyllactamide† $CH_3CH(OH)CONHCH_2CH_2OH$	133	Readily miscible with water	Subcutaneously, 15.8 g/kg (mice); subcutaneously, 16.1 g/kg (rats)

*Mp 26-28°

†Density, 1.192

The PEG are colorless, transparent, involatile, viscous liquids of low hygroscopicity, with a faint characteristic odor. They are used most often in mixture with other solvents to prepare injection solutions of medicinal preparations which easily undergo hydrolytic decomposition.

In spite of their antibacterial properties, it is recommended that the PEG should be sterilized. PEG which have been diluted with water are similar to aqueous media; the pure substances are like oils. Instead of sterilization, one can make use of distillation, collecting the distillate in a sterile receiver [5]. PEG are good solvents for many medicinal preparations which readily undergo hydrolysis. Intramuscular injections are tolerated well. The PEG are isolated from the urine after 24 h; 77% is isolated after 12 h.

Intramuscular injection to rats in doses which exceed the dose for humans 5- or 10-fold causes necrosis of muscle if the dose undergoes infiltration into the muscle ligaments. The reaction of tissues is defined as a mild inflammatory process caused by chemicals. The toxicity of vancomycin has been studied in 50% PEG-200 and in the 100% glycol [16]. The authors stated that the glycol does not exert a toxic action on dogs if it is used in a dose of 1 ml/kg intramuscularly daily for 80 days or in doses of 0.5, 1.0, 2.5, or 5.0 ml/kg intravenously one time only. The content of carbon dioxide in the venous blood, nonprotein nitrogen in the blood, and alkali phosphatase remains within norms. No macro- or microchanges were confirmed in the kidneys, the circulation system, or other organs, although there are data according to which serious poisoning was noted, plus kidney disease, when a solution of nitrofurantoin in PEG-300 was injected intravenously to sick persons. Two fatal cases are known.

It should be emphasized that the toxicity and toxicity level of a biologically active substance can differ considerably after solution in glycol as compared with the toxicity of a solution or emulsion of this substance in water. Pathological changes were not noted in a study of the action of subcutaneous injections of solutions of barbiturates in PEG-200.

In intramuscular injection of aqueous solutions of the sodium salts of barbiturates, a stronger tissue inflammation was noted than when solutions in PEG were injected. The stability of the sodium salt of pentabarbital in an aqueous solution containing 0 to 60% PEG-400 has been studied [17]. A stable solution is obtained at a 30% PEG concentration and pH 10.0. Addition of 10% ethanol makes it possible to sterilize the solution in an autoclave without changing its color. Solutions containing 60% of the glycol and 10% ethanol and having a pH below 8.0 are also stable on heating in an autoclave. A 10% solution of PEG-300 is used to stabilize injection solutions of reserpine (2.5 mg/ml) [17]. The product issued for sale contains either 10% PEG-300 or 25% PEG-400.

It has been observed that phenobarbital forms strong stoichiometric molecular compounds with PEG [18]. Pentabarbital and barbital do not give such compounds. The phenobarbital molecule is bonded to two ethylene oxide residues in the polyether chain. It has been noted that phenolic compounds are bonded by polyethylene glycols in the same way. Compounds of high molecular weight have a definite tendency to form complex compounds. Such compounds as salicylic and p-hydroxybenzoic acids are bonded very weakly. Fifty percent solutions of PEG are used to prepare injection solutions of erythromycin ethyl succinate and secobarbital for intramuscular injection. The stability of the sodium salts of some barbiturates has been studied in PEG solutions (phenobarbital, barbital, pentabarbital, etc.) [19]. It was shown that PEG causes a strong stabilizing effect, the stability of the preparations increasing with rise in PEG concentrations. The least PEG concentration adequate for stabilization was 50%. The barbiturates dissolved in pure PEG were the most stable.

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The solubility of some medicinal materials in PEG-400 and in aqueous solutions of PEG of various molecular weight has been studied [20, 21]. It was noted that substances which have a basic nitrogen in their make-up (glutamic and nicotinic acids) do not dissolve or are poorly dissolved in the presence of PEG. Solubilization is usually attained at a PEG concentration over 30%. In a study of the solubilization of medicines of low solubility it was established that the solubility of benzoic, salicylic, and acetylsalicylic acids; barbital; synthomycin; camphor; anesthesine; codeine base; sulfanilamide compounds; butadione; cortisone acetate; reserpine; phthivazide; erythromycin; phenacetin; and novocaine base in PEG (molecular weight, 400) many times exceeds the solubility of these compounds in water. The following have an exceptionally high solubility: Streptocid (87 g/100 ml), anesthesine (34 g/100 ml), and salicylic acid (31.8 g/100 ml). The solubility is increased (as compared with the solubility in water) in PEG of higher molecular weight (600, 1500, or 4000).

PEG solutions of various concentrations have obtained particularly wide use abroad. PEG enters into many foreign pharmacopoeias. At the present time PEG-400 has not found use as a solvent for preparations for injection in the USSR, since it is thought that the large moisture content of PEG-400 and its hygroscopicity does not permit using it to prepare parenteral solutions.

We have used polyethylene glycol of domestic manufacture to prepare solutions for injection of some sarcolysine derivatives, especially Asalei and Astiron, which have a definite antitumor activity on a number of experimental animal tumors. Asalei and Astiron are practically insoluble in water, ether, propylene glycol, ethylene glycol, diethylene glycol, glycerin, or ethyl oleate. In the presence of moisture they hydrolyze and lose their antitumor activity. As preliminary studies showed, the solubility of Asalei and Astiron in PEG-400 is very small. To increase the solubility, we developed a three-component solvent system, composed of 80 ml PEG-400 and 20 ml of a 0.5% alcoholic solution of Tween-80. In the mixed solvent the preparations dissolved on stirring for a few minutes at room temperature. This made it possible to prepare 2.5% solutions of Asalei or Astiron in PEG-400.

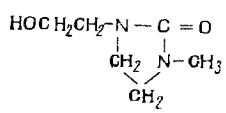
Studies of the stability of Asalei and Astiron to hydrolysis in the solutions obtained were performed by the mercurimetric titration method. The stabilizing properties of the solvents proved to be quite high. Thus, the degree of hydrolysis of the preparations was barely more than 1% on storage for two months in the dark in a cool place. However, after this time interval the solutions changed their outward appearance from colorless to yellow in the case of Asalei, and from yellow to brown in the case of Astiron. This is apparently connected, on one hand, with the ability of chloroethylamine antitumor preparations to enter into chemical reaction with many organic compounds which have in their make-up such functional groups as OH, NH_2, COOH, or the like, and, on the other, with the ability of polyethylene glycols to form complex compounds with some medicinal substances. Taking this fact into consideration, we suggest that solutions of Asalei and Astiron in PEG-400 be made up ex tempore.

The results of preliminary pharmacological studies which we have carried out on animals with experimental transplantable tumors have shown that the activity of preparations is considerably increased in PEG-400 solution. Thus, in a dose equal to one-half the maximum tolerable dose (MTD) for suspensions of these compounds on methyl cellulose, solutions of Asalei and Astiron caused the death of approximately 50-60% of the animals. Reducing the dose to one-fourth the maximum tolerable dose did not cause a reduction in the therapeutic effect, but the loss of animals did not exceed 10%.

The results which we obtained agree with data in the literature, which indicate a considerable change in the toxicity and activity of some medicines used in the form as solutions in PEG, as compared with the same qualities of their aqueous solutions or emulsions [16, 22, 23, 24].

In recent times, steadily increasing attention is being given to other solvents from the groups of ethers amides, heterocyclic compounds, or sulfoxides (Table 6), for example, dimethyl sulfoxide and oximazone.

Oximazone [1-Methyl-3-(2-hydroxyethyl)imidazolidone].



Oximazone mixes in all proportions with water; it is soluble in ethanol, acetone, chloroform, or methylene chloride. Its density is 1.16; bp, about 125-126°; n_D^{21} 1.496; viscosity at 20°, 25 cP. Its LD_{50} is 5600 mg/kg for rats on intravenous injection of a 50% solution in water. Clonic convulsions set in after introduction

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of 4000 mg/kg into animals (secondary effect). The acute toxicity in experiments on rats in oral introduction of a 50% aqueous solution was 10-15 ml/kg, $LD_{50} > 8000$ mg/kg. A dose of 16,000 mg/kg causes the death of 8 animals out of 10. On use of oximazone internally in the form of a 4-20% aqueous solution daily for a period of 4 weeks, a good toleration of this preparation by animals was noted. Appetite, animal weight, state of blood-producing organs, liver function, and urine remained within norms. On subcutaneous injection of a 20% aqueous solution of oximazone over a 4-week period daily, the urine, blood-forming organs, and liver function also remained normal. On local injection of 500 or 1000 mg/kg, inflammatory phenomena were noted at the site of injection. The higher the dose, the greater the inflammation. In a dose of 250 mg/kg, local reaction by the preparation was not observed. When a 10 or 20% aqueous oximazone solution was used intraveneously in experiments on dogs (subacute toxicity) daily, intoxication phenomena were not observed. Injections in some animals were accompanied by a certain bulging of the vein.

On introduction of a 20% aqueous solution to cats in a dose of 1000 mg/kg of body weight, the animals did not experience change in heart-beat or respiratory rate; a 40% aqueous oximazone solution raises the blood pressure. Oximazone in a dose of 1000 mg/ml exerts a cytostatic action. Moreover, aqueous oximazone solutions have a bacteriostatic action. On 1:10 dilution of the oximazone, this action is not observed (bulletin of the Asta company).

Dimethyl sulfoxide (DMSO). CH_3SOCH_3. DMSO is a transparent, colorless liquid with a mild odor; its molecular weight is 78.13; specific gravity, 1.108 at 20°; bp, 189°; mp, 18.4°; n_D 1.4783; viscosity, 2.14 cP at 20°; dipole moment, 4.3; dielectric constant, 48.9. DMSO is very hygroscopic. It absorbs up to 70% water at 20°. It is infinitely miscible with water, methanol, octanol, glycerin, acetaldehyde, acetone, ethanol, diethyl ether, ethyl acetate, toluene, etc.

For laboratory animals, the LD_{50} of DMSO on intravenous introduction is 5.75-8.8 g/kg; on oral introduction, 21.4-28.3 g/kg; the LD_{50} for mice, chickens, or rats is 20 ml/kg. Subdural introduction of DMSO does not change the reflex activity of dogs or monkeys. In a dose of 1 g/kg the preparation does not change the electrocardiograms of monkeys. Intensification of the toxicity of medicines in the presence of DMSO is not observed [25].

As one may convince himself from the review given, a very large number of organic solvents are used in pharmaceutical practice; these have varied dissolving power, antihydrolytic and stabilizing properties, and anesthesizing and bactericidal properties, or the ability to prolong or intensify the action of the active component. But far from all of them are finding wide use. The fatty oils and ethyl oleate, propylene glycol, and polyethylene glycol are used the most often of the nonaqueous solvents. The remaining solvents are used as yet only in exceptional cases. It is quite obvious that the use of nonaqueous solvents makes it possible to expand possibilities of preparing medicinal forms. However, one should take into account the fact that any preparation in a nonaqueous solvent may be new in essence, and should be appropriately studied.

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ATTACHMENT F - COMPILATION

TAB 7

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Tolerability of intramuscular injections of testosterone ester in oil vehicle

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We undertook a prospective survey of the tolerability of deep i.m. injections of testosterone enanthate in a castor oil vehicle, the most widely used form of androgen replacement therapy. Over a period of 8 months, 26 men received 551 weekly injections into the gluteal, deltoid or thigh muscle and side-effects were recorded immediately and 1 week after each injection by the same nurse using a standardized questionnaire. Most injections caused no complaints [389/551, 70.6% (95% confidence interval 66.6–74.4%)] but minor local side-effects, mostly pain and bleeding, were common [162/551, 29.4% (25.6–33.4%)]; no serious side-effects were observed. Considering all side-effects, the gluteal site had fewer complaints and was less prone to bleeding but was painful more often than deltoid or thigh injection sites. The laterality of injection at any site had no significant effect on side-effects. The only systemic side-effect was episodes of sudden-onset, non-productive cough associated with faintness following eight injections [1.5% (0.6–2.9%)] which we speculate may have been due to pulmonary oil microembolism. We conclude that, when administered by an experienced nurse, deep i.m. injection of testosterone enanthate in a castor oil vehicle is generally safe and well tolerated but causes relatively frequent minor side-effects, including pain and bleeding. An improved depot form of testosterone would be highly desirable for androgen replacement therapy and hormonal male contraception.

Key words: androgen replacement therapy/intramuscular injection/laterality/side-effects/testosterone

Introduction

Testosterone has been used clinically in androgen replacement therapy for over 50 years (Nieschlag and Behre, 1990). Over the past few decades the most frequent mode of administering testosterone has been deep i.m. injections of testosterone esters in a vegetable oil vehicle. Despite this long usage, no systematic studies of side-effects from oil-based i.m. injections of testosterone esters could be located after extensive computer-based and manual library searching. The opportunity to study systematically the tolerability of these injections and the pattern of side-effects was provided by an ongoing male contraceptive study requiring healthy men to have weekly i.m. injections of testosterone enanthate in castor oil vehicle administered by the same research nurse for up to 18 months. The aims of this study were to estimate prospectively the pattern and incidence of side-effects of oil-based, deep i.m. injections in normal men and to determine whether anatomical site and/or laterality of injection influences the incidence of these side-effects.

Materials and methods

Study design

This was a prospective survey of adverse effects from i.m. injections of oil-based testosterone enanthate. The injections were given during a World Health Organization (WHO) contraceptive efficacy study of a prototype hormonal male contraceptive and the design and results of that study have been described in detail elsewhere (WHO Task Force on Methods for the Regulation of Male Fertility, 1990). Injections were given and side-effects recorded by the same right-handed research nurse (M.A.M.) both immediately following and 1 week after injection using a standard questionnaire. The questionnaire recorded date, site and side of injection as well as eliciting specific responses to potential side-effects, including pain or stinging, bleeding or bruising, swelling, numbness, muscle twitch, erythema, faintness, coughing. For reported symptoms, the duration, severity and degree of interference with daily living was recorded. For the analysis, the categories of pain and bleeding included both immediate and delayed reports. The criterion for recognition of pain was the subject's response to the question 'Was that injection painful?' and was applied and recorded consistently for each subject.

Subjects and injections

Men involved in this study were 26 healthy males aged between 21 and 45 years recruited from the general population to participate in a multicentre male contraceptive study (WHO Task Force on Methods for the Regulation of Male Fertility, 1990). Entry criteria were that men had to be healthy, in a stable relationship and requiring contraception. Volunteers were required to have their injection administered by the study nurse (M.A.M.) on the same day (± 1 day) each week for up to 18 months. The vials of testosterone enanthate (250 mg in

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1 ml castor oil, Testoviron Depot; Schering AG, Berlin, Germany) were kept at air-conditioned room temperature and injections of 200 mg (0.8 ml) were administered with a 21 gauge (0.80×38 mm) needle into one of three muscular sites; the anatomical site of the injection (gluteal, deltoid, thigh) was chosen by the subjects and injections were routinely alternated from side to side. Deep i.m. injections were given according to standard methods, including aspirating the syringe to exclude vascular puncture before injection and injecting slowly.

Data analysis

Data were cross-tabulated and analysed by appropriate methods for categorical data using BMDP software (BMDP Statistical Software Inc., Los Angeles, CA, USA) implemented on a VAX computer network. Power was estimated using Poisson confidence intervals (Gardner and Altman, 1989) and PASS software (Hintze, 1991).

Results

During 8 months, 602 scheduled injections were given without any injections missed and complete information was available after 551 (92%) injections. The remainder were accounted for by injections administered when men were out of Sydney for work or holidays. During this period, only two out of 26 men changed their preferred site of injection.

Most injections caused no complaints [389/551, 70.6% (95% confidence interval, 66.6–74.4%)] and any adverse effects were recorded after only 162/551 [29.4% (25.6–33.4%)] injections. There were no significant differences in rate of complaints of side-effects according to laterality of injection for gluteal [left 19/68 (27.9%) versus right 27/151 (17.9%)], thigh [left 17/51 (33.3%) versus right 27/85 (31.8%)] and deltoid [left 49/114 (43.0%) versus right 29/82 (35.4%)]. The overall pooled (Mantel–Haenszel) relative risk was 1.40 [95% (confidence interval 0.95–2.06), test for homogeneity of risk across strata $P = 0.61$].

Considering all adverse effects (Table I), the total number of complaints was significantly higher for deltoid [2.0 (1.5–2.8)] and thigh [1.6 (1.1–2.3)] than for gluteal sites of injection. Considering specific adverse effects, gluteal injections caused more complaints of pain [relative risk 2.4 (1.3–4.3)] and fewer of bleeding [0.16 (0.08–0.32)] compared with the other two sites combined (Table I). Immediate bleeding was minor in all cases, requiring only light topical pressure for a few minutes or was recorded in retrospect as minor bloodspot staining of clothing or slight bruising. Pain was usually not sufficient to require analgesia; at worst, discomfort was present for several days on sitting or lying on the injection site. There were no reports of local erythema or acute inflammatory reactions following injections. Apart from coughing episodes, all reported reactions were considered by volunteers and investigators as minor; none ceased injections due to such side-effects during the study.

The only systemic side-effect was coughing fits observed immediately after eight injections [prevalence 1.5% (0.6–2.9%)], associated with faintness and sweating on one occasion. On another occasion, faintness and sweating occurred without coughing. Two characteristic cases are described. In the first, a 25 year old man without known asthma or allergies developed an intense, non-productive cough without wheeze immediately after having received 21 previous i.m. injections into the gluteal muscle uneventfully. He also developed an injection site reaction after withdrawal of the injection needle which required him to remain recumbent until the coughing subsided (5 min). After this episode he had six further weekly injections without recurrence or complaint before he discontinued from the study to initiate a planned pregnancy. In the second, a 35 year old man without known asthma or allergies and having received 24 injections into the deltoid muscle, including one previous similar episode, developed an intense non-productive cough with associated pallor, nausea and chest tightness but no wheeze or injection site reaction which gradually subsided after 10 min. He subsequently had another 35 injections into the gluteal muscle without experiencing further such episodes.

The power of this study was >50, >80 and >90% to detect (one-sided, $\alpha = 0.05$) events with underlying prevalence of 1.3, 1.7 and 2.0% respectively. Conversely in order to detect events with a prevalence of 1.0% with 80% power, a sample size of 4000 observations would have been required. For adverse effects not observed in this study, the upper 95% (Poisson) confidence limit was 0.67%.

Table I. Side-effects of i.m. injections

Side-effect	Deltoid	Thigh	Gluteal	Total	P
Nil	119 (61%)	94 (69%)	176 (80%)	389 (70.6%)	<0.001
Bleeding	49 (25%)	27 (20%)	8 (4%)	84 (15.3%)	<0.001
Pain	13 (7%)	5 (4%)	23 (11%)	41 (7.4%)	0.050
Muscle twitch	10 (5%)	5 (4%)	7 (3%)	22 (4%)	0.598
Cough ± faint	4 (2%)	3 (2%)	2 (1%)	9 (1.6%)	0.552
Other	1 (1%)	2 (1%)	3 (1%)	6 (1.1%)	0.621
Total	196 (100%)	36 (100%)	219 (100%)	551 (100%)	

Discussion

Depot formulations are widely used to enhance therapeutic compliance and convenience by prolonging the duration of drug action. Among the most widely used depot formulations are drug esters administered in an oil vehicle. Esterification of base drugs with appropriate lipophilic fatty acids forms a pro-drug ester whose hydrophobic side-chains partition preferentially into the oil vehicle. Prolongation of pro-drug release is provided by the rate-limiting retarded diffusion of the pro-drug ester into the extracellular fluid where ubiquitous non-specific esterases hydrolyse the ester bond to liberate active drug. In addition to forming a hydrophobic depot, the oil vehicle limits local chemical irritation and cytotoxicity caused by some drugs (Svendsen and Blom, 1984). This oil-based formulation has been widely and successfully used for sex steroids including androgens, oestrogens and progestins as well as psychotrophic drugs such as fluphenazine, haloperidol and related major tranquilizers (Gilman *et al.*, 1990). Oils derived from vegetable sources such as castor or sesame seeds

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or peanuts (*Arachis*) have been widely used whereas mineral oils are too irritating (Symmers, 1955).

Testosterone esters in an oil vehicle have been for decades the most widely used modality of delivering androgen replacement therapy in male hypogonadism (Behre *et al.*, 1990). Despite this long usage, or perhaps because of it, there have been few systematic studies of tolerability of i.m. administration of testosterone esters in oil-based formulations. The general pharmacology of i.m. injections has been reviewed (Schou, 1971; Greenblatt and Koch-Weser, 1976; Zuidema *et al.*, 1988) but most studies concern aqueous formulations of drugs administered to hospitalized patients. For example, the only large survey of i.m. injections reported adverse local effects in only 0.4% of 12 134 hospitalized patients receiving i.m. injections of drugs in aqueous formulations (Greenblatt and Allen, 1978). No comparable surveys in ambulatory care settings or involving oil-based steroid ester formulations are available to our knowledge.

Overall, while nearly 30% of our subjects had some complaints, they were considered by patients and investigators as minor in nature and serious adverse effects were not observed. Satisfaction was greatest for the gluteal site, lowest for the deltoid, with the thigh being intermediate. Discrepancies in patterns of pain and bleeding accounted for these differences. The level of recorded complaints may be conservative as determined among highly motivated volunteers agreeing to participate in a prolonged study requiring weekly i.m. injection for up to 18 months. Administration by less expert staff or by self-injection may lead more frequently to dissatisfaction. Furthermore, the tolerance of discomfort among hypogonadal men requiring life-long androgen replacement therapy or fertile men considering hormonal male contraception among other family planning methods may be lower. Although the sites of injection were not randomized but were selected by the subjects, it is unlikely that this significantly biased the outcomes, unless men predisposed to complain of side-effects were systematically more likely to choose a particular injection site, which seems unlikely. Although this survey included nearly 550 injections, it could provide reliable estimates for only relatively common (>2%) side-effects. The frequency of rare side-effects, especially those not observed during the survey period, could not be reliably estimated. For example, the power of this survey was adequate (>80%) for events with a true underlying rate of occurrence of ≥1.7%, but would need to include more than seven times as many injections to detect events with a 1.0% prevalence.

The lower risk of minor bleeding at the gluteal injection site may be attributed to its lower blood flow (Evans *et al.*, 1975) as well as the fact that most gluteal i.m. injections are actually intralipomatous (Cockshott *et al.*, 1982) and adipose tissue blood flow is even lower than muscle. Conversely, the reason for the higher rate of discomfort following gluteal injections is unclear and conflicts with experimental observations that intralipomatous injection causes less local toxicity than i.m. injection of irritant psychoactive drugs in rabbits (Svendsen *et al.*, 1985). The precise cause of injection pain remains unclear (Travell, 1955), although presumably local cytotoxicity due to insertion of the injection needle as well as the chemical nature of the drug, its vehicle and their local metabolites are relevant factors. Possibly the functional significance of various anatomical sites may also influence injection pain. For example, extrinsic pressure on the injection site may be more common after gluteal injections (e.g. during sleeping or sitting) than for other sites.

More serious local injection site side-effects, including sciatic nerve damage, muscular fibrosis, gas gangrene, and distal ischaemia following intra-arterial injection were not observed in this survey, consistent with their rarity among adults. We also observed no evidence of either acute or chronic inflammatory reactions which have been reported rarely to cause lipogranulomas and/or pseudotumour foreign body reactions (Symmers, 1955; Balogh, 1986; Hamann *et al.*, 1990; Khankhanian and Hammers, 1992) causing diagnostic confusion and serious clinical consequences. As inflammatory reactions have been reported following subdermal injections of vegetable oils alone (Brown *et al.*, 1944) or containing non-steroidal drug esters (Hamann *et al.*, 1990) while aqueous suspensions of testosterone esters are non-irritating (Behre and Nieschlag, 1992), the side-effects observed in this study are most likely to be attributable to the oil vehicle rather than the testosterone ester. As the present survey had sufficient power to exclude non-observed events with an underlying frequency of at least 2%, this figure provides an upper limit for the likelihood of such reactions which were not observed during our study.

The only systemic side-effect observed was coughing reactions consisting of sudden-onset, non-productive coughing with or without faintness which was observed on eight occasions giving a prevalence of 1.5% [95% (confidence interval 0.6–2.9%)]. Although disturbing to subjects, the coughing was transient, lasting for 10 min at most and subsided spontaneously without known sequelae. Acute drug-related respiratory distress not due to bronchospasm or laryngopulmonary oedema is rare but has been described after i.m. administration of an oil-based solution of pitressin tannate (Hoigne *et al.*, 1990). The sudden onset of coughing without wheeze or injection site reaction together with a history of uneventful injections before and after the episodes suggests an idiosyncratic, mechanical phenomenon related to a particular injection. Neither allergy to testosterone enanthate or the castor oil vehicle have been reported and would seem clinically unlikely given the isolated occurrence of the events and speed of onset. We speculate that these respiratory reactions may be due to pulmonary oil microembolization following lymphogenic (Svendsen *et al.*, 1980) or venous absorption of oil (Svendsen and Aaes-Jorgensen, 1979), leading to transient acute pulmonary hypertension possibly related to mechanical vascular occlusion and/or intravascular liberation of free fatty acids from hydrolysis of the oil (Hofmann *et al.*, 1976; Szabo *et al.*, 1977). Clinically significant pulmonary manifestations of oil embolism have been reported following injection of 2.5 ml oil reaching the bloodstream (Bron *et al.*, 1963; Gough and Thomas, 1964). The relatively mild clinical manifestations observed with our smaller injection volume (0.8 ml) are consistent with this mechanism. An alternative, albeit unlikely, explanation that cannot be fully excluded is that intralipomatous injection

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may rarely provoke embolism of cellular fragments such as adipocyte lipids. The low frequency and mild clinical features observed do not require any major change in current standard clinical practice but suggest caution when injecting larger volumes of oil i.m. Apart from the recent addition of warnings concerning the occurrence of 'coughing fits, urge to cough and respiratory distress' to the product information for testosterone enanthate, such side-effects do not appear to have been reported previously.

We conclude that deep i.m. injections of testosterone enanthate in castor oil vehicle are generally safe and reasonably tolerated when administered by a single experienced research nurse. Minor side-effects, mainly pain and bleeding, are relatively common but serious side-effects are rare. The anatomical site, but not laterality, of injections influences tolerance, as the gluteal site has fewer overall side-effects and is less prone to bleeding but more liable to pain than the deltoid or thigh sites. Coughing reactions, not previously reported but observed after 1.5% of injections, we speculate may be due to pulmonary oil microembolization. As our observations reflect the properties of an oil vehicle, similar findings would be expected with other similarly formulated drugs. These findings highlight the need for better depot testosterone formulations for patients requiring life-long androgen replacement therapy, as well as for future regimens for hormonal male contraception.

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ATTACHMENT F - COMPILATION

TAB 8

REVIEW ARTICLE

Excipients and Their Use in Injectable Products

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ABSTRACT: Formulation of a new drug product with excipients, that have been previously added to an approved injectable product, may save pharmaceutical companies developmental time and cost. The Physicians' Desk Reference (PDR) and Handbook on Injectable Drugs were reviewed, extracting all information on excipients. The information was consolidated into eight tables, categorizing excipients as 1) Solvents and Co-solvents, 2) Solubilizing, Wetting, Suspending, Emulsifying or Thickening agents, 3) Chelating Agents, 4) Antioxidants and Reducing Agents, 5) Antimicrobial Preservatives, 6) Buffers and pH Adjusting Agents, 7) Bulking Agents, Protectants, and Tonicity Adjustors, and 8) Special Additives. Where applicable, tables list frequency of use, concentration, and an example of a commercial product containing the excipient. Excipients which are included in the 1996 FDA 'Inactive Ingredient Guide,' but do not appear in the PDR or Handbook on Injectable Drugs, were included as a separate list.

Introduction

Injectable products require a unique formulation strategy. The formulated product has to be sterile, pyrogen free and, in the case of solutions, free of particulate matter. Preferably, the formulation will be isotonic, and depending on the route of administration (for instance, for intra-spinal or intra-cisternal routes), antioxidants and preservatives may not be allowed. For a given drug, the risk of adverse events is higher if it is administered as an injection versus a non-parenteral route. The requirement for sterility demands that the excipients be able to withstand autoclaving or other sterilization processes. These factors limit the choice of excipients available to the formulators.

Generally, a knowledge of which excipients have been deemed safe by the FDA or are already present in a marketed product provides increased assurance to the formulator that these excipients will probably be safe for their new drug product. However, there is no guarantee that the new drug product will be safe as excipients are combined with other additives and/or with a new drug, creating unforeseen potentiation or synergistic toxic effects. Regulatory bodies may view an excipient previously approved in an injectable dosage form favorably, and will frequently require less safety data. A new additive in a formulated product will always require additional studies adding to the cost and timeline of product development.

The purpose of this paper is to present the various excipients that have been included in the formulation of injectable products marketed in the USA. This information is not readily available. A literature search indicates that the last paper dealing with this was published in 1980 (1). Products approved outside the US are not covered in this review. Also, sterile dosage forms not administered parenterally, such as solutions for irrigation, ophthalmic or otic drops, and ointments were excluded.

Methodology

Physicians' Desk Reference published in 1994 & 1996 (2, 3), and Handbook on Injectable Drugs (4) were used as the primary source of information. Entries on all injectable drugs were summarized in an Excel worksheet. Each product was classified by Manufacturer, Trade name, Drug name, Route of Administration, SVP/LVP, pH of Product, Solvent Used, Solubilizing/Suspending Agent, Preservative, Antioxidant, Chelator and Other Formulation Additives.

The resulting Excel sheet had information on more than 700 products. This information was condensed into easy-to-read tables. Each table has been categorized based on the primary function of excipient in the formulation. For example, citrates are classified as buffers and not as chelating agents, and ascorbates are categorized as antioxidants, although they can serve as buffers. This classification system was based on our experience in formulation development and on the published literature. Such simplification avoids duplication of entries and provides the audience with easy-to-read tables.

Some duplication was unavoidable. Tables VII and VIII contain some excipients which may have also been listed in the first six tables. Whenever the reference specifically designated a specific function to an ingredient it was re-listed in Tables VII and VIII. For example, glycine can be used as a buffer or as a stabilizing (protecting) agent. Therefore, glycine is listed in Tables VI and VII. Methyl paraben is a preservative (Table V) but also has a special function in Adriamycin RDF® formulation (Table VIII).

The concentration of excipients is listed as percentages weight by volume (w/v) or volume by volume (v/v). If the product was listed as lyophilized or powder, these percent-

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TABLE I
Solvents and Co-solvents

Excipient	Frequency	Range	Example
Benzyl Benzoate	2	20% v/v	Depo-Testosterone® (Upjohn) 20% v/v
Cottonseed Oil	1	73.6% w/v	Depo-Testosterone® (Upjohn) 73.6% w/v
N,N Dimethylacetamide	1	6% w/v	Vumon® (Bristol Myers) 6% w/v
Ethanol	24	0.6–80%	Prograf® (Fujisawa) 80% v/v
Glycerin (Glycerol)	9	1.6–70% w/v	Multitest CMI® (Connaught) 70% w/v
Peanut oil	1	*	Bal in Oil® (Becton Dickinson)
Polyethylene glycol			
PEG	4	0.15–50%	Secobarbital sodium (Wyeth-Ayerst) 50%
PEG 300	2	50–65%	VePesid® (Bristol Myers) 65% w/v
PEG 400	2	*	Ativan® (Wyeth-Ayerst)
PEG 3350	5	0.3–3%	Depo-Medrol® (Upjohn) 2.95% w/v
Poppyseed oil	1	1%	Ethiodol® (Savage) 1%
Propylene Glycol	25	0.2–75.2%	Terramycin Solution (Roerig) 75.2%
Safflower oil	2	5–10%	Liposyn II® (Abbott) 10%
Seasme oil	6	*	Solganal Inj.® (Schering)
Soybean oil	4	5–20% w/v	Intralipid® (Clintec) 20%
Vegetable oil	2	*	Virilon IM Inj.® (Star Pharmaceuticals)

* No data available.

ages were derived based on the reconstitution volume commonly used. The tables list the range of concentration used, typical or most common concentration employed, and examples of products containing the excipient, specifically those which use extremely low or high concentrations.

Discussions

Table I list solvents and co-solvents used in parenteral products. Water for injection is the most common solvent but may be combined or substituted with a co-solvent to improve the solubility or stability of drugs. Oils like safflower and soybean are used in total parenteral nutrition products where they serve as a fat source and as carriers for fat-soluble vitamins. Ethanol and propylene glycol are used, either alone or in combination with other solvents, in more than 50% of parenteral co-solvent systems. It is surprising to see propylene glycol used more often than polyethylene glycols (PEGs) in spite of its higher myotoxicity and hemolyzing effects (5, 6). Probably, the presence or generation of peroxides in PEGs is a major limitation.

Table II includes a broad category of excipients whose function in formulation could be—(1) Viscosity imparting or suspending agents like carboxy methyl cellulose, sodium carboxy methyl cellulose, sorbitol, acacia, Povidone, hydrolyzed gelatin; (2) Solubilizing, wetting or emulsifying agents like Cremophore EL, sodium desoxycholate, Polysorbate 20 or 80, PEG 40 castor oil, PEG 60 castor oil, sodium dodecyl sulfate, lecithin or egg yolk phospholipid; (3) Aluminum monostearate which is added to fixed oil to form viscous or gel-like suspending medium. Polysorbate 80 is the most common and versatile solubilizing, wetting and emulsifying agent.

Only a limited number of chelating agents are used in parenteral products (Table III). They serve to complex heavy

TABLE II
Solubilizing, Wetting, Suspending, Emulsifying or Thickening Agents

Excipient	Frequency	Range	Example
Acacia	2	7%	Tuberculin Old Test® (Lederle) 7%
Aluminum monostearate	1	2%	Solganal Inj.® (Schering) 2%
Carboxy methyl cellulose	4	1%	Bicillin® (Wyeth-Ayerst) 0.55%
Carboxy methyl cellulose, sodium	9	0.1–0.75%	Lupron Depot® (TAP) 0.75% w/v
Cremophore EL*	3	50–65% w/v	Sandimmune® (Sandoz) 65% w/v
Desoxycholate sodium	1	0.4% w/v	Fungizone® (Bristol Myers) 0.41% w/v
Egg yolk phospholipid	3	1.2%	Intralipid® (Clintec) 1.2%
Gelatin, Hydrolzyed	1	16% w/v	Cortone® (Merck) 16% w/v
Lecithin	7	0.4–1.2% w/v	Diprivan® (Zeneca) 1.2% w/v
Polyoxyethylated fatty acid	1	7% w/v	AquaMephyton® (Merck) 7% w/v
Polysorbate 80 (Tween 80)	31	0.01–12%	Cordarone X I.v.®. (Wyeth-Ayerst) 10%
Polysorbate 20 (Tween 20)	5	0.01–0.4%	Calcijex® (Abbott) 0.4% w/v
PEG 40 castor oil**	1	11.5% v/v	Monistat® (Janssen) 11.5% v/v
PEG 60 castor oil***	1	20% w/v	Prograf® (Fujisawa) 20% w/v
Povidone (Polyvinyl pyrrolidone)	6	0.5–0.6% w/v	Bicillin® (Wyeth-Ayerst) 0.6% w/v
Sodium dodecyl sulfate (Na lauryl sulfate)	1	0.018% w/v	Proleukin® (Cetus) 0.018% w/v
Sorbitol	3	25–50%	Aristrospan® (Fujisawa) 50% v/v

* Cremophor EL: Etocas 35, polyethoxylated castor oil, polyoxyethylene 35 castor oil.
** PEG 40 castor oil; polyoxyl 40 castor oil, castor oil POE-40, Croduret 40, polyoxyethylene 40 castor oil, Protachem CA-40.
*** PEG 60 hydrogenated castor oil; Cremophor RH 60, hydrogenated castor oil POE-60, Protachem CAH-60.

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TABLE III
Chelating Agents

Excipient	Frequency	Range	Example
Calcium disodium EDTA*	9	0.01–0.1%	Wydase® (Wyeth-Ayerst) 0.1% w/v
Disodium EDTA	34	0.01–0.1%	Calcijex® (Abbott) 0.11% w/v
Sodium EDTA	1	0.20%	Folvite® (Lederle) 0.2%
DTPA**	1	0.04%	Magnevist® (Berlex) 0.04%

* EDTA = Ethlenediaminetetraacetic acid.
** DTPA = Diethylenetriaminepentaacetic acid; Pentetic acid.

metals and therefore can improve the efficacy of antioxidants or preservatives. In our opinion, calcium EDTA has an advantage over tetrasodium salt by not contributing sodium and not chelating calcium from the blood.

An antioxidant as a class is defined as those compounds that can act as reducing agents or may serve as free radical scavengers. Table IV summarizes the antioxidants, their frequency of use, concentration range and examples of products containing them. Sulfite, bisulfite, and metabisulfite constitute the majority of antioxidants used in parenteral products despite several reports of incompatibilities and toxicity (7, 8). Butylated hydroxy anisole, butylated hydroxy toluene and propyl gallate are primarily used in semi/non-aqueous vehicles because of their low aqueous solubility. Ascorbic acid/sodium ascorbate may serve as an antioxidant, buffer, and chelating agent in the same formulation.

Benzyl alcohol was the most common antimicrobial preservative present in parenteral formulations (Table V). This is consistent with other surveys (9). Parabens are the next most common preservatives. Thirty-nine products had a combination of methyl and propyl parabens; eleven had only methyl, and one had only propyl paraben. Thimerosal was surprisingly common, especially in vaccines, even though some individuals have sensitivity to mercurics. Chlorocresol is purported to be a good preservative for parenterals, but our survey did not find any examples of commercial products containing chlorocresol.

Table VI lists buffers and chemicals used to adjust the pH of formulations. Phosphate, citrate, and acetate are the most common buffers used in parenteral products. Mono and diethanolamine are added to adjust pH and form corresponding salts. Hydrogen bromide, sulfuric acid, benzene sulfonic acid and methane sulfonic acids are added to drugs which are bromide (Scopolamine HBr, Hyoscine HBr, UDL), sulfate (Nebcin, Tobramycin sulfate, Lilly), besylate

TABLE IV
Antioxidants and Reducing Agents

Excipient	Frequency	Range	Example
Acetone sodium bisulfite	4	0.2–0.4% w/v	Novocaine® (Sanofi-Winthrop) 0.4% w/v
Ascorbate (sodium/acid)	7	0.1–4.8% w/v	Vibramycin® (Roerig) 4.8% w/v
Bisulfite sodium	28	0.02–0.66% w/v	Amikin® (Bristol Myers) 0.66% w/v
Butylated hydroxy anisole (BHA)	3	0.00028–0.03% w/v	Aquasol® (Astra) 0.03%
Butylated hydroxy toluene (BHT)	3	0.00116–0.03% w/v	Aquasol® (Astra) 0.03%
Cystein/Cysteinate HCl	2	0.07–0.10% w/v	Acthar Gel® (Rhone-Poulanc) 0.1% w/v
Dithionite sodium (Na hydrosulfite, Na sulfoxylate)	1	0.10%	Numorphan® (DuPont) 0.10%
Gentisic acid	1	0.02% w/v	OctreoScan® (Mallinckrodt)
Gentisic acid ethanolamine	1	2%	M.V.I. 12® (Astra) 2%
Glutamate monosodium	2	0.1% w/v	Varivas® (Merck) 0.1% w/v
Formaldehyde sulfoxylate sodium	9	0.075–0.5% w/v	Terramycin Solution (Roerig) 0.5% w/v
Metabisulfite potassium	1	0.10%	Vasoxyl® (Glaxo-Wellcome) 0.10%
Metabisulfite sodium	29	0.02–1% w/v	Intropin® (DuPont) 1% w/v
Monothioglycerol (Thioglycerol)	6	0.1–1%	Terramycin Solution (Roerig) 1%
Propyl gallate	2	0.02%	Navane® (Roerig)
Sulfite sodium	7	0.05–0.2% w/v	Enion® (Ohmeda) 0.2% w/v
Thioglycolate sodium	1	0.66% w/v	Sus-Phrine® (Forest) 0.66% w/v

TABLE V
Antimicrobial Preservatives

Excipient	Frequency	Range	Example
Benzalkonium chloride	1	0.02% w/v	Celestone Soluspan® (Schering) 0.02% w/v
Benzethonium chloride	4	0.01%	Benadryl® (Parke-Davis) 0.01% w/v
Benzyl alcohol	74	0.75–5%	Dimenhydrinate® (Steris) 5%
Chlorobutanol	17	0.25–0.5%	Codine phosphate (Wyeth-Ayerst) 0.5%
m-Cresol	3	0.1–0.3%	Humatrope® (Lilly) 0.30%
Myristyl gamma-picolinium chloride	2	0.0195–0.169% w/v	Depo-Provera® (Upjohn) 0.169% w/v
Paraben methyl	50	0.05–0.18%	Inapsine® (Janssen) 0.18% w/v
Paraben propyl	40	0.01–0.1%	Xylocaine w/Epinephrine (Astra) 0.1% w/v
Phenol	48	0.2–0.5%	Calcimar® (Rhone Poulanc) 0.5% w/v
2-Phenoxyethanol	3	0.50%	Havrix® (SmithKline Beecham) 0.50% w/v
Phenyl mercuric nitrate	3	0.001%	Antivenin® (Wyeth-Ayerst) 0.001%
Thimerosal	46	0.003–0.01%	Atgam® (Upjohn) 0.01%

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InnoPharma Exhibit 1046.0345

TABLE VI
Buffers and pH Adjusting Agents

Excipient	Example
Acetate	
Sodium	Miacalcin Injection® (Sandoz)
Acetic acid	Miacalcin Injection® (Sandoz)
Glacial acetic acid	Brevibioc Injection® (Ohmeda)
Ammonium	Bumex Injection® (Roche)
Ammonium hydroxide	Triostat Injection® (SmithKline Beecham)
Benzene sulfonic acid	Tracrium Injection® (Glaxo-Wellcome)
Benzoate Sodium/acid	Valium Injection® (Roche)
Bicarbonate Sodium	Cefotan Injection® (Zeneca)
Carbonate Sodium	HypoRho-D® (Bayer)
Citrate	
Acid	DTIC-Dome® (Bayer)
Sodium	Ceredase® (Genzyme)
Disodium	Cerezyme® (Genzyme)
Trisodium	Cerezyme® (Genzyme)
Diethanolamine	Bactrim IV® (Roche)
Glucono delta lactone	Quinidine® (Lilly)
Glycine	Hep-B Gammagee® (Merck)
Hydrochloric acid	Amicar® (Immunex)
Hydrogen bromide	Scopolamine (UDL)
Lactate acid/Sodium	Fentenyl citrate & Droperidol (Astra)
Lysine	Eminase Injection® (Roberts)
Maleic acid	Librium Injection® (Roche)
Methanesulfonic acid	DHE-45 Injection® (Sandoz)
Monoethanolamine	Terramycin Solution (Roerig)
Phosphate	
Acid (phosphoric)	Humegon® (Organon)
Monobasic potassium	Zantac Injection® (Glaxo-Wellcome)
Monobasic sodium*	Pregnyl® (Organon)
Dibasic sodium**	Prolastin® (Bayer)
Tribasic sodium	Synthroid® (Knoll)/
Sodium hydroxide	Optiray® (Mallinckrodt)
Sulfuric acid	Nebcin® (Lilly)
Tartrate acid/sodium	Methergine Injection® (Sandoz)
Tromethamine	Optiray® (Mallinckrodt)

* Sodium biphosphate, Sodium dihydrogen phosphate or Na dihydrogen orthophosphate.

** Sodium phosphate, Disodium hydrogen phosphate.

(Tracrium Inj., Atracurium besylate) or mesylate (DHE 45 Injection, Dihydroergotamine mesylate) salts. Glucono delta lactone is used to adjust the pH of Quinidine gluconate (Lilly). Benzoate buffer, at a concentration of 5%, is used in Valium Injection. Citrates are common buffers that can have a dual role as chelating agents. Lysine and glycine are amino acids which function as buffers and stabilize protein and peptide formulations. These amino acids are also used as lyo-additives and may prevent cold denaturation. Lactate and tartrate are occasionally used as buffer systems.

Table VII lists additives which are used to modify osmolality, and as bulking or lyo-cryo protective agents. Dextrose and sodium chloride are used to adjust tonicity in the majority of formulations. Some amino acids, glycine, alanine, histidine, imidazole, arginine, asparagine, aspartic acid, are used as bulking agents for lyophilization and may serve as stabilizers for proteins or peptides and as buffers. Monosaccharides (dextrose, glucose, lactose), disaccharide (sucrose), polyhydric alcohols (inositol, mannitol, sorbitol), glycol (PEG 3350), Povidone (polyvinylpyrrolidone), and proteins (albumin, gelatin) are commonly used as lyo-additives.

TABLE VII
Bulking Agents, Protectants, and Tonicity Adjustors

Excipient	Example
Alanine	Thrombate III® (Bayer)
Albumin	Bioclate® (Arco)
Albumin human	Botox® (Allergan)
Amino acids	Havrix® (SmithKline Beecham)
L-Arginine	Activase® (Genentech)
Asparagine	Tice BCG® (Oganon)
L-Aspartic acid	Pepcid® (Merck)
Calcium chloride	Phenergan Injection® (Wyeth-Ayerst)
Citric acid	Sensorcaine-MPF® (Astra)
Dextrose	Betaseron® (Berlex)
Gelatin hydrolyzed	Acthar® (Rhone-Poulanc Rorer)
Glucose	Iveegam® (immuno-US)
Glycerin	Tice BCG® (Oganon)
Glycine	Atgam Injection® (Upjohn)
Histidine	Antihemophilic Factor, human (Am. Red Cross)
Imidazole	Helixate® (Armour)
Inositol	OctreoScan® (Mallinckrodt)
Lactose	Caverject® (Upjohn)
Magnesium chloride	Terramycin Solution® (Roerig)
Magnesium sulfate	Tice BCG® (Oganon)
Mannitol	Elspar® (Merck)
Polyethylene glycol 3350	Bioclate® (Arco)
Polysorbate 80	Helixate® (Armour)
Potassium chloride	Varivax® (Merck)
Povidone	Alkeran® (Glaxo-Wellcome)
Sodium chloride	WinRho SD® (Univax)
Sodium succinate	Actimmune® (Genentech)
Sodium sulfate	Depo-Provera® (Upjohn)
Sorbitol	Panhematin® (Abbott)
Sucrose	Prolastin® (Bayer)

Special Additives

These additives have been included in pharmaceutical formulation to serve specific functions (Table VIII). Below is a summary of the special additives along with their intended use—

(1) Calcium gluconate injection (American Regent) is a saturated solution of 10% w/v; calcium d-saccharate tetrahydrate 0.46% w/v is added to prevent crystallization during temperature fluctuations.

(2) Cipro IV® (Ciprofloxacin, Bayer) contains lactic acid as a solubilizing agent for the antibiotic.

(3) Premarin Injection® (Conjugated Estrogens, Wyeth-Ayerst Labs) is a lyophilized product that contains simethicone to prevent formation of foam during reconstitution.

(4) Dexamethasone acetate (Dalalone DP, Forest, Decadron-LA, Merck, Dalalone DP Injection, UAD Labs) and Dexamethasone Na phosphate (Merck) are available as suspension or solution. These dexamethasone formulations contain creatine or creatinine as an additive.

(5) Adriamycin RDF® (Doxorubicin hydrochloride, Pharmacia) contains methyl paraben, 0.2 mg/mL, to increase dissolution (10).

(6) Ergotrate maleate (Ergonovine maleate, Lilly) contains 0.1% ethyl lactate as a solubilizing agent.

(7) Estradurin Injection® (Polyestradiol phosphate, Wyeth-Ayerst Labs) uses Niacinamide (12.5 mg/ml)

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TABLE VIII
Special Additives

Excipient	Example
Acetyl tryptophanate	Human Albumin (American Red Cross)
Aluminum hydroxide	Recombinant HB® (Merck)
Aluminum phosphate	Tetanus Toxoid Adsorbed® (Lederle)
Aluminum potassium sulfate	TD Adsorbed Adult® (Connaught)
E-Aminocaproic acid	Eminase® (Roberts)
Calcium d-saccharate	Calcium Gluconate (American Regent)
Caprylate sodium	Human Albumin (American Red Cross)
8-Chlorotheophylline	Dimenhydrinate (Steris)
Creatine	Dalalone DP® (Forest)
Creatinine	Hydrocortone Phosphate (Merck)
Diatrizoic acid	Conray (Mallinckrodt)
Gamma Cyclodextrin	Cardiotec (Squibb)
Ethyl lactate	Ergotrate maleate® (Lilly)
Ethylenediamine	Aminophylline® (Abbott)
L-Glutamate sodium	Kabikinase® (Pharmacia)
Iron ammonium citrate	Tice BCG® (Oganon)
Lactic acid	Cipro IV® (Bayer)
D,L-Lactic and Glycolic acid copolymer	Zoladex® (Zeneca)
Maltose	Gamimune® (Bayer)
Meglumine	Magnevist® (Berlex)
Niacinamide	Estradurin® (Wyeth-Ayerst)
Paraben methyl	Adriamycin RDF® (Pharmacia)
Protamine	Insulatard NPH® (Novo Nordisk)
Simethicone	Premarin Injection® (Wyeth-Ayerst)
Sodium saccharin	Compazine Injection® (Smith-Kline Beecham)
Tri-n-butyl phosphate	Venoglobulin® (Apha Therapeutic)
von Willebrand factor	Bioclate® (Arco)
Zinc	Lente Insulin® (Novo Nordisk)

TABLE IX
List of Excipient from 1996 FDA 'Inactive Ingredient Guide'

Ammonium sulfate	Pentetate (DTPA) calcium trisodium
Benzyl chloride	Poloxamer 165
Butyl paraben	PEG 4000
Caldiamide sodium	PEG 600
Calteridol calcium	Polyglactin
Castor oil	Polylactide
Cellulose (microcrystalline)	Polyoxyethlene fatty acid esters
Cholesterol	Polyoxyethylene sorbitan monosterate
Deoxycholic acid	Polyoxyl 35 Castor oil
Diatrizoic acid	Polysorbate 40
Dicyclohexyl carbodiimide	Polysorbate 85
Diethyl amine	Potassium hydroxide
Dimyristoyl lecithin	Potassium phosphate, dibasic
Dimyristoyl phosphatidyl-glycerol	Sodium bisulfate
Disofenin	Sodium chlorate
Docusate sodium	Sodium hypochloride
Edamine	Sodium iodide
Exametazime	Sodium pyrophosphate
Gluceptate sodium	Sodium thiosulfate, anhydrous
Gluceptate calcium	Sodium trimetaphosphate
Glucuronic acid	Sorbitan monopalmitate
Guanidine HCl	Stannous chloride
Iofetamine HCl	Stannous fluoride
Lactobionic acid	Stannous tartrate
Lecithin hydrogenated soy	Starch
Lidofenin	Succimer
Medrofenin	Succinic acid
Medronate disodium	Sulfurous acid
Medronic acid	Tetrakis (1-isocyano-2-methoxy-2,methyl-propante) copper (I) Te
Methyl boronic acid	Thiazoximic acid
Methyl cellulose	Trithiazoximic acid
Methylene blue	Urea
N-(carbamoyl-methoxy poly-ethylene-glycol 2000)-1,2-distearoyl	Zinc acetate
N-2-hydroxyethyl piperazine N'-2' ethane sulphonic acid	Zinc chloride
Nioxime	Zinc oxide
Nitric acid	2-ethyl hexanoic acid
Oxyquinoline	PEG vegetable oil

as a solubilizing agent. Hydeltrasol® (Merck) also contains niacinamide.

(8) Aluminum in the form of aluminum hydroxide, aluminum phosphate or aluminum potassium sulfate is used as adjuvant in various vaccine formulations to elicit an increased immunogenic response.

(9) Zoladex® (Goserelin acetate, Zeneca) is administered subcutaneously as microspheres. These spheres are made of D,L-lactic and glycolic acid copolymer. Lupron Depot Injection® (TAP) are lyophilized microspheres of gelatin and glycolic-lactic acid for intramuscular injection.

(10) Gamma cyclodextrin is used as a stabilizer in Cardiotec® at a concentration of 50 mg/mL.

(11) Sodium caprylate (sodium octoate) has antifungal properties, but it is also used to improve the stability of albumin solution against effects of heat. Albumin solution can be heat pasteurized by heating at 60°C for 10 hours in the presence of sodium caprylate. Acetyl tryptophanate sodium is also added to albumin formulations.

(12) Meglumine (N-methylglucamine) is used as an excipient and to form in-situ salt. For example, diatrizoic acid, an X-ray contrast agent, is more stable when autoclaved as meglumine salt than as sodium salt (11). Meglumine is also added to Magnevist®, a magnetic resonance contrast agent, formulation.

(13) Surprisingly, sodium saccharine is used in Stelazine® and Compazine® formulations; our guess is that it serves as a stabilizer and tonicity adjuster.

(14) Tri-n-butyl phosphate is present as an excipient in human immune globulin solution (Venoglobulin®). Its exact function in the formulation is not known, but it may serve as a scavenging agent.

(15) von Willebrand factor is used to stabilize recombinant antihemophilic factor (Bioclate®).

(16) Maltose serves as a tonicity adjuster and stabilizer in immune globulin formulation (Gamimune N®).

(17) Epsilon amino caproic acid (6-amino hexanoic acid) is used as a stabilizer in anistreplase (Eminase injection®).

(18) Zinc and protamine have been added to insulin to form complexes and control the duration of action.

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Recently, FDA has published 'Inactive Ingredient Guide' which lists all the excipients in alphabetical order. Each ingredient is followed by the route of administration (for example, iv, oral) and, in some cases, the range of concentration used in the approved drug product. However, this list does not provide the name of commercial product(s) corresponding to each excipient. Table IX is a summary of all the excipients which are included in the 'Inactive Ingredient Guide,' but do not appear in PDR or Handbook on Injectable Drugs.

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ATTACHMENT F - COMPILATION

TAB 9

PDR

27 EDITION

1973

Physicians' Desk Reference®

To Pharmaceutical Specialties and Biologicals

Publisher: CHARLES E. BAKER, Jr.
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...two 100 mg. tablets (150 or 200 mg.) ...ur to six hours. Once a satisfactory ...has been achieved, it may be desirable ...inister one-half to one 100 mg. PRAN... tablet (50 to 100 mg.) every four to six ...to prevent recurrence. Increase in the ...ance dosage is suggested during peri... ...heightened emotional stress or psychic ...and at intervals when experience in... ...ulcer may recur.

Supplied: PRANTAL **Tablets**, 100 mg., ...bottle of 100.

...ight © 1966, 1972, Schering Corpora... ...l rights reserved.

...GYNON®

...ol, estradiol, N.F.
...ous Suspension

...tion: **Aqueous suspension** of estra... ...otonic solution for intramuscular in... ...ontains in each cc 1.0 mg. estradiol, ...mg. polysorbate 80, with 0.5% phenol ...ervative. **Pellets** of estradiol 25 mg. for ...aneous implantation; the pellets con... ...excipient or binder.

...: Estradiol, one of the more potent of ...ural estrogenic compounds, is identical ...estrogenic hormone produced by the ...ovary. Estradiol exerts a developmen... ...on the female generative tract, has ...ibitory effect upon the pituitary in ...doses, and produces a marked constitu... ...effect with an increase in muscular ...th, bodily vigor, and mental acumen. It ...s follicular hormone in cases where es... ...ic activity is depressed, insufficient, or ...

...: In PROGYNON **Aqueous Suspension** ...ilize solution is absorbed rapidly and ...re crystalline estradiol remains in the ...as a depot from which absorption be... ...promptly and continues for a long pe... ...The vials should be shaken immediately ...using in order to suspend the estradiol ...ntly. It is intended for intramuscular ...istration. The PROGYNON **Pellets** are ...ical, with an approximate diameter of ...and length of 3.5 mm. Pellet therapy ...advantage of high efficiency from the ...oint of the quantity of hormone admin... ...and the further advantage that a sin... ...tment has effect continuously for sev... ...nths.

...ions: **In the female**—PROGYNON **...Suspension** is indicated in mono... ...syndrome, hypogenitalism and sexual ...ism, oligomenorrhea associated with ...nadism, and postpartum breast en... ...gement.

...NON **Aqueous Suspension** is also in... ...for inoperable breast carcinoma in ...menopausal women, senile vaginitis, and ...s or kraurosis vulvae.

...NON **Pellets** are indicated in condi... ...where constant and prolonged estrogen ...is required. The pellets may be used ...ve symptoms of estrogen deficiency ...in the menopausal syndrome and ...adism, as replacement therapy in ...d females; in the male—carcinoma of ...state (palliative).

...ndications: Familial or personal his... ...carcinoma (also precancerous lesions) ...dicates use of estrogens, unless spe... ...indicated as therapy for carcinoma. ...ns administered continuously are con... ...ated in thrombophlebitis, pulmonary ...s, and liver dysfunction or disease. ...y of hypersensitivity or toxic reac... ...any of the components contraindi... ...use.

...ions: Hypercalcemia and sodium ...retention may occur with continued ...rge doses of estrogens; use cautiously ...in patients with cardiac or renal disease, or epilepsy.

As with all estrogens, undesirable uterine growth may occur; as a consequence withdrawal endometrial bleeding may occur; uterine fibroids may increase in size.

Diabetic patients should be observed carefully for regulation during medication with estrogens.

Use estrogens judiciously in young patients in whom bone growth is not complete; estrogens may effect epiphyseal closure.

Thrombophlebitis and pulmonary embolism have occasionally occurred with estrogen therapy; although no definitive relationship exists, physicians should be alert to the earliest manifestations of these conditions.

In patients with histories of psychic abnormalities, estrogen therapy should be terminated if symptoms of such abnormalities reoccur.

Adverse Reactions: Gastrointestinal disturbances (nausea, vomiting, mild diarrhea), headache, edema due to salt retention, soreness of breast or gynecomastia (may occur in treatment of prostatic carcinoma), vertigo, chloasma, cholestatic jaundice, erythema multiforme, hemorrhagic eruption, allergic rash, itching, amenorrhea, mental depression, hypercalcemia with large doses.

Dosage and Administration: Menopausal syndrome:—In average cases, 1.0 mg. of estradiol intramuscularly two or three times weekly for 2 or 3 weeks; in more severe cases, 1.0 to 1.5 mg. of estradiol. Thereafter, dosage is gradually reduced to minimum requirement, usually within the range of 0.5 to 1.0 mg. of estradiol twice weekly. In all cases the objective should be determination of the minimum amount of hormone that will maintain the patient symptom-free. With adequate clinical improvement, usually obtainable in two weeks or less, gradual reductions in dosage are advisable. Subcutaneous implantation—implant one 25 mg. PROGYNON Pellet and repeat when necessary. The pellets provide constant estrogen levels for approximately 3 months.

Hypogenitalism and Sexual Infantilism:—1.5 mg. of estradiol intramuscularly two or three times weekly. Subcutaneous implantation—Implant one 25 mg. pellet and repeat when necessary.

Amenorrhea and Oligomenorrhea Associated with Hypogonadism: 1.5 mg. of estradiol intramuscularly two or three times weekly during the first two weeks of an arbitrary 28-day menstrual cycle; progesterone is given during the last two weeks of the theoretical cycle. This regimen is continued for 3-6 months. The patient then is allowed to go untreated for 2 months to determine whether or not she can maintain the cycle without hormonal therapy. If not, additional courses of therapy as outlined should be prescribed.

Postpartum Breast Engorgement:—1.5 mg. of estradiol is administered intramuscularly daily beginning at the first sign of engorgement and continuing until symptoms are controlled. Restriction of fluids and a tight binder should also be employed.

Inoperable Breast Carcinoma in Postmenopausal Women:—1.5 mg. of estradiol intramuscularly three or more times weekly according to the severity of the pain.

Carcinoma of the Prostate:—1.5 mg. of estradiol intramuscularly three times weekly. Subcutaneous implantation—implant one 25 mg. pellet and repeat when necessary.

Senile Vaginitis; Pruritus Vulvae; Kraurosis vulvae:—Initially, 1.0 to 1.5 mg. of estradiol intramuscularly three times weekly for two or three injections, then 0.5 to 1.0 mg. of estradiol twice weekly for maintenance. Oral estrogen therapy may be preferred for maintenance.

PROGYNON (estradiol) Aqueous Suspension should be injected intramuscularly. Never intravenously. A 21-gauge 1½-inch needle is best suited for injecting the suspension well into the muscle.

The pellets may be implanted conveniently and quickly by means of an injector or they may be administered by making an incision in the skin. Either method, though readily carried out in the physician's office, is a minor surgical procedure, and all aseptic precautions must be observed. *BY INJECTOR:* The pellet may be quickly and easily implanted by means of the Kearns or Porloff Pellet Injectors. The areas usually selected for implantation are the infrascapular region or the posterior axillary line. Aseptic precautions must be observed as for any surgical procedure. The skin is carefully cleaned, followed by the application of iodine and alcohol. The area is infiltrated with procaine 1:100. Make a very small incision (about 2 mm. long and 1 mm. deep) into the skin with a sharp scalpel to allow free passage of the large injector needle. The injector needle of the Kearns injector, with sharp plunger in place, is inserted into the incision and gently forced into the subcutaneous tissue at the desired site of implantation. The sharp plunger is withdrawn, and the pellet inserted into the hollow needle. The simplest method for placing the pellet in the needle is to allow the pellet to slide from the vial in which it is packed into the slot provided in the needle. The pellet is pushed as far as possible through the needle by means of the blunt plunger and held in place with the plunger while the needle is gently withdrawn. When the needle comes in contact with the knob of the plunger, both are withdrawn together. When the injector has been withdrawn, the wound may be closed with a single stitch or a skin clip. In many instances, apposition of the edges of the wound with adhesive tape is sufficient. *BY INCISION:* The infrascapular region or the posterior axillary line are convenient sites for implanting pellets. The operative field is prepared in the usual manner with iodine and alcohol and the area is infiltrated with procaine 1:100 solution. An incision about one centimeter in length is made. With blunt dissection, a pocket about two centimeters in depth is prepared in the subcutaneous tissue below and away from the incision. The edges of the pocket may be held apart by a small dilator and the pellet inserted into the bottom of the pocket with small forceps. Force should not be used in inserting pellets. The incision is closed with one or two sutures.

How Supplied: Aqueous Suspension—multiple-dose vials of 10 cc., 1.0 mg./cc., boxes of 1 and boxes of 6 are available. Store away from heat. **Pellets**—vial of one 25 mg. pellet, box of 3.

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PROLUTON®

brand of progesterone injection, N.F.
Injection

Description: PROLUTON achieves all of the definitely established effects of the corpus luteum hormone on the uterus. It causes the secretory phase of the endometrium to devel-

Continued on next page

Information on Schering products appearing on these pages is effective as of September 30, 1972. Schering products whose active ingredients are listed in Medicare-approved pharmaceutical compendia appear at the beginning of the Schering Product Information Section.

InnoPharma Exhibit 1046.0351

Schering—Cont.

op and attain up to ten times its original thickness, with distention and activity of the glands and profound hyperemia. Greatest effectiveness of progesterone depends on previous priming of the endometrium with estrogens. PROLUTON for intramuscular administration contains in each cc. of solution progesterone, N.F., 50 mg.; benzyl alcohol, N.F., 50 mg.; benzyl benzoate, U.S.P., 150 mg.; propylparaben, U.S.P., 1.0 mg.; and sesame oil, U.S.P.

Indications: PROLUTON is indicated in habitual and threatened abortion, premature labor, functional uterine bleeding, functional dysmenorrhea, premenstrual tension, primary and secondary amenorrhea and female hypogonadism.

Contraindications: Hypersensitivity or toxic reactions to any of the components contraindicates its use. Progesterone is also contraindicated in patients with impaired renal function, missed or incomplete abortion, carcinoma of the breast, and undiagnosed genital bleeding.

A history or the presence of thrombophlebitis, thromboembolic disorders, cerebrovascular accident, or pulmonary embolism also contraindicates the use of this product.

Precautions: Administer cautiously in patients who have had periodic attacks of asthma, migraine, or epilepsy; these conditions may be exacerbated by progesterone. Patients with a history of psychic depression should be carefully observed; the drug should be discontinued if the depression recurs to a serious degree. Fluid retention may occur; observe patients with cardiac or renal dysfunction carefully.

Adverse Reactions: Edema, urticaria, pruritus vulvae, gastrointestinal disturbances (nausea, vomiting, diarrhea), ulcerative stomatitis, headache, weight gain, and local irritation.

Dosage and Administration: *Habitual Abortion*—PROLUTON 5 to 20 mg., should be given three times a week, commencing therapy with the early diagnosis of pregnancy and continuing through the eighth month. At times of stress and calculated menses, 25 mg. should be given daily. *Threatened Abortion*—In addition to usual measures, PROLUTON 25 to 50 mg. daily should be administered as long as there are pains and bleeding. When symptoms have subsided, the dosage is reduced to 10 to 25 mg. daily, and maintained at this level through the eighth month of pregnancy. When estrogen therapy is preferred during crises, PROGYNON® (estradiol Benzoate, 1.666 mg. may be given at two-hour intervals until symptoms are controlled. *Premature Labor*—PROLUTON 25 to 50 mg., may be given daily until symptoms subside. *Functional Uterine Bleeding*—5 to 10 mg. daily or 25 mg. on alternate days, should be administered starting eight to ten days before the patient is expected to menstruate. In severe cases, 50 mg. daily may be used. *Functional Dysmenorrhea, Premenstrual Tension*—Recommended dosage is 10 to 25 mg. daily during the last eight to ten days before the patient is expected to menstruate. *Primary and Secondary Amenorrhea, Female Hypogonadism*—Recommended dosage is 25 mg. three times weekly during the last two weeks of a calculated menstrual cycle after estrogen therapy during the first two weeks of the calculated cycle.

PROLUTON should be injected intramuscularly, never intravenously. Subcutaneous injection at times may give rise to painful local reactions. Immersion of the vial momentarily in warm water will facilitate aspiration into the syringe. A 21-gauge, 1½-inch needle is best suited for injecting the oil solution well into the muscular tissue. For obese patients, a 20-gauge, 2-inch needle may be used. The site usually selected for injection is the upper outer quadrant of the gluteal region. Aspiration should be done before expelling the contents of the syringe in order to make certain a blood vessel has not been entered.

How Supplied: PROLUTON Injection, 10 cc. multiple-dose vials, boxes of 1 and 6.

NOTE: In cool weather, crystals may appear in the vials, in which case the vials should be warmed to bring the crystals back into solution before using.

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RELA®

brand of carisoprodol

Tablets

Description: Carisoprodol is N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate.*

Actions: Carisoprodol produces muscle relaxation in animals by blocking interneuronal activity in the descending reticular formation and spinal cord. There are no peripheral or autonomic effects. Relief of symptoms usually begins within 30 minutes and lasts four to six hours.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: for symptomatic relief in conditions characterized by skeletal muscle spasm and mild to moderate pain.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Carisoprodol is contraindicated in patients who have had allergic or idiosyncratic reactions to it or to related compounds such as meprobamate or mebutamate and also in patients who have porphyria or in whom porphyria is suspected.

Warnings: The patient should be warned that carisoprodol may impair the mental and/or physical abilities required for the performance of hazardous tasks such as driving a motor vehicle or operating machinery.

Use carisoprodol with caution in addiction-prone individuals. Withdrawal symptoms including abdominal cramps, insomnia, chilliness, headache, and nausea have occurred following abrupt cessation of higher than recommended dosage. There have been rare instances of psychological dependence.

On very rare occasions, the first dose of carisoprodol has been followed by idiosyncratic symptoms appearing within minutes or hours. Symptoms reported include extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion, and disorientation. Symptoms usually subside over the course of the next several hours. Supportive and symptomatic therapy, including hospitalization, may be necessary.

Usage in pregnancy: Safe usage of this drug in pregnant women has not been established. Therefore, the expected benefits must be weighed against the potential hazards. In lactating mothers receiving carisoprodol, the concentration in breast milk is two to four times that of maternal plasma. This factor should be taken into account when use of the drug is contemplated in nursing mothers.

Use of this drug in children is not recommended.

Since the effects of carisoprodol and alcohol or carisoprodol and other CNS depressants may be additive, appropriate caution should be exercised.

Precautions: Carisoprodol is metabolized in the liver and excreted by the kidneys; to avoid its excess accumulation, caution should be exercised in administration to patients with compromised liver or kidney function.

Adverse Reactions: *Central nervous system reactions:* Drowsiness and other CNS effects may require dosage reduction. Other adverse reactions include dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia.

Allergic or idiosyncratic reactions: Allergic or idiosyncratic reactions occasionally develop. They are usually seen within the period of the first to fourth dose in patients having had no previous contact with the drug. Skin rash, erythema multiforme, pruritus, eosinophilia, and fixed drug eruption with cross reaction to meprobamate have been reported with carisoprodol. Severe reactions have been manifested by asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension, and anaphylactoid shock.

If such reactions do occur, discontinue carisoprodol and initiate appropriate symptomatic therapy, utilizing epinephrine, antihistamines, and possibly corticosteroids. In evaluating possible allergic reactions, also consider allergy to excipients.

Cardiovascular reactions: Tachycardia, postural hypotension, and facial flushing have been reported.

Gastrointestinal reactions: Nausea, vomiting, hiccup, and epigastric distress have been reported.

Hematologic reactions: Leukopenia, for which other drugs or viral infection may have been responsible, and pancytopenia, attributed to phenylbutazone, have been reported. No serious blood dyscrasias have been attributed to carisoprodol.

Dosage and Administration: The recommended dosage for adults is one RELA® 350 mg. four times daily, the last dose taken at bedtime. Use of this drug in children is not recommended.

Overdosage: Overdosage of carisoprodol produced stupor, coma, shock, respiratory depression, and, very rarely, death. Any drug remaining in the stomach should be removed and symptomatic therapy given. If respiration or blood pressure becomes compromised, respiratory assistance, central nervous system stimulants, and pressor agents should be administered cautiously as indicated.

Carisoprodol is metabolized in the liver and excreted by the kidney. Although carisoprodol overdosage experience is limited, the following types of treatment have been used successfully with the related drug meprobamate: diuresis, osmotic (mannitol), peritoneal dialysis, and hemodialysis (carisoprodol is dialysable).

Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration. Carisoprodol can be measured in biological fluids by gas chromatography (Douglas JF, et al; J Pharm Sci 1968).

How Supplied: RELA Tablets are round, sugar-coated, pink tablets imprinted with a brown Schering trademark and product identification letters, AHRI on the tablets.

*Licensed under U.S. Pat. No. 2,937,119.

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[Shown in Product Identification]

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Squibb—Cont.

dumone has been discontinued for 60 days before the test. Because of osteoblastic action of estrogens, patients with metabolic bone disease or renal disease should be carefully observed. Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely. Any effect of prolonged use of this drug on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further studies.

Adverse Reactions: In therapeutic doses, undesirable hormonal effects are generally minimal. However, because of excessive androgenic or estrogenic stimulation, they may occur.

The following adverse reactions have been observed following Deladumone therapy:

Virilization, manifested by hirsutism, changes in the voice (hoarseness or deepening), and acne. The phenomena of virilization appear to be reversible except for some instances of voice changes. Virilization may be controlled by use of supplementary injections of estradiol valerate; excessive endometrial or breast stimulation may be controlled by the use of supplemental injections of testosterone enanthate.

Other adverse reactions which have been reported are delayed menses followed by profuse bleeding, excessive and prolonged vaginal bleeding, mastodynia, edema, erythema and edema of the vulva, convulsions, pain at the site of injection, sterile abscess, incomplete suppression of lactation and/or breast engorgement, and localized dermatitis.

Dosage and Administration: The usual dosage for all indications except prevention of postpartum lactation, breast engorgement, and subsequent pain is 1 cc. every 4 weeks, depending on the clinical response. To alter the amount of therapy, it is recommended that the change be made in the quantity per injection (range 1 to 4 cc.) rather than in the time interval between injections.

For the prevention of postpartum lactation, breast engorgement, and subsequent pain, 4 cc. should be given as a single injection just prior to the onset of the second stage of labor because the percentage of favorable results has been shown to decline when the dose is administered at a later time. A second injection is not recommended.

Care should be taken to inject Deladumone deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

Storage: Vials of Deladumone may be stored at room temperature. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on warming. Deladumone in Unimatic® single-dose preassembled syringes and cartridge-needle units should be stored at room temperature.

How Supplied: Deladumone, vials of 5 cc.; Unimatic® single dose preassembled syringes of 1 cc. and cartridge-needle units of 1 cc.

DELADUMONE® OB

Testosterone Enanthate [360 mg.] And Estradiol Valerate [16 mg.] Injection

Description: Deladumone OB is a sterile, long-acting preparation for the prevention of lactation, providing a precisely balanced combination of the naturally-occurring testicular and follicular hormones in ester form dissolved in a vehicle of sesame oil with 2% (w/v) benzyl alcohol as a preservative. Each 2 cc. Deladumone OB contains 360 mg. testosterone enanthate and 16 mg. estradiol valerate. (180 mg. testosterone enanthate and 8 mg. estradiol valerate per cc.).

Actions: Deladumone OB is a long-acting androgen-estrogen preparation. When used for the prevention of lactation, a single 2 cc. injection, administered as directed, effectively inhibits the release of lactogenic hormone from the pituitary, thereby preventing lactation and the painful breast engorgement which accompanies it. However, if breast feeding is desired after Deladumone OB has been administered, satisfactory release of the lactogenic hormone and lactation may be induced by the stimulus of suckling by the infant. Involution of the uterus and resumption of menstrual cycles are generally not affected by Deladumone OB.

Deladumone OB contains the same hormonal agents as Deladumone (Testosterone Enanthate and Estradiol Valerate Injection) but at twice the potency, in order to provide a high dosage concentration in a low volume. The optimal balance of androgenic and estrogenic hormones obviates the disadvantages inherent in single hormone therapy, minimizing the likelihood of virilization, withdrawal bleeding, or other unwanted effects.

Indications: Deladumone OB is specifically indicated for the prevention of postpartum lactation, breast engorgement, and subsequent pain.

Contraindications: Deladumone OB is contraindicated in patients with a history of established or suspected mammary or genital malignancy, or hepatic dysfunction or disease.

Precautions: Because normal endogenous hormone production varies individually, certain patients may be unusually responsive and may exhibit undesirable manifestations of excessive androgenic or estrogenic stimulation (see *ADVERSE REACTIONS*).

Although edema has not been found to be a problem when Deladumone OB is used as recommended in the control of postpartum lactation and breast engorgement, nevertheless, caution should be taken in administering the drug to patients with cardiac or renal disease, and to patients with epilepsy, migraine, or asthma.

Adverse Reactions: When properly given, injections of Deladumone OB are generally well tolerated. In therapeutic doses, undesirable hormonal effects are generally minimal. The following adverse reactions have been reported: Virilization, manifested by hirsutism, changes in the voice (hoarseness or deepening), and acne. The phenomena of virilization appear to be reversible except for some instances of voice changes. Virilization may be controlled by use of supplementary injections of estradiol valerate. Excessive endometrial or breast stimulation has been reported; these effects may be controlled by the use of supplemental injections of testosterone enanthate.

Other adverse reactions that have been reported are pain at the site of injection, convulsions, sterile abscess, incomplete suppression of lactation and/or breast engorgement, uterine bleeding, mastodynia, and localized dermatitis.

Dosage and Administration: For the prevention of postpartum lactation, breast engorgement, and subsequent pain, 2 cc. of Deladumone OB should be given as a single intramuscular injection. It appears that the optimal time for administration of Deladumone OB is just prior to the onset of the second stage of labor. It is worthwhile noting, however, that the preparation has been successfully used from the early first stage of labor to as late as 10 hours after expulsion of the placenta. A second injection is not recommended.

Care should be taken to inject Deladumone OB deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

Because of the viscosity of the preparation, and since Deladumone OB provides a high concentration in a small volume, particular care should be taken to administer the full dose. A slow, steady pressure on the syringe plunger is recommended.

Storage: Vials of Deladumone OB should be stored at room temperature. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on warming. Deladumone OB in Unimatic single dose preassembled syringes and cartridge-needle units should be stored at room temperature.

How Supplied: Vials of 2 cc. (Military Stock #FSN-6505-823-7903), Unimatic® single dose preassembled syringes of 2 cc. and cartridge-needle units of 2 cc.

DELALUTIN®

(Hydroxyprogesterone Caproate Injection U.S.P.)

Description: Delalutin is a sterile, long-acting preparation of the caproate ester of the naturally occurring progestational hormone, hydroxyprogesterone, in an oil solution for intramuscular use.

Actions: Hydroxyprogesterone is a potent, long-acting, progestational steroid ester which transforms proliferative endothelium into secretory endothelium, induces mammary gland duct development, and inhibits the production and/or release of gonadotropic hormone; it also shows slight estrogenic, androgenic, or corticoid effects as well, but should not be relied upon for these effects.

In advanced adenocarcinoma of the uterine corpus, Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) in a dosage of 100 mg. or more, one or more times each week, often induces regressive changes.

Indications

Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

Effective: In non-pregnant women, Delalutin is indicated for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV) and in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer. Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) is also indicated for use as a test for continuous endogenous progesterone production (a presumptive test for pregnancy), as a test for endogenous estrogen production ("Medical D and C"), and for the production of secretory endometrium and desquamation.

Probably effective: Habitual and threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Hydroxyprogesterone caproate is contraindicated in patients with markedly impaired liver function, carcinoma of the breast, undiagnosed abnormal genital

ossible revisions

ing, missed abortion, and in th
ry of hypersensitivity to the d
ge regimens requiring estroge
dicated in women with a kno
d genital malignancy, and i
thrombophlebitis, thromboe
rs, cerebral apoplexy, or a past
e conditions.
nings: Discontinue the medica
examination if there is a sudd
mplete loss of vision, or if the
onset of proptosis, diplopia, or
ication should be stopped if ex
als papilledema or retinal v
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ctable amounts of progestins
ified in the milk of mother
drug. The effect of this on t
nt has not been determined.
culinization of the female fe
ed when progestins have be
gnant women.
physician should watch for
nifestations of thrombotic
mbophlebitis, cerebrovascula
lmonary embolism, and retina
If these occur or are suspect
uld be discontinued immed
ONTRAINDICATIONS).
ecautions: Like other proges
xyprogesterone caproate may
tion and/or release of gonad
nes, particularly the luteinizin
pic hormones; this should be c
management of sexually-ma
h regular normal menses, dur
t of the ovarian cycle.
droxyprogesterone caproate s
inistered with caution to those
om periodic attacks of certain
ions such as asthma, migraine,
diac or renal dysfunction, are
acerbated by progesterone.
e pretreatment physical
ould include examination of
d pelvic organs, and a Papanic
relation to irregular bleeding
t respond predictably to the h
y, nonfunctional causes should
ind and adequate diagnostic m
ted.
ome compounds with progestat
ay induce fluid retention.
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edication on pituitary, ovarian
tic or uterine function aw
udy.
e pathologist should be advi
rone therapy when relevant s
bmitted.
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ression should be carefully obs
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serious degree.
boratory test results, parti
itic and endocrine functions,
d by progesterone and/or estr
ests to evaluate endocrine a
ion should not be considered
as therapy has been discon
east 60 days.
Adverse Reactions: The follo
ion is pertinent whenever
preparations are used with est
known at the present time if th
re applicable to progesterone:
A. A statistically significant
been demonstrated betwe
trogen-progesterone com
thrombophlebitis, pulmor
and cerebrovascular accid
B. Although such a relatio
neither confirmed nor re
evidence is suggestive of
between the use of prog
estrogens and the followi
fects: neuro-ocular lesio

InnoPharma Exhibit 1046.0353

bleeding, missed abortion, and in those with a history of hypersensitivity to the drug.

Dosage regimens requiring estrogens are contraindicated in women with a known or suspected genital malignancy, and in patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.

Warnings: Discontinue the medication pending examination if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia, or migraine. Medication should be stopped if examination reveals papilledema or retinal vascular lesions.

Detectable amounts of progestins have been identified in the milk of mothers receiving the drug. The effect of this on the nursing infant has not been determined.

Masculinization of the female fetus has occurred when progestins have been used in pregnant women.

The physician should watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). If these occur or are suspected the drug should be discontinued immediately (see CONTRAINDICATIONS).

Precautions: Like other progestogens, hydroxyprogesterone caproate may inhibit production and/or release of gonadotropic hormones, particularly the luteinizing and luteotropic hormones; this should be considered in the management of sexually-mature women with regular normal menses, during the first part of the ovarian cycle.

Hydroxyprogesterone caproate should be administered with caution to those patients in whom periodic attacks of certain medical conditions such as asthma, migraine, epilepsy, or cardiac or renal dysfunction, are known to be exacerbated by progesterone.

The pretreatment physical examination should include examination of the breasts and pelvic organs, and a Papanicolaou smear.

In relation to irregular bleeding which does not respond predictably to the hormone therapy, nonfunctional causes should be borne in mind and adequate diagnostic measures instituted.

Some compounds with progestational activity may induce fluid retention.

Any influence of prolonged sex hormone medication on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

The pathologist should be advised of progesterone therapy when relevant specimens are submitted.

Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Laboratory test results, particularly of hepatic and endocrine functions, may be affected by progesterone and/or estrogen therapy. Tests to evaluate endocrine and liver function should not be considered definitive unless therapy has been discontinued for at least 60 days.

Adverse Reactions: The following information is pertinent whenever progesterone preparations are used with estrogens; it is not known at the present time if these statements are applicable to progesterones alone.

A. A statistically significant association has been demonstrated between the use of estrogen-progesterone combinations and thrombophlebitis, pulmonary embolism, and cerebrovascular accidents.

B. Although such a relationship has been neither confirmed nor refuted, available evidence is suggestive of an association between the use of progesterones with estrogens and the following untoward effects: neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis); nausea; vomiting; anorexia; gastrointestinal symptoms (such as abdominal cramps or bloating); edema; breakthrough bleeding, spotting, or withdrawal bleeding; breast tenderness and enlargement; changes in body weight (increase or decrease); headache; increase in cervical mucus; allergic rash; sterile abscess; pain at the injection site; post-injection flare; reactivation of endometriosis; aggravation of migraine headaches; and hepatic cutaneous porphyria becoming manifest.

C. The following adverse reactions are known to occur in patients receiving both progesterones and estrogens: chloasma or melasma, cholestatic jaundice, rise in blood pressure in susceptible individuals, mental depression, and amenorrhea during or after treatment.

D. The following adverse reactions have been reported with the concomitant use of progesterones and estrogens; a cause and effect relationship has been neither confirmed nor refuted: post-treatment anovulation, cystitis-like syndrome, hirsutism, loss of scalp hair, erythema nodosum, hemorrhagic eruption, premenstrual-like syndrome, changes in libido, changes in appetite, nervousness, dizziness, fatigue, backache, erythema multiforme, itching, and hypomenorrhea, oligomenorrhea, or amenorrhea.

E. The following laboratory tests may give altered results by the concomitant use of progesterones and estrogens: hepatic function (increased sulfobromophthalein retention and other tests); coagulation tests (increase in prothrombin and Factors VII, VIII, IX, and X); metyrapone test; pregnanediol determination; and thyroid function tests (increase in PBI and butanol extractable protein-bound iodine, decrease in T3 uptake values, and possible diminution in lactation when given immediately post-partum).

Female fetal masculinization has been observed in patients who received hydroxyprogesterone caproate.

A few instances of coughing, dyspnea, constriction of the chest, and/or allergic-like reactions have occurred following hydroxyprogesterone caproate therapy; the likelihood of these occurring may be increased at higher dosage levels.

Dosage and Administration: Suggested dosages are presented below. Because of the low viscosity of the vehicle, Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) may be administered with a small gauge needle. (The Unimatic single dose syringe contains a 20 gauge needle.) Care should be taken to inject the preparation deeply into the upper outer quadrant of the gluteal muscle following the usual precautions for intramuscular injection. Since the 250 mg. potency provides a high concentration in a small volume, particular care should be observed to administer the full dose.

Note: Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

Cyclic therapy is a 28-day cycle repeated every 4 weeks. The Cyclic Therapy Schedule is as follows: 20 mg. Estradiol Valerate Injection U.S.P. is administered on Day 1 of each cycle; two weeks after Day 1, 250 mg. Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) and 5 mg. Estradiol Valerate Injection U.S.P. are administered; four weeks after Day 1 is Day 1 of next cycle.

Suggested Cyclic Regimen—Non-Pregnant Women: *Amenorrhea (primary and secondary); Abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer.* Administer 375 mg. Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) any time. After 4 days of desquamation or, if there is no bleeding, 21 days after Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) alone, start Cyclic Therapy Schedule; repeat Cyclic Therapy Schedule every 4 weeks; stop after 4 cycles. Genital malignancy should be excluded before hormone therapy is started. Hydroxyprogesterone caproate is used as a "Medical D and C" to eliminate any proliferated endometrium from previous estrogenic action by conversion to secretory endometrium and desquamation. To determine onset of normal cyclic function, patient should be observed for 2 to 3 cycles after cessation of therapy.

Production of secretory endometrium and desquamation. In patients not on estrogen therapy, start Cyclic Therapy Schedule any time; repeat every 4 weeks; stop when cyclic therapy is no longer required. If estrogen deficiency has been prolonged, menstruation may not occur until estrogen has been given for several months. In patients currently on estrogen therapy, administer 375 mg. Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) any time; start Cyclic Therapy Schedule after 4 days of desquamation or, if there is no bleeding, 21 days after Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) alone; repeat Cyclic Therapy Schedule every 4 weeks; stop when cyclic therapy is no longer required. If estrogen deficiency has been prolonged, menstruation may not occur until estrogen has been given for several months.

Suggested Non-Cyclic Regimen—Non-Pregnant Women: *Adenocarcinoma of uterine corpus in advanced stage (Stage III or IV).* 1000 mg. or more at once; repeat one or more times each week (1-7 grams per week); stop when relapse occurs, or after 12 weeks with no objective response. Should not be used in early stage (Stage I or II) in place of established anti-cancer therapy. May be used in advanced stage concomitantly with other anti-cancer therapy (surgery, or radiation, or chemotherapy, or a combination of these). Treatment results reported to date have been better in histologically well-differentiated forms of endometrial adenocarcinoma.

Pregnant Women: *Habitual Abortion.* 250 mg. or more as soon as possible after start of pregnancy; repeat once each week; stop 2 weeks before expected delivery. A single injection is of limited value.

Threatened Abortion. 250 mg. or more at once; repeat one or more times daily; stop when symptoms are controlled; thereafter treat as for habitual abortion (see above). In threatened abortion, large amounts of hydroxyprogesterone caproate are required.

Tests: *As a Test for Endogenous Estrogen Production ("Medical D and C").* 250 mg. as a single injection. In non-pregnant patients with responsive endometrium, bleeding 7 to 14 days after injection indicates endogenous estrogen. The test may be confirmed by a second injection 4 weeks after the first.

As a Test for Continuous Endogenous Progesterone Production. (This procedure is a presumptive test for pregnancy) 250 mg. as a single injection; in the patient with a responsive endometrium and endogenous estrogen production, failure to bleed indicates an endogenous source of progesterone, as in pregnancy; to confirm this test, a second dose may be given 4 weeks after first injection.

Storage: Delalutin (Hydroxyprogesterone

Continued on next page

For information on Squibb products write to: Squibb Professional Services Department, Lawrenceville-Princeton Rd., Princeton, N.J. 08540.

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Squibb—Cont.

Caproate Injection U.S.P.) should be stored at room temperature. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on heating the vials in boiling water. Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) in Unimatic single dose preassembled syringes and cartridge-needle units should be stored at room temperature.

How Supplied: Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) is available in vials providing hydroxyprogesterone caproate in potencies of 125 mg. and 250 mg. per cc. The 125 mg. potency is formulated in sesame oil and 30% benzyl benzoate and the 250 mg. potency is formulated in castor oil and 46% benzyl benzoate; both potencies also contain 2% (w/v) benzyl alcohol as a preservative. The 125 mg. potency is supplied in vials of 10 cc. (Military Stock # FSN-6505-656-1022) and vials of 2 cc. The 250 mg. potency is supplied in vials of 5 cc. (Military Stock # FSN-6505-864-5221), Unimatic® single dose preassembled syringes of 1 cc. and cartridge-needle units of 1 cc.

DELATESTRYL®

(Testosterone Enanthate Injection U.S.P.)

Description: Delatestryl (Testosterone Enanthate Injection U.S.P.) is a sterile solution of testosterone enanthate for intramuscular use.

Actions: Delatestryl is intended for androgen therapy, particularly when prolonged action is desirable. Following a single intramuscular injection, the androgenic effect is sustained over a period of about 4 weeks. This continous flow of hormone is thought to resemble closely the endogenous production of testosterone.

Testosterone enanthate is primarily used for its protein anabolic effect and its catabolic inhibiting effect on tissue. Nitrogen balance is improved with anabolic agents but only when there is sufficient intake of calories and protein. Whether this positive nitrogen balance is of primary benefit in the utilization of protein-building dietary substances has not been established.

Enhancement of protein anabolism is manifest by conservation of sodium, nitrogen, phosphorus, potassium, sulfur, and water in the proportions of physiologic protein tissues, and of calcium with additional phosphorus in the proportions of physiologic osseous tissues.

Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. The actions of anabolic steroids are therefore similar to those of male sex hormones with the possibility of causing serious disturbances of growth and sexual development if given to young children. They suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes.

Indications: In males, Delatestryl (Testosterone Enanthate Injection U.S.P.) is indicated in the treatment of eunuchism, eunuchoidism, deficiency after castration, male climactericlike symptoms when these are secondary to androgen deficiency, and oligospermia.

Contraindications: Androgens are contraindicated in male patients with prostatic or breast cancer, in those elderly patients in whom overstimulation is to be avoided, and in those cases of benign prostatic hypertrophy with obstructive symptoms. Androgens are also contraindicated in patients with nephrosis or the nephrotic phase of nephritis.

Precautions: If symptomatic hypercalcemia occurs, discontinue androgen therapy and institute appropriate measures.

Caution is required in administering androgens to patients with cardiac, renal, or hepatic disease. Edema may occur occasionally. Concomitant administration with adrenal steroids or ACTH may add to the edema.

Anabolic steroids may increase sensitivity to anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain the prothrombin time at the desired therapeutic level.

Anabolic steroids have been shown to alter glucose tolerance tests. Diabetics should be followed carefully and the insulin or oral hypoglycemic dosage adjusted accordingly.

Serum cholesterol may increase or decrease during therapy. Because of its hypercholesterolemic effects, caution is required when administering this drug to patients with a history of myocardial infarction or coronary artery disease. Serial determinations of serum cholesterol should be made and therapy adjusted accordingly. A cause and effect relationship between myocardial infarction and hypercholesterolemia has not been established.

Inhibition of testicular function and decrease in ejaculatory volume may occur when the drug is administered in doses greater than those used for replacement therapy in hypogonadal males.

Adverse Reactions: In males, the following post-pubertal adverse reactions have occurred: inhibition of testicular function, testicular atrophy and oligospermia, impotence, chronic priapism, gynecomastia, epididymitis, and bladder irritability. In addition, the following reactions are known to occur with anabolic steroids: increased or decreased libido, flushing of the skin, acne, habituation, excitation and sleeplessness, chills, leucopenia, and bleeding in patients on concomitant anticoagulant therapy.

Intramuscular preparations of anabolic steroids have been associated with urticaria at the injection site, post-injection induration, and furunculosis.

Alterations may occur in the following clinical laboratory tests: metyrapone test, fasting blood sugar (FBS) and glucose tolerance test, thyroid function tests [decrease in protein bound iodine (PBI), thyroxine-binding capacity, and radioactive iodine uptake, and an increase in T^3 uptake by the red blood cells or resin: free thyroxine levels remain normal and the altered tests usually persist for 2-3 weeks after stopping anabolic therapy], electrolytes (retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates), blood coagulation tests (increase in clotting factors II, V, VII, and X), and miscellaneous laboratory tests (decreased creatinine and creatine excretion lasting up to two weeks after discontinuing therapy and increased 17-ketosteroid excretion).

Dosage and Administration: When properly given, injections of Delatestryl (Testosterone Enanthate Injection U.S.P.) are well tolerated. Care should be taken to inject the preparation deeply into the gluteal muscle following the usual precautions for intramuscular administration. In general, total doses above 400 mg. per month are not required because of the prolonged action of the preparation. Injections more frequently than every two weeks are rarely indicated. NOTE: Use of a wet needle or wet syringe may cause the solution to become cloudy: however, this does not affect the potency of the material.

In male hypogonadism (i.e., eunuchism, eunuchoidism, severe deficiency after castration, male climacteric-like symptoms when secondary to androgen deficiency), the suggested dosage is 200-400 mg. every four weeks. Androgen therapy is regarded as replacement therapy, being effective only as long as continued; prolonged treatment with chorionic gonadotropin is also recommended.

In the treatment of oligospermia, the suggested dosage is 100-200 mg. every 4-6 weeks for the development and maintenance of testicular tubular function: for suppression and rebound stimulation, the recommended dosage is 200 mg. every week for 6-12 weeks.

Storage: Vials should be stored at room temperature. Warming and shaking the vial will redissolve any crystals that may have formed during storage at low temperatures. Unimatic single dose preassembled syringes and cartridge-needle units should be stored at room temperature.

How Supplied: Delatestryl (Testosterone Enanthate Injection U.S.P.) is available in vials of 5 cc. and Unimatic® single dose preassembled syringes of 1 cc. and cartridge-needle units of 1 cc. Each cc. of sterile solution provides 200 mg. testosterone enanthate in sesame oil with 0.5% chlorobutanol (chloral derivative) as a preservative.

DELESTROGEN®

(Estradiol Valerate Injection U.S.P.)

Description: Delestrogen (Estradiol Valerate Injection U.S.P.) is a long-acting sterile estrogen preparation for intramuscular use. It is available in potencies of 10 mg., 20 mg., and 40 mg. per cc. The 10 mg. potency is formulated in a sesame oil vehicle with 0.5% chlorobutanol (chloral derivative) as a preservative. The 20 mg. potency is formulated in castor oil and 20% benzyl benzoate and the 40 mg. potency is formulated in castor oil and 40% benzyl benzoate; both also contain 2% (w/v) benzyl alcohol as a preservative.

Actions: Estradiol valerate is a hormone with a potent and prolonged estrogenic effect. It promotes the growth of the endometrium; promotes thickening, stratification, and cornification of the vagina; causes growth of mammary gland ducts; and inhibits the anterior pituitary gland. The estrogenic effect occurs soon after administration and lasts for approximately two to three weeks after a single intramuscular injection.

Indications: Delestrogen (Estradiol Valerate Injection U.S.P.) is indicated for replacement therapy of estrogen deficiency associated with menopausal syndrome, amenorrhea, female castration, primary ovarian failure, senile vaginitis, and kraurosis vulvae with or without pruritus. Delestrogen is also indicated for the prevention of postpartum breast engorgement and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology. Delestrogen (Estradiol Valerate Injection U.S.P.) may also be used to treat inoperable, progressing prostatic cancer (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred).

Contraindications: Estradiol valerate is contraindicated in patients with a known or suspected mammary or genital malignancy (except prostatic carcinoma). It is also contraindicated in thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions, as well as in patients with pulmonary embolism, liver dysfunction or disease, undiagnosed abnormal genital bleeding, or a history of hypersensitivity to estradiol valerate.

Warnings: The physician should watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). If these occur or are suspected, the drug should be discontinued immediately.

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discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Medication should be stopped if examination reveals papilledema or retinal vascular lesions.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Since the safety of estrogens and progestogenes given in conjunction with each other in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the regimen.

Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation such as abnormal or excessive uterine bleeding, mastodynia, edema, etc.

When large doses of estrogens are used, urinary stress incontinence may occur in non-pregnant females.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the nursing infant has been described. The long range effect on the nursing infant is not known at this time.

Pre-existing fibroid tumors of the uterus may enlarge during therapy.

Precautions: The pretreatment physical examination should include examination of the breasts and pelvic organs, and a Papanicolaou smear. In cases of irregular bleeding which does not respond predictably to the hormone therapy, non-functional causes should be borne in mind and adequate diagnostic measures instituted.

Estrogen therapy may induce fluid retention. Its use in cardiac failure, in disease states associated with edema, and with epilepsy should be carefully controlled. Estrogen therapy should be used with caution in patients with a history of cerebrovascular accident.

A decrease in glucose tolerance has been observed in patients receiving estrogenic drugs. Diabetic patients should be carefully observed for regulation during medication with estrogenic therapy.

Because of the effects of estrogens on epiphyseal closure, estradiol valerate should be used judiciously in young patients in whom bone growth is not complete.

Any influence of prolonged sex hormone medication on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. It is known, however, that prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

Medication should be discontinued in patients with a history of psychic abnormalities if exaggeration of symptoms occurs.

Endocrine and liver function may be influenced by estrogen therapy. Estrogens may cause an elevation in the PBI and the BEI, and a decrease in the T3 uptake. Tests to evaluate endocrine and liver function should not be considered definitive unless therapy has been discontinued for at least 60 days. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Adverse Reactions: The following information is pertinent whenever estrogen preparations are used with progesterones; it is not known at the present time if these statements are applicable to estrogens alone.

A. A statistically significant association has been demonstrated between the use of estrogen-progesterone combinations and thrombophlebitis, pulmonary embolism, and cerebrovascular accidents.

B. Although such a relationship has been neither confirmed nor refuted, available evidence is suggestive of an association between the use of estrogens with progesterones and the following untoward effects: neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis); nausea; vomiting; anorexia; gastrointestinal symptoms (such as abdominal cramps or bloating); edema; breakthrough bleeding, spotting, or withdrawal bleeding; breast tenderness and enlargement; changes in body weight (increase or decrease); headache; increase in cervical mucus; allergic rash; loss of libido and gynecomastia in the male; sterile abscess; pain at the injection site; post-injection flare; reactivation of endometriosis; aggravation of migraine headaches; and hepatic cutaneous porphyria becoming manifest.

C. The following adverse reactions are known to occur in patients receiving both estrogens and progesterones: chloasma or melasma, cholestatic jaundice, rise in blood pressure in susceptible individuals, mental depression, and amenorrhea during and after treatment.

D. The following adverse reactions have been reported with the concomitant use of estrogens and progesterones; a cause and effect relationship has been neither confirmed nor refuted: post-treatment anovulation, cystitis-like syndrome, hirsutism, loss of scalp hair, erythema nodosum, hemorrhagic eruption, premenstrual-like syndrome, changes in libido, changes in appetite, nervousness, dizziness, fatigue, backache, erythema multiforme, itching, hypomenorrhea, oligomenorrhea, or amenorrhea.

E. The following laboratory tests may give altered results by the concomitant use of estrogens and progesterones: hepatic function (increased sulfobromophthalein retention and other tests); coagulation tests (increase in prothrombin and Factors VII, VIII, IX, and X); metyrapone test; pregnanediol determination; and thyroid function tests (increase in PBI and butanol extractable protein-bound iodine, decrease in T3 uptake values, and possible diminution in lactation when given immediately post-partum).

When estrogens are used for the treatment of prostatic carcinoma, hypercalcemia may develop.

Dosage and Administration: Care should be taken to inject deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. By virtue of the low viscosity of the vehicles, the various preparations of Delestrogen (Estradiol Valerate Injection U.S.P.) may be administered with a small gauge needle. Since the 40 mg. potency provides a high concentration in a small volume, particular care should be observed to administer the full dose.

Note: A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

For Castration; Primary ovarian failure; Menopausal syndrome; Senile vaginitis; Kraurosis vulvae with or without pruritus. Administer 10-20 mg. Delestrogen (Estradiol Valerate Injection U.S.P.) any time; repeat 2-3 weeks after initial injection; stop after second injection. Continuous therapy with estrogen alone may induce dysfunctional uterine bleeding.

For Inoperable, progressing prostatic carcinoma (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred). 30 mg. or more every 1 to 2 weeks. Close medical supervision is mandatory. Suspend therapy if there is a relapse. Soreness of the breasts or gynecomastia may occur; hypercalcemia may develop.

For Prevention of postpartum breast engorgement. 10-25 mg. as a single injection at the end of the first stage of labor.

As Part of Cyclic Therapy Schedule. The Cyclic Therapy Schedule is as follows: 20 mg. Delestrogen (Estradiol Valerate Injection U.S.P.) is administered on Day 1 of each cycle; two weeks after Day 1, 250 mg. Hydroxyprogesterone Caproate Injection U.S.P. and 5 mg. Delestrogen (Estradiol Valerate Injection U.S.P.) are administered; four weeks after Day 1 is Day 1 of next cycle.

Amenorrhea; Abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology. Administer 375 mg. Hydroxyprogesterone Caproate Injection U.S.P. any time. After 4 days of desquamation or, if there is no bleeding, 21 days after hydroxyprogesterone caproate alone, start Cyclic Therapy Schedule; repeat Cyclic Therapy Schedule every 4 weeks; stop after 4 cycles. Genital malignancy should be excluded before hormone therapy is started. Hydroxyprogesterone caproate is used as a "Medical D and C" to eliminate any proliferated endometrium from previous estrogenic action by conversion to secretory endometrium and desquamation. To determine onset of normal cyclic function, patient should be observed for 2 to 3 cycles after cessation of therapy.

Storage: Vials should be stored at room temperature. Storage at low temperature may result in the separation of some crystalline material which redissolves readily on warming. Unimatic single dose preassembled syringes and cartridge-needle units should be stored at room temperature.

How Supplied: The 10 mg. potency is available in 1 cc. and 5 cc. vials. The 20 mg. potency is available in 5 cc. vials and in 1 cc. Unimatic® single dose preassembled syringes and cartridge-needle units. The 40 mg. potency is available in 5 cc. vials.

DELUTEVAL® 2X

(Hydroxyprogesterone Caproate and Estradiol Valerate Injection)

Description: Deluteval 2X is a long-acting sterile preparation for intramuscular use providing an esterified derivative of the naturally-occurring progestational hormone, hydroxyprogesterone, and the valeric acid ester of naturally-occurring estradiol. Each cc. of Deluteval 2X provides 250 mg. hydroxyprogesterone caproate and 5 mg. estradiol valerate in castor oil and 45% benzyl benzoate with 1.6% (w/v) benzyl alcohol as a preservative.

Continued on next page

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...range flavored and colored) in 60 cc. ... assembly bottles with dropper cali... at 0.5 cc. (0.25 mg.), 1 cc. (0.5 mg.), 1.5 ... mg.), and 2 cc. (1 mg.); and in pint ... bottles.

...—Multiple-dose vials of 10 cc., Uni... single dose preassembled syringes of 1 ... cartridge-needle units of 1 cc.

[Shown in Product Identification Section]

...LIXIN® ENANTHATE

...nazine Enanthate Injection N.F.)

...iption: Prolixin Enanthate (Fluphena... Enanthate Injection N.F.) is an esterified ...romethyl phenothiazine derivative, ...ically designated as 4-[3-[2-(trifluorome... phenothiazin-10-yl]propyl]-1-piperazino... heptanoate (enanthate). It is a highly ... behavior modifier with a markedly ex... duration of effect, available for intra... or subcutaneous administration in ... Unimatic® single dose preassembled sy... and cartridge-needle units providing ... fluphenazine enanthate per cc. in a ... oil vehicle, with 1.5% (w/v) benzyl al... as a preservative. At the time of manu... the air in the vials is replaced by ni...

...ions: The basic effects of fluphenazine ...anthate appear to be no different from ... of fluphenazine hydrochloride, with the ...ception of duration of action. The esterifi... of fluphenazine markedly prolongs the ...rug's duration of effect without unduly at... its beneficial action. The onset of ...ction generally appears between 24 to 72 ...hours after injection, and the effects of the ...rug on psychotic symptoms become signifi... within 48 to 96 hours. Amelioration of ...ymptoms then continues for 1 to 3 weeks or ...nger, with an average duration of effect of ...bout 2 weeks.

Fluphenazine has activity at all levels of the ...entral nervous system as well as on multiple ...ystem systems. The mechanism whereby its ...herapeutic action is exerted is unknown.

Fluphenazine differs from other phenothia... derivatives in several respects: it is more ...otent on a milligram basis; it has less poten...iating effect on central nervous system de...pressants and anesthetics than do some of the ...phenothiazines and appears to be less sedat...ing; and it is less likely than some of the older ...phenothiazines to produce hypotension (nev...ertheless, appropriate cautions should be ob...served—see sections on "Precautions" and "Adverse Reactions").

...ndications: Prolixin Enanthate (Fluphena... Enanthate Injection N.F.) is indicated in ...the management of manifestations of psy...chotic disorders. In the treatment of these ...conditions, the drug often maintains relief of ...such target symptoms as agitation, hostility, ...and anxiety. Prolixin Enanthate (Fluphena... Enanthate Injection N.F.) finds useful ...application not only in the hospital milieu, ...but also in the long-term maintenance ther...apy of chronically psychotic patients who are ...treatable on an out-patient basis.

Contraindications: Phenothiazines are con...traindicated in patients with suspected or es...tablished subcortical brain damage.

Phenothiazine compounds should not be used ...in patients receiving large doses of hypnotics.

Prolixin Enanthate (Fluphenazine Enanthate ...Injection N.F.) is contraindicated in comatose ...or severely depressed states.

The presence of blood dyscrasia, liver dam...age, or renal insufficiency precludes the use ...of fluphenazine enanthate.

Fluphenazine enanthate is not indicated for ...use in children under 12 years of age.

Prolixin Enanthate is contraindicated in pa...tients who have shown hypersensitivity to ...fluphenazine; cross-sensitivity to phenothia...zine derivatives may occur.

Warnings: The use of this drug may impair the mental and physical abilities required for driving a car or operating heavy machinery. Physicians should be alert to the possibility that severe adverse reactions may occur which require immediate medical attention.

Potentiation of the effects of alcohol may oc...cur with the use of this drug.

Usage in Pregnancy:—The safety for the use of this drug during pregnancy has not been established; therefore, the possible hazards should be weighed against the potential bene...fits when administering the drug to pregnant patients.

Precautions: Because of the possibility of cross-sensitivity, fluphenazine enanthate should be used cautiously in patients who have developed cholestatic jaundice, derma...toses, or other allergic reactions to phenothia...zine derivatives.

Psychotic patients on large doses of a pheno...thiazine drug who are undergoing surgery should be watched carefully for possible hy...potensive phenomena. Moreover, it should be remembered that reduced amounts of anes...thetics or central nervous system depressants may be necessary.

The effects of atropine may be potentiated in some patients receiving fluphenazine because of added anti-cholinergic effects.

Fluphenazine enanthate should be used cau...tiously in patients exposed to extreme heat or phosphorus insecticides or in patients who have a history of ulcer disease, since aggrava...tion of peptic ulcer has occurred.

The preparation should be used with caution in patients with a history of convulsive disor...ders, since grand mal convulsions have been known to occur.

Use with caution in patients with special medical disorders such as mitral insufficiency or other cardiovascular diseases and pheo...chromocytoma.

The possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia should be remembered when patients are on prolonged therapy.

Outside state hospitals or other psychiatric institutions, fluphenazine enanthate should be administered under the direction of a phy...sician experienced in the clinical use of psychotropic drugs, particularly phenothia...zine derivatives. Furthermore, facilities should be available for periodic checking of hepatic function, renal function, and the blood picture. Renal function of patients on long-term therapy should be monitored; if BUN (blood urea nitrogen) becomes abnor...mal, treatment should be discontinued.

As with any phenothiazine, the physician should be alert to the possible development of "silent pneumonias" in patients under treat...ment with fluphenazine enanthate.

Adverse Reactions: *Central Nervous Sys...tem:* The side effects most frequently report...ed with phenothiazine compounds are extra...pyramidal symptoms including pseudopar...kinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyper-re...flexia. Most often these extrapyramidal symptoms are reversible; however, they may be persistent (see below). The frequency of such reactions is related in part to chemical structure: one can expect a higher incidence with fluphenazine enanthate than with less potent piperazine derivatives or with straight-chain phenothiazines such as chlor...promazine. With any given phenothiazine de...rivative, the incidence and severity of such reactions depend more on individual patient sensitivity than on other factors; but dosage level and patient age are also determinants.

Extrapyramidal reactions may be alarming, and the patient should be forewarned and re...assured. These reactions can usually be con...trolled by administration of anti-parkinsonian drugs such as Benztropine Mesylate or In...travenous Caffeine and Sodium Benzoate In...jection U.S.P. and by subsequent reduction of dosage.

A persistent pseudo-parkinsonian syndrome may develop after chronic administration of phenothiazine compounds. The syndrome is characterized by rhythmic, stereotyped dyski...netic involuntary movements, particularly of the face, mouth, tongue and jaw, resembling the facial grimaces of encephalitis. These may be accompanied by choreiform move...ments of the limbs. The symptoms persist af...ter drug withdrawal and in some patients ap...pear to be irreversible. Anti-parkinsonian a...gents are seldom of benefit. The risk ap...pears to be greatest in elderly female patients with organic brain disease or damage who have been receiving fairly large doses of phe...nothiazines for a prolonged period.

Drowsiness or lethargy, if they occur, may necessitate a reduction in dosage; the induc...tion of a cataleptic-like state has been known to occur with dosages of fluphenazine far in excess of the recommended amounts. As with other phenothiazine compounds, reactivation or aggravation of psychotic processes may be encountered.

Phenothiazine derivatives have been known to cause, in some patients, restlessness, ex...citement, or bizarre dreams.

Autonomic Nervous System: Hypertension and fluctuations in blood pressure have been reported with fluphenazine enanthate.

Hypotension has rarely presented a problem with fluphenazine. However, patients with pheochromocytoma, cerebral vascular or re...nal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to hypotensive reac...tions with phenothiazine compounds and should therefore be observed closely when the drug is administered. If severe hypoten...sion should occur, supportive measures in...cluding the use of intravenous vasopressor drugs should be instituted immediately. Lev...arterenol Bitartrate Injection U.S.P. is the most suitable drug for this purpose; *epineph...rine should not be used* since phenothiazine derivatives have been found to reverse its ac...tion, resulting in a further lowering of blood pressure.

Autonomic reactions including nausea and loss of appetite, salivation, polyuria, perspira...tion, dry mouth, headache, and constipation may occur. Autonomic effects can usually be controlled by reducing or temporarily discon...tinuing dosage.

In some patients, phenothiazine derivatives have caused blurred vision, glaucoma, blad...der paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion.

Metabolic and Endocrine: Weight change, pe...ripheral edema, abnormal lactation, gynecco...mastia, menstrual irregularities, false results on pregnancy tests, impotency in men and in...creased libido in women have all been known to occur in some patients on phenothiazine therapy.

Allergic Reactions: Skin disorders such as itching, erythema, urticaria, seborrhea, pho...tosensitivity, eczema and even exfoliative dermatitis have been reported with phenothi...azine derivatives. The possibility of anaphy...lactoid reactions occurring in some patients should be borne in mind.

Hematologic: Routine blood counts are advis...

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Squibb—Cont.

able during therapy since blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazine derivatives. Furthermore, if any soreness of the mouth, gums, or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic: Liver damage as manifested by cholestatic jaundice may be encountered, particularly during the first months of therapy; treatment should be discontinued if this occurs. An increase in cephalin flocculation, sometimes accompanied by alterations in other liver function tests, has been reported in patients receiving fluphenazine enanthate who have had no clinical evidence of liver damage.

Others: Sudden, unexpected and unexplained deaths have been reported in hospitalized psychotic patients receiving phenothiazines. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown sudden flare-ups of psychotic behavior patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions.

Although this is not a general feature of fluphenazine, potentiation of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) may occur.

The following adverse reactions have also occurred with phenothiazine derivatives: hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use—skin pigmentation, and lenticular and corneal opacities.

Injections of fluphenazine enanthate are extremely well tolerated, local tissue reactions occurring only rarely.

Dosage and Administration: Prolixin Enanthate (Fluphenazine Enanthate Injection N.F.) may be given intramuscularly or subcutaneously. A dry syringe and needle of at least 21 gauge should be used. Use of a wet needle or syringe may cause the solution to become cloudy.

To begin therapy with Prolixin Enanthate (Fluphenazine Enanthate Injection N.F.) the following regimens are suggested:

For most patients a dose of 25 mg. (1 cc.) every 2 weeks should prove to be adequate, and therapy may be started on that basis. Subsequent adjustments in the amount and the dosage interval may be made, if necessary, in accordance with the patient's response.

It may be advisable that patients who have had no history of taking phenothiazines should be treated initially with a shorter acting form of fluphenazine before administering the enanthate to determine the patient's response to fluphenazine and to establish appropriate dosage. Since the dosage comparability of the shorter-acting forms of fluphenazine to the longer-acting enanthate is not known, special caution should be exercised when switching from the shorter-acting forms to the enanthate.

Severely agitated patients may be treated initially with a rapid-acting phenothiazine compound such as Prolixin Injection (Fluphenazine Hydrochloride Injection N.F.—see package insert accompanying that product for complete information). When acute symptoms have subsided, 25 mg. (1 cc.) of Prolixin Enanthate (Fluphenazine Enanthate Injection N.F.) may be administered; subsequent dosage is adjusted as necessary.

"Poor risk" patients (those with known hypersensitivity to phenothiazines, or with disorders that predispose to undue reactions): Therapy may be initiated cautiously with oral or parenteral fluphenazine hydrochloride (see package inserts accompanying these products for complete information). When the pharmacologic effects and an appropriate dosage are apparent, an equivalent dose of Prolixin Enanthate (Fluphenazine Enanthate Injection N.F.) may be administered. Subsequent dosage adjustments are made in accordance with the response of the patient.

The optimal amount of the drug and the frequency of administration must be determined for each patient, since dosage requirements have been found to vary with clinical circumstances as well as with individual response to the drug. Although in a large series of patients the optimal dose was usually 25 mg. every 2 weeks, the amount required ranged from 12.5 to 100 mg. (0.5 to 4 cc.). The interval between doses ranged from 1 week to 3 weeks in most instances, but some patients required doses as often as once a day for the first few days of treatment, while the response to a single dose was found to last as long as 6 weeks in a few patients on maintenance therapy.

Dosage should not exceed 100 mg. If doses greater than 50 mg. are deemed necessary, the next dose and succeeding doses should be increased cautiously in increments of 12.5 mg.

How Supplied: Vials of 5 cc., Unimatic Single Dose Pronssomixed Syringes of 1 cc., and cartridge-needle units of 1cc.

PRONESTYL® CAPSULES R
(Procainamide Hydrochloride Capsules U.S.P.)
PRONESTYL INJECTION R
(Procainamide Hydrochloride Injection U.S.P.)

Description: Pronestyl is the amide analogue of procaine hydrochloride. It is available as gelatin capsules supplying 250 mg., 375 mg., and 500 mg. for oral use and as a 10% sterile aqueous solution (100 mg./cc.) for parenteral use.

The parenteral solution contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives; the pH has been adjusted to 4.0-6.0 with hydrochloric acid or sodium hydroxide. The solution, which is colorless initially, may in time develop a slightly yellow color. This does not indicate a change which would prevent its use, but a solution any darker than light amber or discolored in any other way should not be used.

Actions: Procainamide depresses the excitability of cardiac muscle to electrical stimulation, and slows conduction in the atrium, the bundle of His, and the ventricle. The refractory period of the atrium is considerably more prolonged than that of the ventricle. Contractility of the heart is usually not affected nor is cardiac output decreased to any extent unless myocardial damage exists. In the absence of any arrhythmia, the heart rate may occasionally be accelerated by conventional doses, suggesting that the drug possesses anticholinergic properties. Larger doses can induce atrioventricular block and ventricular extrasystoles which may proceed to ventricular fibrillation. These effects on the myocardium are reflected in the electrocardiogram; a widening of the QRS complex occurs most consistently; less regularly, the P-R and Q-T intervals are prolonged, and the QRS and T waves show some decrease in voltage.

The action of procainamide begins almost immediately after intramuscular or intravenous administration. Plasma levels after intramuscular injection are at their peak in 15 to 60 minutes. Following oral administration plasma levels of the drug are comparable to those obtained parenterally and are maximal within an hour; therapeutic levels are usually attained in half that time.

Procainamide is less readily hydrolyzed than procaine, and plasma levels decline slowly—about 10% to 20% per hour. The drug is excreted primarily in the urine, about 10% as free and conjugated *p*-aminobenzoic acid and about 60% in the unchanged form. The fate of the remainder is unknown.

Indications: The effects of Pronestyl (Procainamide Hydrochloride), are more beneficial in ventricular than in auricular arrhythmias. Ventricular extrasystoles and ventricular tachycardia are controlled within an hour after oral or intramuscular administration or within a few minutes after intravenous infusion. Digitalis-induced ventricular extrasystoles and tachycardia may at times be suppressed by careful and judicious administration of the drug. Pronestyl may also be of value in the control of an auricular arrhythmia particularly if the condition is of recent development. Atrial fibrillation of short duration may be converted to a normal sinus rhythm, and chronic atrial fibrillation may occasionally benefit as well. The drug is also worthy of trial in paroxysmal atrial tachycardia that cannot be controlled by reflex vagal stimulation or other measures.

The correction of cardiac arrhythmias which may occur during anesthesia constitutes an important indication for procainamide. The drug is especially valuable with cyclopropane anesthesia and for intrathoracic surgery; endotracheal intubation, or surgery in cardiac patients for whom the incidence of potentially severe arrhythmias is high. It may be given prophylactically before surgery to patients with known heart conditions or to those undergoing thoracic surgery.

Contraindications: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block.

Precautions: During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation with resultant forceful contractions of the atrium, may cause a dislodgement of atrial thrombi and produce an embolic episode. However, it has been suggested that the patient who is already discharging emboli procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as heart block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or cardiac arrest.

Parenteral administration should be monitored electrocardiographically when practicable. If electrocardiograms g

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ATTACHMENT F - COMPILATION

TAB 10

Compendium of Excipients for Parenteral Formulations

MICHAEL F. POWELL, TUE NGUYEN*, and LISA BALOIAN

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Overview

The selection of excipients in parenteral formulation design is often both rational and empirical. It is rational in the sense that certain types of excipients are added to alter the formulation properties: i) buffers of appropriate pKa are added to control hydrogen ion concentration at a desired pH, ii) tonicifiers are added for biocompatibility, iii) surfactants are added when necessary to prevent aggregation, adsorption to surfaces, or increase solubility, iv) antioxidants are included to prevent unwanted oxidation of the drug, and so on. The inclusion of various classes of formulation components, and the concentration used is often quite rational, in that their behavior and properties are known, and they are added to prevent specific problems that would arise in their absence. On the other hand, however, the selection of the *exact* excipient used is far from rational; it is empirical in the first order, satisfying only one question, "Has it been used previously in a similar parenteral formulation?"

Many prototype formulations have been terminated because one or more of the selected excipients was not found in a previously approved parenteral product. In fact, there have been a handful of excipients with striking favorable properties, such as trehalose with its ability to confer solid state stabilization of several types of proteins, or EDTA and its antioxidants by metal ion chelation. These excipient compounds, and many others, have not been used widely, largely because of concerns with unknown toxicity, continued production supply, or cost.

Thus, the formulation scientist is often faced with a dilemma—which excipients are truly available for use (based on what has been used previously), and which are not? For example, PEG 400 has been added to several parenteral formulations, but what about PEG 1200, or PEG 4000? And at what concentrations, and by what route? Sodium citrate is an excellent buffer for many formulations at 5 mM, but is too painful in most instances for subcutaneous use at 50 mM. High concentrations of propylene glycol may be used in a slow intravenous infusion, but would produce unwanted hemolysis and pain if given by subcutaneous or intramuscular injection. It is often the case that the "safe level" of an excipient may depend on the route of administration. These are only a few examples of factors which must be considered when designing a formulation; there are dozens more based on empirical information required for efficient formulation design, but thus far a compendium has not been published. This review was written to fill this void.

Herein are listed the excipients found in most of the approved and marketed parenteral formulations, given systematically by excipient name. In this format it is easy to determine what concentrations were used, the route of administration, the main rationale for addition of that excipient, the drug that was formulated, the manufacturer, brand name, etc. The information found in this table comes from several sources, including package inserts, the Physician's Desk Reference (PDR '97), as well as personal correspondence from the companies supplying the products. The published excipient concentration was often given in different units, including: mg/mL, mOs, Molar, sodium equivalents, biological Units, Molal, weight percent, etc., and provided one of the greatest challenges in putting this compendium together. We sought to list all the excipients (where possible) in common units (i.e., mg/mL), so that a rapid comparison of the different formulations could be made at a glance. (This is not easy to do, for example, when comparing Tween 20 concentrations at 0.0001 M, 0.01% and 1 mg/mL; fortunately, the average molecular weight is known for most excipients, permitting a standardization of excipient concentrations). This standardization of excipient concentrations is perhaps the greatest value of this compendium, but also represents one of the greatest sources of potential error. The recalculation of excipient concentrations, often from scant or nondescriptive data, is not trivial and there may be an occasional discrepancy despite cross-checking with the original sources.[1] Nevertheless, this compendium represents a comprehensive survey of parenteral excipients used today, and is a resource for the parenteral formulation scientist.

Notes

In putting together this excipient compendium, there were a number of points that should be noted, so that the reader understands the limitations and assumptions in some of the calculations.

1) Concentrations are listed in weight/volume% unless otherwise noted. In some cases values are listed in volume/volume% or the manufacturer did not specify what kind of percentage they were using (and in this case it was assumed weight/volume %).

2) Sterile water for injection is included in the excipient list when used in solution formulations; however, in most

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[1] If discrepancies are found, e-mail them to nguyen.tue@gene.com for correction to subsequent compendiums of this nature.

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cases the quantity or percentage of water in the formulation was not indicated by the manufacturer or identified only as q.s. We have kept the same conventions here.

3) Excipients listed are present in the drug formulation itself, and do not include excipients present in diluent (for example, when a lyophilized formulation is diluted with bacteriostatic water containing benzyl alcohol). In some cases, a diluent is supplied that contains several additional excipients and, in the case or provided diluent, these excipients are listed in the excipient category and designated with a "D" in addition to their usual excipient type (the D stand for present in diluent).

4) If no excipients are listed, it means that no excipients were revealed by the manufacturer. In some cases, this is because there are no excipients in the formulation, but this should not be assumed. In some cases, there may be excipients present but the manufacturer has not disclosed them to us, largely for proprietary reasons. Specific follow-up about these drugs should be referred to the manufacturer.

5) The given drug concentration is usually the concentration of the compound listed in the drug name category, unless identified as otherwise. For example, many drugs are formulated as salts such that the salt name is listed in the drug name category (for example, mitoxantrone hydrochloride). However, in the drug concentration category, the concentration of the active component is usually listed (for example, equivalent to 2 mg/mL mitoxantrone free base), so as to have a correct concentration of the active drug form.

6) When concentrations of excipients and drugs are listed as a range it implies that these values could only be approximated. Frequently, a range is given because the product is available in a variety of storage containers, or having several dilution schemes. The ranges given are approximations only, based on the available information. In no way should these ranges be assumed to encompass all possible dilution schemes or configurations.

7) Preservatives (such as benzyl alcohol) that are present only in one configuration of a drug (for example in the multiple-dose product, but not in the single-use product) may be listed as a range (0–x%). This was to avoid making two or more records for essentially the same product configuration.

8) For drugs that are given as a salt form, the counter ion may not be listed as an excipient. To search for counter ions (like sodium or potassium) one may look in the drug name fields (where the entire salt is often listed) or in the comments section (where the quantity of the counter ion per gram of drug is often provided) as well as in the excipient section.

9) If a pH value is listed for a lyophilized product, in most cases, it is the pH of the drug after its initial reconstitution with diluent, not the pH at lyophilization.

10) The concentration values given for excipients and active drug product in lyophilized products are usually those present at the initial reconstitution step, and are not necessarily the concentrations present at delivery (often further dilution occurs). This applies to solution formulations as well. Further, excipient concentrations may not take into account additive effects from the diluent (for example, a drug containing sodium chloride and reconstituted with 0.9% Sodium Chloride usually lists the concentration of sodium chloride present in the undiluted state).

11) When the excipient concentration is calculated for a lyophilized product, it is usually done by dividing the weight of the material by the volume of liquid added. Note that this does not take into account the additive volume of mixing that occurs, so such values are to be considered only approximations. In cases where the manufacturer provided the total volume after mixing, this final volume was used for calculations.

12) For drugs requiring reconstitution/dilution, in most cases a diluent recommended by the manufacturer is identified. In cases where multiple compatible diluents are possible, or when dilution schemes are complicated, one will see the note "Consult PDR for appropriate dilution." In some cases, often when the recommended diluent is provided, the manufacturer would not reveal the identity of the diluent for proprietary reasons.

13) Finally, most of the entries herein have been sent to the manufacturer for their correction and final notes. Many manufacturers participated in checking the data; others did not. We want to make this compendium as correct as possible, and so if errors are found, please e-mail them to nguyen.tue@gene.com for correction.

Acknowledgments

This compendium would not have been possible without the diligent work of Milianne Chin. She compiled much of the data, engineered the database, and contacted dozens of different companies to ensure that the listings are up to date.

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
			paravertebral	sarracenia purpurea, pitcher plant distillate	Sarapin	High Chemical Company	Solution	multidose vial
		6.0 - 7.0	IV - intravenous	Provides Rose's recommended daily intake of essential	5.4% NephrAmine "	R&D Laboratories Inc.	Solution	glass containers
acacia	7.0		ID - intradermal	Old Tuberculin	Tuberculin, Old, Tine Test	Lederle Laboratories	Solution	disposable
acacia (gum arabic)	7.0		ID - intradermal	tuberculin, purified protein derivative	(PPD) Tine Test	Lederle Laboratories	Solution	multiple-puncture
acetate	0.059	4.0	IV - intravenous	filgrastim (recombinant methionyl human	Neupogen ®	Amgen, Inc.	Solution	single dose vial
acetate		neutral	SC - subcutaneous	Lente (R) human insulin zinc suspension	Novolin ® L	Novo Nordisk Pharmaceuticals	Suspension	vials
acetate		neutral	SC - subcutaneous	Lente (L) Purified Pork Insulin Zinc Suspension, USP	Lente (L) Purified Pork Insulin Zinc Suspension,	Novo Nordisk Pharmaceuticals	Suspension	vials
acetic acid	0.435		IV - intravenous	ritodrine hydrochloride	Yutopar	Astra USA, Inc.	Solution	vial
acetic acid			SC - subcutaneous	leuprolide acetate	Lupron Injection	TAP Pharmaceuticals	Solution	multidose vial
acetic acid			IM - intramuscular	calcitonin-salmon	Calcimar ® Injection; Synthetic	Rhone-Poulenc Rorer	Solution	vials
acetic acid			IV - intravenous	albumin (human), 25%	Albuminar ®-25	Armour Pharmaceutical	Solution	vials
acetic acid		6.9 ± 0.5	IV - intravenous	albumin (human) 5%	Albuminar ®-5	Armour Pharmaceutical	Solution	bottles
acetic acid		3.5 - 5.5	IV - intravenous	vincristine sulfate, USP	Oncovin ®	Eli Lilly & Company	Solution	vials
acetic acid	0.01	~4.0	IV - intravenous	flumazenil	Romazicon ™	Roche Laboratories	Solution	vials
acetic acid	<2.5 (w/w)		SC - subcutaneous	goserelin acetate implant	Zoladex ®	Zeneca Pharmaceuticals	Solid Implant	disposable
acetic acid	0.46	3.0 - 4.5	IV - intravenous	mitoxantrone hydrochloride	Novantrone	Immunex Corporation	Solution	multidose vials
acetic acid		2.5 - 4.5	IM - intramuscular	oxytocin	Oxytocin Injection	Wyeth-Ayerst	Solution	sterile cartridge
acetic acid			IM - intramuscular	promethazine hydrochloride	Phenergan Injection (ampuls)	Wyeth-Ayerst	Solution	ampuls
acetic acid			IM - intramuscular	promethazine hydrochloride	Phenergan Injection	Wyeth-Ayerst	Solution	sterile cartridge
acetic acid		~5.9	IM - intramuscular	neostigmine methylsulfate	Prostigmin Injectable	ICN Pharmaceuticals	Solution	multidose vial
acetic acid	0.225		IM - intramuscular	calcitonin-salmon	Miacalcin ®	Sandoz Pharmaceuticals	Solution	vial
acetic acid		6.4 - 7.2	IM - intramuscular	tetanus immune globulin (human) primarily IgO	Hyper-Tet ®	Bayer Corporation-Biologi	Solution	prefilled
acetic acid		4.0	IV - intravenous	rocuronium bromide	Zemuron ™ Injection	Organon	Solution	multidose vial
acetic acid (ampul)			IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals,	Lyophilized	single dose vials
acetic acid (glacial)	0.2	4.2 ± 0.3	IV - intravenous	octreotide acetate injection	Sandostatin ®	Sandoz Pharmaceuticals	Solution	ampuls

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
acetic acid NF			IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
acetic acid NF		4.0 ± 0.3	IM - intramuscular	oxytocin	Syntocinon ®	Sandoz	Solution	ampul
acetone sodium	0.1	4.0 - 5.0	IM - intramuscular	pentazocine lactate	Talwin Injection (cartridge needle)	Sanofi Winthrop	Solution	cartridge needle
acetone sodium	0.2	4.0 - 5.0	IM - intramuscular	pentazocine lactate	Talwin Injection (multidose vial)	Sanofi Winthrop	Solution	multidose vials
acetone sodium	0.4		spinal anesthesia	procaine hydrochloride	Novocain	Sanofi Winthrop	Solution	ampuls
acetone sodium	≤ 0.2	3.2 - 6.0	spinal anesthesia	tetracaine hydrochloride	Pontocaine Hydrochloride 1% Solution	Sanofi Winthrop	Solution	ampuls
alanine	0.668 - 1.11	6.0 - 7.5	IV - intravenous	antithrombin III (human)	Thrombate III ®	Bayer Corporation-Biologi	Lyophilized	single dose vials
albumin	0.25	5.8 - 7.2	IV - intravenous	epoetin alfa	Procrit	Ortho Biotech, Inc.	Solution	single dose vial
albumin	<10.0		IM - intramuscular	rabies virus prepared from strain	Imovax ® Rabies Vaccine	Connaught Laboraties Inc.	Freeze-dried	single dose vial
albumin (human)	≤1.25		IV-intravenous	Antihemophilic Factor (recombinant)	Bioclate ™	Armour Pharmaceutical	Lyophilized	single-dose
albumin (human)	≤0.3	6.8 ± 0.4	IV-intravenous	Immune Globulin Intravenous (human) (IGIV)	Gammagard ® S/D	Baxter Healthcare Corporation	Lyophilized	single use bottles
albumin (human)	0.04-1.0		IV - intravenous	antihemophilic factor (recombinant)	Kogenate ®	Bayer Corporation-Biologi	Lyophilized	single dose vial
albumin (human)	≤1.0		IV - intravenous	antihemophilic factor (Human)	Koate ®-HP	Bayer Corporation-Biologi	Lyophilized	single dose bottle
albumin (human)	0.4-1.0		IV - intravenous	antihemophilic factor (recombinant)	Helixate ™	Armour Pharmaceutical	Lyophilized	single dose
albumin (human)	0.0063 - 0.05		IM - intramuscular	botulinum toxin type A	Botox ®	Allergan Inc.	Lyophilized	ampuls
albumin (human)	5.0		IV - intravenous	urokinase for injection	Abbokinase	Abbott Laboratories	Lyophilized	vial
albumin (human)	0.25	6.9 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ®	Amgen, Inc.	Solution	single dose vial
albumin (human)	0.25	6.1 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ® - multidose	Amgen, Inc.	Solution	multidose vial
albumin (human)	3.0	6.8 ± 0.4	IV - intravenous	immune globulin IV (human) primarily IgG	Gammar ®-IV	Armour Pharmaceutical	Lyophilized	single dose vials
albumin (human)	1.0 - 2.0		IV - intravenous	monoclonal antibody purified human	Monoclate-P ® Factor VIII: C Pasteurized	Armour Pharmaceutical	Lyophilized	single dose vial
albumin (human)	1.25		SC - subcutaneous	interferon beta-1b	Betaseron ®	Berlex Laboratories	Lyophilized	single use vial
albumin (human)	1.0		IV - intravenous	cytomegalovirus immune globulin intravenous	CytoGam ®	MedImmune, Inc.	Sterile Liquid	single dose vial
albumin (human)	0.5		SC - subcutaneous	poliovirus vaccine inactivated; type 1 (Mahoney), type 2	Poliovax ®	Connaught Laboratories, Inc.	Suspension	ampoules
albumin (human)	0.5		IM - intramuscular	interferon alfa-2a, recombinant	Roferon ®-A	Roche Laboratories	Solution	vial

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
albumin (human)	0.167		IM - intramuscular	interferon alfa-2a, recombinant	Roferon®-A (powder)	Roche Laboratories	Powder (sterile)	vial
albumin (human)	0.1		IL - intralesional	interferon alfa-2b, recombinant	Intron A	Schering Corporation	Powder	vial
albumin (human)	0.1		IM - intramuscular	interferon alfa-2b, recombinant	Intron A (solution)	Schering Corporation	Solution	vials
albumin (human)	0.6		IV - intravenous	anistreplase	Eminase ®	Roberts Pharmaceutical	Lyophilized	vial
albumin (human)	0.4 - 0.8		IV - intravenous	antihemophilic factor (human) (Factor VIII, AHF)	Humate-P ™	Armour Pharmaceutical	Lyophilized	single dose vial
albumin human USP	1.0		IV - intravenous	alglucerase injection	Ceredase ®	Genzyme Corporation	Solution	glass bottle
alcohol	30.5 (v/v%)	3.0 - 4.0	IV-intravenous	Etoposide	VePesid	Bristol-Myers Squibb-Oncology	Solution	multiple dose
alcohol	6.8 (v/v)		IV - intravenous	liothyronine sodium injection (T3)	Triostat	SmithKline Beecham Pharmaceuticals	Solution	amber-glass vials
alcohol	10.0	6.8 - 7.2	IM - intramuscular	digoxin	Lanoxin	Glaxo-Wellcome	Solution	ampul
alcohol	6.1 (v/v)	3.6 ± 0.4	IM - intramuscular	dihydroergotamine mesylate	D.H.E. 45 ®	Sandoz	Solution	ampuls
alcohol	10.0	~9.5	IM - intramuscular	pentobarbital sodium injection	Nembutal Sodium Solution	Abbott Laboratories	Solution	ampul
alcohol	10.0	6.8 - 7.2	IM - intramuscular	digoxin	Lanoxin (Digoxin) Injection	Glaxo Wellcome	Solution	ampuls
alcohol	10.0	12.0	IV - intravenous	phenytoin sodium injection, USP	Dilantin	Parke-Davis	Solution	steri-vials
alcohol	10.0		IM - intramuscular	ketorolac tromethamine	Toradol	Syntex Laboratories	Solution	Tubex cartridge
alcohol (Ph. Helv)	32.9 (v/v)		IV - intravenous	cyclosporine concentrate for injection USP	Sandimmune ®	Sandoz Pharmaceuticals	Solution	Ampul
alcohol (USP)	0.61 (v/v)	4.0 ± 0.3	IM - intramuscular	oxytocin	Syntocinon ®	Sandoz	Solution	ampul
alcohol (USP)	6.1 (v/v%)	3.6 ± 0.4	IM - intramuscular	dihydroergotamine mesylate injection, USP	D.H.E. 45 ® or Dyhdergot ®	Sandoz	Solution	ampuls
alpha	1.0		IM - intramuscular	oxytetracycline	Terramycin	Roerig	Solution	multidose vial
aluminum	≤0.17		IM-intramuscular	Diphtheria and Tetanus Toxoids and Acellular	Acel-Imune	Lederle Laboratories	Suspension(aft	multidose vial
aluminum	≤0.0001		IV - intravenous	antihemophilic factor (Human)	Koate®-HP	Bayer Corporation-Biologi	Lyophilized	single dose bottle
aluminum	≤0.034	~ 7.4	IM-intramuscular	Diphtheria & Tetanus Toxoids and Acellular	Tripedia ™	Connaught Laboratories, Inc.	Solution/Suspe	vial
aluminum	≤0.16		IM - intramuscular	combination of refined tetanus & diphtheria toxoids	Tetanus & Diphtheria Toxoids Adsorbed (Adult	Lederle Laboratories	Suspension	vial
aluminum	≤0.16		IM - intramuscular	refined tetanus toxoid	Tetanus Toxoid Adsorbed, aluminum	Lederle Laboratories	Suspension	vial
aluminum	≤0.16		IM - intramuscular	diphtheria & tetanus toxoids & Pertussis Vaccine	Tri-Immunol	Lederle Laboratories	Suspension(aft	multidose vials

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc, %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
aluminum	0.05		IM - intramuscular	hepatitis A vaccine	Havrix (Hepatitis A Vaccine, Inactivated)	SmithKline Beecham Biologicals	Suspension	single dose vial
aluminum	0.04 - 0.12		IM - intramuscular	combination of purified tetanus & diphtheria	Diphtheria & Tetanus Toxoids & Pertussis	SmithKline Beecham Pharmaceuticals	Suspension	vials
aluminum	≤0.034		IM - intramuscular	combines diphtheria & tetanus toxoids	Diphtheria & Tetanus Toxoids & Pertussis	Connaught Laboratories, Inc.	Turbid Liquid	vial
aluminum	≤0.16		IM - intramuscular	combination of refined diphtheria & tetanus toxoids	Diphtheria & Tetanus Toxoids Adsorbed,	Lederle Laboratories	Suspension(aft	vial
aluminum	≤0.17		IM - intramuscular	Diphtheria & Tetanus Toxoids and Pertussis	Tetramune, (DTP-HbOC)	Lederle Laboratories	Suspension(aft	vial
aluminum	0.045		IM - intramuscular	haemophilus b conjugate vaccine (meningococcal	PedvaxHIB	Merck & Company	Lyophilized	single dose vials
aluminum	~0.05		IM - intramuscular	hepatitis B vaccine (recombinant)	Recombivax HB	Merck & Company	Suspension	single dose vial
aluminum	0.05		IM - intramuscular	hepatitis B vaccine (recombinant)	Engerix-B	SmithKline Beecham Pharmaceuticals	Suspension	single dose vial
aluminum	2.0		IM - intramuscular	aurothioglucose	Solganal	Schering Corporation	Suspension	multidose vial
aluminum phosphate	≤0.2		IM - intramuscular	inactivated CVS Kissling/MDPII rabies virus	Rabies Vaccine Adsorbed	SmithKline Beecham Pharmaceuticals	Suspension	vial
amino acid	0.3		IM - intramuscular	hepatitis A vaccine	Havrix (Hepatitis A Vaccine, Inactivated)	SmithKline Beecham Biologicals	Suspension	single dose vial
ammonia	0.219		IV - intravenous	liothyronine sodium injection (T3)	Triostat	SmithKline Beecham Pharmaceuticals	Solution	amber-glass vials
ammonium acetate	0.4	~7.0	IM - intramuscular	bumetanide	Bumex ®	Roche Laboratories	Solution	ampuls
ammonium hydroxide			SC - subcutaneous	pentagastrin	Peptavlon	Wyeth-Ayerst	Solution	ampules
anhydrous citric acid	0.0175		IV - intravenous	liothyronine sodium injection (T3)	Triostat	SmithKline Beecham Pharmaceuticals	Solution	amber-glass vials
anhydrous citric acid	0.08	6.8 - 7.2	IM - intramuscular	digoxin	Lanoxin	Glaxo-Wellcome	Solution	ampul
anhydrous citric acid		3.0 - 4.0	IV - intravenous	dacarbazine	DTIC-Dome Sterile	Bayer Corporation-Pharma	Solid	vials
anhydrous citric acid	0.08	6.8 - 7.2	IM - intramuscular	digoxin	Lanoxin (Digoxin) Injection	Glaxo Wellcome	Solution	ampuls
anhydrous dextrose	4.5	3.0 - 4.0	IV - intravenous	labetalol hydrochloride	Trandate Injection ®	Glaxo Wellcome	Solution	vials
anhydrous dextrose	4.5	3.0 - 4.0	IV - intravenous	labetalol HCl	Normodyne	Schering Corporation	Solution	multidose vial
anhydrous dextrose	5.0		IM - intramuscular	buprenorphine hydrochloride	Buprenex	Reckitt & Colman Pharmaceuticals	Solution	glass snap-ampuls
anhydrous sodium	6.0	9.5 - 11.0	IV - intravenous	Methohexital Sodium for injection	Brevital Sodium	Eli Lilly & Company	Freeze-dried	vials
arginine	1.56 - 26.0	4.5 - 7.5	IM - intramuscular	aztreonam for injection	Azactam for Injection	Bristol-Myers Squibb-Oncology	Lyophilized	vials
ascorbic acid	0.048 - 0.48		IV - intravenous	doxycycline hyclate for injection	Vibramycin Intravenous	Roerig	Powder	vial

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
ascorbic acid	0.1		IM - intramuscular	imipramine hydrochloride USP	Tofranil	CibaGeneva Corporation	Solution	ampuls
ascorbic acid	0.2		IM - intramuscular (see	chlorpromazine hydrochloride	Thorazine-ampule	SmithKline Beecham	Solution	ampule
ascorbic acid	0.2		IM - intramuscular (see	chlorpromazine hydrochloride	Thorazine	SmithKline Beecham	Solution	multidose vials
ascorbic acid	0.2	3.4 - 4.5	various	bupivacaine hydrochloride and epinephrine	Marcaine Hydrochloride with Epinephrine	Sanofi Winthrop	Solution	single dose vials
ascorbic acid	1.0		SC - subcutaneous	Epinephrine	Sus-phrine ®	Forest Pharmaceuticals Inc.	Suspension	ampul
ascorbic acid USP	0.1		IM - intramuscular	thiethylperazine malate USP	Torecan ®	Roxane Laboratories, Inc.	Solution	ampul
asparagine			IVS - intravesical	an attenuated live culture preparation of BCG vaccine	TICE ® BCG	Organon	Freeze-dried	ampules
benzalkonium	0.02	6.8 - 7.2	ID - intradermal	betamethasone sodium phosphate & betamethasone	Celestone Soluspan Suspension	Schering Corporation	Suspension	multidose vial
benzenesulfonic acid		3.25 - 3.65	IV - intravenous	atracurium besylate	Tracrium	Glaxo Wellcome	Solution	single use vial
benzethonium	0.0 - 0.01*	5.0 - 6.0	IM - intramuscular	diphenhydramine hydrochloride	Benadryl	Parke Davis	Solution	ampules
benzethonium	0.0 - 0.01		IM - intramuscular	butorphanol tartrate	Stadol ® Injection	Apotheeon/Bristol-Myers Squibb	Solution	vial
benzyl alcohol	3.0	3.0 - 4.0	IV-intravenous	Etoposide	VePesid	Bristol-Myers Squibb-Oncology	Solution	multiple dose
benzyl alcohol	0.9	5.0 - 7.5	IM-intramuscular	Dexamethasone Acetate Suspension	Dalalone D.P. ®	Forest Pharmaceuticals	Suspension	vials
benzyl alcohol	0.9	5.0 - 7.0	IM-intramuscular	Cortisone Acetate	Cortone Acetate	Merck & Company	Suspension	vials
benzyl alcohol	0.9	5.0 - 7.5	IM-intramuscular	dexamethasone acetate	Decadron-LA	Merck & Company	Suspension	vials
benzyl alcohol	0.9	6.0 - 8.0	IAR - intraarticular	Prednisolone Tebutate	Hydeltra T. B. A.	Merck & Company	Suspension	vials
benzyl alcohol	0.9	5.0 - 7.0	IAR - intraarticular	Hydrocortisone acetate	Hydrocortone Acetate	Merck & Company	Suspension	vials
benzyl alcohol	0.89-0.93	3.5 - 7.0	IM - intramuscular	Methylprednisolone acetate	Depo-Medrol	The Upjohn Company	Suspension	single dose vial
benzyl alcohol	0.90	~6.0	IM - intramuscular	triamcinolone diacetate	Aristocort Forte (P)	Fujisawa	Micronized	vial
benzyl alcohol	0.90	~6.0	IL - intralesional	triamcinolone diacetate	Aristocort	Fujisawa USA, Inc.	Micronized	vial
benzyl alcohol	0.90	4.5 - 6.5	IL - intralesional	triamcinolone hexacetonide suspension	Aristospan Suspension 5 mg/ml	Fujisawa USA, Inc.	Suspension	vial
benzyl alcohol	2.02		IV - intravenous	amiodarone Hcl	Cordarone Intravenous (Cordarone IV)	Wyeth-Ayerst	Solution	ampuls
benzyl alcohol	0.9		IV - intravenous	Enalaprilat	Vasotec I.V.	Merck & Company	Solution	vial
benzyl alcohol	1.0	~3.0	IV - intravenous	midazolam hydrochloride	Versed	Hoffman - LaRoche Inc.	Solution	vials

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
benzyl alcohol	0.9		IM - intramuscular	hydroxyzine hydrochloride	Vistaril	Roerig	Solution	multidose vials
benzyl alcohol	0.5	5.8 - 6.5	IM - intramuscular	gold sodium thiomalate	Myochrysine	Merck & Company	Solution	ampuls
benzyl alcohol	1.0	3.5 - 6.0	IM - intramuscular	netilmicin sulfate, USP	Netromycin Injection	Schering Biochem. Corporation	Solution	vials
benzyl alcohol	0.9	3.9 - 5.0	IV - intravenous	doxacurium chloride	Nuromax	Glaxo Wellcome	Solution	multidose vial
benzyl alcohol	1.2		IM - intramuscular	haloperidol decanoate	Haldol Decanoate 50 and 100	McNeil Pharmaceutical	Solution (in	ampuls
benzyl alcohol	3.0	~5.0	IV - intravenous	teniposide	Vumon Injection Concentrate (VM-26)	Bristol-Myers Squibb-Oncology	Solution	ampules
benzyl alcohol	1.0	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra I.V. Infusion	Glaxo Wellcome	Solution	multidose vials
benzyl alcohol	2.0		IM - intramuscular	lorazepam	Ativan	Wyeth-Ayerst	Solution	sterile cartridge
benzyl alcohol	0.9	~4.5	IM - intramuscular	methotrimeprazine as the hydrochloride salt	Levoprome	Immunex Corporation	Solution	vials
benzyl alcohol	1.5	~3.0	IM - intramuscular	chlordiazepoxide hydrochloride	Librium Injectable (IM)	Roche Products, Inc.	Crystalline	amber ampuls
benzyl alcohol	0.945		IM - intramuscular	lincomycin hydrochloride	Lincocin sterile solution	The Upjohn Company	Solution	vials
benzyl alcohol	0.9		SC - subcutaneous	leuprolide acetate	Lupron Injection	TAP Pharmaceuticals,	Solution	multidose vial
benzyl alcohol	0.84		ICN - intracavernosal	alprostadil	Caverject Sterile Powder	The Upjohn Company	Freeze-dried	vial
benzyl alcohol	0.9	~6.8	IV - intravenous	aminocaproic acid	Amicar Injection, USP	Immunex Corporation	Solution	vial
benzyl alcohol	2.0		IM - intramuscular	physostigmine salicylate	Antilirium	Forest	Solution	ampuls
benzyl alcohol	1.0	~7.0	IM - intramuscular	bumetanide	Bumex ®	Roche Laboratories	Solution	ampuls
benzyl alcohol	0.945		IM - intramuscular	clindamycin phosphate	Cleocin Phosphate Sterile Solution	The Upjohn Company	Solution	vials
benzyl alcohol	1.5		IM - intramuscular	diazepam	Valium Injectable	Roche Products	Solution	ampuls
benzyl alcohol	2.0		IM - intramuscular (see	chlorpromazine hydrochloride	Thorazine	SmithKline Beecham	Solution	multidose vials
benzyl alcohol	0.75		IM - intramuscular	prochlorperazine as the edisylate	Compazine	SmithKline Beecham Pharmaceuticals	Solution	vials
benzyl alcohol	1.0	6.1 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ® - multidose	Amgen, Inc.	Solution	multidose vial
benzyl alcohol	1.2		IM - intramuscular	fluphenazine decanoate injection	Prolixin Decanoate	Apothecon/Bristol-Myers Squibb	Solution	single dose
benzyl alcohol	1.5		IM - intramuscular	fluphenazine Enanthate Injection	Prolixin Enanthate	Apothecon/Bristol-Myers Squibb	Solution	vials
benzyl alcohol	0.9	5.0 - 7.0	IM - intramuscular	phytonadione (vitamin K1)	AquaMephyton	Merck & Company	Aqueous	ampuls

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
benzyl alcohol	0.9		IM - intramuscular	chorionic gonadotropin for injection, USP	Pregnyl ®	Organon	Powder	multidose vials
benzyl alcohol	0.9	~8.5	IA - intraarterial	methotrexate sodium	Methotrexate Sodium Injection	Immunex Corporation	Solution	vial
benzyl alcohol	1.0	~10.0	IV - intravenous	trimethoprimand sulfamethoxazole	Septra IV Infusion	Glaxo Wellcome	Solution	vial
benzyl alcohol	1.0	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra IV Infusion ADD	Glaxo Wellcome	Solution	vial
benzyl alcohol	0.0 - 0.91	7.0 - 8.0	IM - intramuscular	hydrocortisone sodium succinate	Solu-Cortef Sterile Powder	The Upjohn Company	Powder	Act-O-vial
benzyl alcohol	0.02 (v/v)	7.9	IV - intravenous	sodium tetradecyl sulfate injection	Sotradecol ®	Elkins-Sinn Inc.	Solution	ampul
benzyl alcohol	0.75		IM - intramuscular	trifluoperazine hydrochloride	Stelazine	SmithKline Beecham Pharmaceuticals	Solution	multidose vial
benzyl alcohol	2.0 (v/v)	8.0 - 9.0	IV - intravenous	ethanolamine oleate	Ethamolin ® Injection	Schwarz Pharmaceutical	Solution	ampules
benzyl alcohol	2.0		IV - intravenous	gonadorelin hydrochloride	Factrel	Wyeth-Ayerst	Lyophilized	single dose Secule
benzyl alcuhol	≤1.0		IV - intravenous	heparin sodium	Heparin Lock Flush Solution, USP	Wyeth-Ayerst	Solution	Tubex Blunt
benzyl alcohol	≤1.0	5.0 - 7.5	IV - intravenous	heparin sodium	Heparin Sodium Injection USP	Wyeth-Ayerst	Solution	Tubex sterile
benzyl alcohol	0.945	5.0 - 7.5	IV - intravenous	heparin sodium	Heparin Sodium Injection	The Upjohn Company	Solution	vial
benzyl alcohol	1.0		IV - intravenous	heparin sodium	Heparin Sodium Injectio -Eli Lilly	Eli Lilly & Company	Solution	multidose vial
benzyl alcohol NF	0.9	3.5 - 5.0	IV - intravenous	doxapram hydrochloride injection USP	Dopram Injectable	A. H. Robins Company	Solution	multidose vials
benzyl alcohol NF	0.9	2.0 - 3.0	IM - intramuscular	glycopyrrolate, USP	Robinul Injectable	A. H. Robins Company	Liquid	multidose vial
benzyl alcohol	0.90	4.5 - 6.5	IAR - intrarticular	triamcinolone hexacetonide	Aristospan Suspension 20 mg/ml	Fujisawa	Micronized	vials
benzyl alcohol (see	0 - 0.9	3.25 - 3.65	IV - intravenous	atracurium besylate	Tracrium	Glaxo Wellcome	Solution	single use vial
benzyl alcohol (see	0.0 - 0.9	3.5 - 5.0	IV - intravenous	mivacurium chloride	Mivacron Injection	Glaxo Wellcome	Solution	single dose vials
benzyl alcohol (see	0.0 - 0.9		IM - intramuscular	furosemide	Lasix ®	Hoechst-Roussel Pharmaceuticals	Solution	ampuls
benzyl alcohol (see	0.0 - 0.104	6.5 - 8.5	IV - intravenous	mesna	Mesnex Injection	Bristol-Myers Squibb-Oncology	Solution	multidose vial
benzyl alcohol (see	0.0 - 0.9		IV - intravenous	famotidine	Pepcid Injection	Merck & Company	Solution	multidose vial
benzyl alcohol (see	0.0 - 1.0	5.8 - 7.2	IV - intravenous	epoetin alfa	Procrit	Ortho Biotech, Inc.	Solution	single dose vial
benzyl alcohol (see	0.0 - 8.92	7.0 - 8.0	IM - intramuscular	methylprednisolo ne sodium succinate, USP	Solu-Medrol Sterile Powder	The Upjohn Company	Powder	Act-O-vial
bovine serum	<0.0001		SC - subcutaneous	poliovirus vaccine inactivated; type 1 (Mahoney), type 2	Poliovax ®	Connaught Laboratories, Inc.	Suspension	ampoules
buffered sodium			SC - subcutaneous	typhoid vaccine	Typhoid Vaccine USP	Wyeth-Ayerst	Suspension	vials

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
buffered sodium			ID - intradermal	equal parts of Ogawa and Inaba serotypes of killed	Cholera Vaccine USP	Wyeth-Ayerst	Suspension	vials
butylated	0.03		IM-intramuscular	Vitamin A Palmitate as retinol	Aquasol A Parenteral	Astra USA, Inc.	Solution	single-dose vial
butylated	0.03		IM-intramuscular	Vitamin A Palmitate as retinol	Aquasol A Parenteral	Astra USA, Inc.	Solution	single-dose vial
calcium	≤0.02		IV-intravenous	Antihemophilic Factor (recombinant)	Recclate ™	Armour Pharmaceutical	Lyophilized	single-dose
calcium chloride	0.022-0.056		IV - intravenous	antihemophilic factor (recombinant)	Kogenate ®	Bayer Corporation-Biologi	Lyophilized	single dose vial
calcium chloride	≤0.03327		IV - intravenous	antihemophilic factor (Human)	Koate ®-HP	Bayer Corporation-Biologi	Lyophilized	single dose bottle
calcium chloride	0.022-0.05		IV - intravenous	antihemophilic factor (recombinant)	Helixate ™	Armour Pharmaceutical	Lyophilized	single dose
calcium chloride	0.033	4.5 - 6.8	various	mepivacaine hydrochloride	Carbocaine Hydrochloride-single	Sanofi Winthrop	Solution	single dose vials
calcium chloride	0.048	7.0 - 7.5	ITO - intraocular	sodium hyaluronate	Amo ® Vitrax ®	Allergan Inc.	Solution	disposable glass
calcium chloride	0.022 - 0.056		IV - intravenous	monoclonal antibody purified human	Monoclate-P ® Factor VIII: C Pasteurized	Armour Pharmaceutical	Lyophilized	single dose vial
calcium chloride	0.048	7.2 ± 0.4	ITO - intraocular	purified hydroxypropylmethylcellulose	Ocucoat	Storz Ophthalmics	Solution	syringes
calcium chloride	0.004		IM - intramuscular	promethazine hydrochloride	Phenergan Injection (ampuls)	Wyeth-Ayerst	Solution	ampuls
calcium chloride	0.004		IM - intramuscular	promethazine hydrochloride	Phenergan Injection	Wyeth-Ayerst	Solution	sterile cartridge
calcium chloride	0.004		IM - intramuscular	meperidine hydrochloride & promethazine	Mepergan	Wyeth-Ayerst	Solution	sterile cartridge
carbon dioxide		8.0 - 9.0	IV - intravenous	cyclophosphamide for injection, USP	Lyophilized Neosar ®	Pharmacia	Lyophilized	vials
carbon dioxide gas			IM - intramuscular	thiethylperazine malate USP	Torecan ®	Roxane Laboratories, Inc.	Solution	ampul
carbon dioxide gas			IM - intramuscular	mesoridazine besylate USP	Serentil ®	Boehringer Ingelheim	Solution	ampuls
carboxymethylcellul	0.55		IM - intramuscular	penicillin G benzathine and penicillin G	Bicillin C-R 900/300	Wyeth-Ayerst	Suspension	sterile cartridge
carboxymethylcellul	0.6		IM - intramuscular	penicillin G benzathine suspension	Bicillin L-A	Wyeth-Ayerst	Suspension	disposable
carboxymethylcellul	0.55		IM - intramuscular	penicillin G benzathine and penicillin G	Bicillin C-R	Wyeth-Ayerst	Suspension	disposable
carboxymethylcellul	0.05	5.0 - 7.5	IM-intramuscular	Dexamethasone Acetate Suspension	Dalalone D.P. ®	Forest Pharmaceuticals	Suspension	vials
carboxymethylcellul	0.5		IM - intramuscular	leuprolide acetate	Lupron Depot 3.75	TAP Pharmaceuticals	Lyophilized	single dose vial
carboxymethylcellul	0.5		IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
carboxymethylcellul	0.5		IM - intramuscular	leuprolide acetate	Lupron Depot-3 month, 22.5	TAP Pharmaceuticals	Lyophilized	vial

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
carboxymethylcellul	0.5		IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals	Lyophilized	single dose vials
chloride	0.355-0.461		IV - intravenous	antihemophilic factor (recombinant)	Kogenate ®	Bayer Corporation-Biologi	Lyophilized	single dose vial
chloride	0.355-0.46		IV - intravenous	antihemophilic factor (recombinant)	Helixate ™	Armour Pharmaceutical	Lyophilized	single dose
chloride	0.213 - 0.638	6.6 - 7.4	IV - intravenous	alpha1-proteinase inhibitor (human)	Prolastin ®	Bayer Corporation-Biologi	Lyophilized	single dose vials
chloride	0.390-0.744	6.0 - 7.5	IV - intravenous	antithrombin III (human)	Thrombate III ®	Bayer Corporation-Biologi	Lyophilized	single dose vials
chlorobutanol	0.5		IM-intramuscular	Vitamin A Palmitate as retinol	Aquasol A Parenteral	Astra USA, Inc.	Solution	single-dose vial
chlorobutanol	0.25	6.0 - 7.0	IM - intramuscular		Nydrazid Injection	Apothecon/Bristol-Myers Squibb	Solution	vial
chlorobutanol	≤0.5		IM - intramuscular	L-epinephrine hydrochloride (injection),	Ana-Kit	Bayer Corporation-Pharma	Solution	syringe
chlorobutanol	0.5	2.5 - 4.5	IM - intramuscular	oxytocin	Oxytocin Injection	Wyeth-Ayerst	Solution	sterile cartridge
chlorobutanol	0.5		IM - intramuscular	testosterone enanthate 200mg/mL	Delatestryl	BioTechnology General Corp.-BTG	Solution	single dose
chlorobutanol	0.5		IM - intramuscular	dicyclomine hydrochloride	Bentyl Injection	Merrell Dow Pharmaceuticals	Solution	multidose vial
chlorobutanol, NF	0.5	4.0 ± 0.3	IM - intramuscular	oxytocin	Syntocinon ®	Sandoz	Solution	ampul
chlorobutanol (see	0.0-0.5	4.0	IV - intravenous	desmopressin acetate	DDAVP ® Injection	Rhone-Poulenc Rorer	Solution	ampuls
chlorobutanol (see	0.0 - 0.5		IM - intramuscular	papverine hydrochloride	Papverine Hydrochloride Injection, USP	Eli Lilly & Company	Solution	multidose vials
citrate	~1.0		IV - intravenous	alglucerase injection	Ceredase ®	Genzyme Corporation	Solution	glass bottle
citric acid	0.1		IM-intramuscular	Vitamin A Palmitate as retinol	Aquasol A Parenteral	Astra USA, Inc.	Solution	single-dose vial
citric acid	0.2	3.0 - 4.0	IV-intravenous	Etoposide	VePesid	Bristol-Myers Squibb-Oncology	Solution	multiple dose
citric acid		~6.1	IV - intravenous	imiglucerase	Cerezyme ™	Genzyme Corporation	Lyophilized	vial
citric acid	0.02	~5.0	IM - intramuscular	trimethobenzamide HCl	Tigan ®-ampuls	Roberts Pharmaceuticals	Solution	ampuls
citric acid	0.02	~5.0	IM - intramuscular	trimethobenzamide HCl	Tigan ®-vials	Roberts Pharmaceuticals	Solution	multiple dose vial
citric acid	0.02	~5.0	IM - intramuscular	trimethobenzamide HCl	Tigan ®-syringe	Roberts Pharmaceuticals	Solution	disposable
citric acid		5.5 - 6.5	IV - intravenous	atenolol	Tenormin I. V. Injection	Zeneca Pharmaceuticals	Solution	ampules
citric acid		~ 5.4	IV - intravenous	edrophonium chloride	Tensilon	ICN Pharmaceuticals	Solution	multidose vials
citric acid			IVS - intravesical	an attenuated live culture preparation of BCG vaccine	TICE ® BCG	Organon	Freeze-dried	ampules

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
citric acid	0.02	3.3 - 5.5	various	lidocaine hydrochloride and epinephrine at	Xylocaine with Epinephrine	Astra USA, Inc.	Solution	multidose vials
citric acid	0.02	3.3 - 5.5	various	lidocaine hydrochloride and epinephrine at	Xylocaine MPF with epinephrine	Astra USA, Inc.	Solution	ampules
citric acid	0.2		IM - intramuscular	hydromorphone hydrochloride	Dilaudid	Knoll Laboratories	Solution	ampules
citric acid	0.2		IM - intramuscular	hydromorphone hydrochloride	Dilaudid-HP Injection	Knoll Laboratories	Solution	amber ampules
citric acid			IV - intravenous	propranolol hydrochloride	Inderal	Wyeth-Ayerst	Solution	ampuls
citric acid	1.0		IM - intramuscular	oxytetracycline	Terramycin	Roerig	Solution	multidose vial
citric acid	0.075	3.7 - 4.1	IV - intravenous	diltiazem hydrochloride	Cardizem	Marion Merrell Dow Inc.	Solution	vial
citric acid			IV - intravenous	perphenazine	Trilafon Injection	Schering Corporation	Solution	ampul
citric acid	0.006	6.9 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ®	Amgen, Inc.	Solution	single dose vial
citric acid	0.011	6.1 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ® - multidose	Amgen, Inc.	Solution	multidose vial
citric acid		6.8 ± 0.4	IV - intravenous	immune globulin IV (human) primarily IgG	Gammar ®-IV	Armour Pharmaceutical	Lyophilized	single dose vials
citric acid	0.02	3.0 - 4.5	various	etidocaine HCl and epinephrine as bitartarate	Duranest Injections	Astra USA, Inc.	Solution	single dose vial
citric acid		6.0 - 8.5	IM - intramuscular	penicillin G potassium	Buffered Pfizerpen for Injection	Roerig	Powder	vials
citric acid	0.006 - 0.011	5.8 - 7.2	IV - intravenous	epoetin alfa	Procrit	Ortho Biotech, Inc.	Solution	single dose vial
citric acid		~5.0	IM - intramuscular	pyridostigmine bromide	Mestinon Injectable	ICN Pharmaceuticals	Solution	ampuls
citric acid	0.33		IM - intramuscular	butorphanol tartrate	Stadol ® Injection	Apothecon/Bristol-Myers Squibb	Solution	vial
citric acid	0.03	6.7 - 7.3	IV - intravenous	ranitidine hydrochloride	Zantac Injection Premixed	Glaxo Wellcome	Solution	flexible plastic
citric acid	0.052	3.0 - 4.0	IV - intravenous	ondansetron hydrochloride dihydrate	Zofran ® Injection Premixed	Glaxo Wellcome	Solution	single dose
citric acid	0.023	5.0 - 7.0	IV - intravenous	metronidazole	Flagyl IV RTU	SCS	Solution	single dose
citric acid (additional)		3.5	IV - intravenous	nicardipine HCl	Cardene	Wyeth-Ayerst	Solution	ampuls
citric acid anhydrous	1.0	6.5 - 6.9	LI - local injection	dexamethasone sodium phosphate-lidocai	Decadron Phosphate with Xylocaine Injection	Merck & Company	Solution	vials
citric acid anhydrous	0.21	4.0	IV - intravenous	vecuronium bromide	Norcuron ®	Organon	Freeze-dried	vials
citric acid	0.02	3.3 - 5.5	various	bupivacaine hydrochloride and epinephrine as	Sensorcaine ®-MPF with epinephrine	Astra USA, Inc.	Solution	single dose vials
citric acid anhydrous	0.5		IV - intravenous	methyldopate HCl	Aldomet Ester Hydrochloride	Merck & Company	Solution	vials

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
citric acid anhydrous	0.3		IM - intramuscular	metboxamine hydrochloride	Vasoxyl	Glaxo Wellcome	Solution	ampuls
citric acid anhydrous	1.26		IM - intramuscular	nalbuphine hydrochloride	Nubain	DuPont Pharma	Solution	ampuls
citric acid anhydrous	1.26		IM - intramuscular	nalbuphine hydrochloride	Nubain (ampules)	DuPont Pharma	Solution	ampules
citric acid anhydrous	2.2	3.5 - 3.5	IV - intravenous	streptozocin	Zanosar Sterile Powder	The Upjohn Company	Freeze-dried	vial
citric acid	0.1		SC - subcutaneous	phenylephrine hydrochloride injection	Neo-Synephrine hydrochloride	Sanofi Winthrop	Solution	ampuls
citric acid		3.0 - 4.0	IV - intravenous	labetalol HCl	Normodyne	Schering Corporation	Solution	multidose vial
citric acid	0.053	3.5	IV - intravenous	nicardipine HCl	Cardene	Wyeth-Ayerst	Solution	ampuls
citric acid	0.05	3.3 - 4.0	IV - intravenous	ondansetron hydrochloride dihydrate	Zofran ® Injection	Glaxo Wellcome	Solution	single dose vial
citric acid		3.0 - 4.0	IV - intravenous	labetalol hydrochloride	Trandate Injection ®	Glaxo Wellcome	Solution	vials
citric acid US,		~4.5	IM - intramuscular	methotrimeprazine as the hydrochloride salt	Levoprome	Immunex Corporation	Solution	vials
colloidal silicon	9.6		ICV - intracervical	dinoprostone	Prepidil Gel	The Upjohn Company	Viscous Gel	syringe
creatinine	0.5	5.0 - 7.5	IM-intramuscular	Dexamethasone Acetate Suspension	Dalalone D.P. ®	Forest Pharmaceuticals	Suspension	vials
creatinine	0.5	5.0 - 7.5	IM-intramuscular	dexamethasone acetate	Decadron-LA	Merck & Company	Suspension	vials
creatinine	0.8	7.5 - 8.0	IV - intravenous	Dexamethasone sodium phosphate , USP	Decadron Phosphate Injection	Merck & Company	Solution	vials
creatinine	0.8	6.5 - 6.9	LI - local injection	dexamethasone sodium phosphate-lidocai	Decadron Phosphate with Xylocaine Injection	Merck & Company	Solution	vials
creatinine	0.8	7.5 - 8.5	IM - intramuscular	hydrocortisone sodium phosphate	Hydrocortone Phosphate	Merck & Company	Solution	multidose vial
Cremophor ® EL	52.7		IV - intravenous	paclitaxel	Taxol	Bristol-Myers Squibb-Oncology	Nonaqueous	single dose vials
Cremophor(R) EL	50.0	~5.0	IV - intravenous	teniposide	Vumon Injection Concentrate (VM-26)	Bristol-Myers Squibb-Oncology	Solution	ampules
Cremophor(R) EL	65.0		IV - intravenous	cyclosporine concentrate for injection USP	Sandimmune ®	Sandoz Pharmaceuticals	Solution	Ampul
crosslinked gelatin	0.5 - 1.25		IV - intravenous	streptokinase	Streptase	Astra USA, Inc.	Lyophilized	vial
D,L-lactic + glycolic	74.3 - 84.6 (w/w)		SC - subcutaneous	goserelin acetate implant	Zoladex ®	Zeneca Pharmaceuticals	Solid Implant	disposable
D-mannitol	0.66		IM - intramuscular	leuprolide acetate	Lupron Depot 3.75	TAP Pharmaceuticals	Lyophilized	single dose vial
D-mannitol	5.0		IM - intramuscular	leuprolide acetate	Lupron Depot 3.75	TAP Pharmaceuticals	Lyophilized	single dose vial
D-mannitol	1.32		IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals	Lyophilized	single dose vials

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
D-mannitol	1.32-2.64		IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
D-mannitol	5.0		IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
d-mannitol	5.0		IM - intramuscular	leuprolide acetate	Lupron Depot-3 month, 22.5	TAP Pharmaceuticals	Lyophilized	vial
d-mannitol	2.59		IM - intramuscular	leuprolide acetate	Lupron Depot-3 month, 22.5	TAP Pharmaceuticals	Lyophilized	vial
D-mannitol (ampul)	5.0		IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals	Lyophilized	single dose vials
d-sorbitol	45.0	6.0 - 8.0	IAR - intraarticular	Prednisolone Tebutate	Hydeltra T. B. A.	Merck & Company	Suspension	vials
dehydrated alcohol	42.7 (v/v)	~5.0	IV - intravenous	teniposide	Vumon Injection Concentrate (VM-26)	Bristol-Myers Squibb-Oncology	Solution	ampules
dehydrated alcohol	49.7 (v/v)		IV - intravenous	paclitaxel	Taxol	Bristol-Myers Squibb-Oncology	Nonaqueous	single dose vials
dehydrated alcohol			IV - intravenous	alprostadil, (prostaglandin E1)	Prostin VR Pediatric Sterile Solution	The Upjohn Company	Solution	ampoules
dehydrated alcohol,	80.0 (v/v)		IV - intravenous	tacrolimus injection	Prograf	Fujisawa USA, Inc.	Solution	ampules
dextrose	8.25	3.3 - 5.5	spinal anesthesia	bupivacaine hydrochloride	Sensorcaine ®-MPF Spinal	Astra USA, Inc.	Solution	ampules
dextrose	4.4		IM - intramuscular	amitriptyline HCl	Elavil	Zeneca Pharmaceuticals	Solution	vials
dextrose	5.0		IV - intravenous	clindamycin phosphate	Cleocin Phosphate IV Solution	The Upjohn Company	Premixed	Galaxy (R) plastic
dextrose	1.25		SC - subcutaneous	interferon beta-1b	Betaseron ®	Berlex Laboratories	Lyophilized	single use vial
dextrose	5.0	3.5 - 4.6	IV - intravenous	ciprofloxacin	Cipro ® IV	Bayer Corporation-Pharma	Ready-to-Use	flexible
dextrose	8.25	4.0 - 6.5	SA - subarachnoid	bupivacaine hydrochloride	Marcaine Spinal	Sanofi Winthrop	Solution	single dose ampul
dextrose	3.75	5.0 - 7.0	IM - intramuscular	phytonadione (vitamin K1)	AquaMephyton	Merck & Company	Aqueous	ampuls
dextrose	30.0		ID - intradermal	tuberculin, purified protein derivative	(PPD) Tine Test	Lederle Laboratories	Solution	multiple-puncture
dextrose	10.0		IU - intrauterine	dextran 70	Hyskon ® Hysteroscopy Fluid	Medisan Pharmaceuticals	Solution	bottles
dextrose	5.0	3.0 - 4.0	IV - intravenous	ondansetron hydrochloride dihydrate	Zofran ® Injection Premixed	Glaxo Wellcome	Solution	single dose
dextrose	5.0	3.8 - 5.8	IV - intravenous	ofloxacin injection	Floxin ® IV - premixed	Ortho Pharmaceutical	Premixed	single use flexible
dextrose	3.2 - 4.4	5.0 - 7.5	IV - intravenous	ceftazidime sodium injection	Fortaz ® Injection	Glaxo Wellcome	Frozen	Galaxy plastic
dextrose anhydrous	4.7 - 4.94	3.2 - 4.0	IV - intravenous	milrinone lactate injection	Primacor	Sanofi Winthrop	Solution	single dose vials
dextrose (D-glucose)	7.5	5.5 - 7.0	spinal anesthesia	lidocaine hydrochloride	Xylocaine MPF 1.5%/5% with 7.5%	Astra USA, Inc.	Solution	ampules
dextrose hydrous	5.6	3.5 - 6.5	IV - intravenous	fluconazole	Diflucan Injection	Roerig	Solution	Viaflex Plus

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
dextrose hydrous	1.4 - 3.4	5.0 - 7.5	IV - intravenous	cefotaxime sodium injection	Premixed Claforan ® Injection	Hoechst-Roussel Pharmaceuticals	Frozen	Galaxy single
dextrose hydrous	2.4 - 3.8		IV - intravenous	ceftriaxone sodium injection	Rocephin Injection	Roche Laboratories	Premixed	Galaxy single
dextrose hydrous	2.2 - 4.0	~6.5	IV - intravenous	cefoxitin sodium injection	Premixed Intravenous Solution Mefoxin	Merck & Company	Solution	single dose
dextrose hydrous	2.2 - 3.8	4.2 - 6.2	IV - intravenous	cefmetazole sodium injection	Zefazone ® IV solution	The Upjohn Company	premixed	plastic Galaxy
dextrose hydrous	0.0 - 2.8	5.0 - 7.5	IV - intravenous	cefuroxime sodium injection	Zinacef ®	Glaxo Wellcome	Frozed	Galaxy plastic
dextrose hydrous USP	1.9 - 3.8	5.5 - 8.0	IV - intravenous	ceftizoxime sodium injection	Ceftizox	Fujisawa USA, Inc.	frozen	single dose
dextrose hydrous USP	4.0 - 4.8		IV - intravenous	cefazolin sodium injection	Ancef (solution)	SmithKline Beecham Pharmaceuticals	Solution	single dose
dextrose hydrous USP	3.6 - 4.6		IV - intravenous	cefoperazone sodium injection	Cefobid	Roerig Division of Pfizer	Premixed	plastic containers
dextrose injection	5.0	3.5 - 5.0	IV - intravenous	mivacurium chloride	Mivacron Premixed Infusion	Glaxo Wellcome	Solution	flexible plastic
dextrose USP	2.2 - 3.8	4.0 - 6.5	IV - intravenous	cefotetan disodium injection	Cefotan ®	Zeneca Pharmaceuticals	Premixed	Galaxy (R) plastic
diabasic sodium	0.44 - 1.1	7.0 - 8.0	IM - intramuscular	hydrocortisone sodium succinate	Solu-Cortef Sterile Powder	The Upjohn Company	Powder	Act-O-vial
diacetylated	5.0	~8.0	IV - intravenous	diazepam emulsified injection	Dizac	Ohmeda PPD, Inc.	Emulsion	single dose vial
dibasic potassium	0.24	6.7 - 7.3	IM - intramuscular	ranitidine hydrochloride	Zantac Injection	Glaxo Wellcome	Solution	single dose vial
dibasic sodium	0.18	7.0 ± 0.5	IV - intravenous	muromonab-CD3 biochemically purified IgG2a	Orthoclone OKT3	Ortho Biotech Inc.	Solution	ampule
dibasic sodium	0.0226	~7.5	IM - intramuscular	somatropin rDNA origin for injection	Humatrope ®	Eli Lilly & Company	Lyophilized	vials
dibasic sodium		6.3 ± 0.6	IV - intravenous	cladribine	Leustatin Injection	Ortho Biotech, Inc.	Solution	single use vials
dibasic sodium	0.71	6.8 - 7.2	ID - intradermal	betamethasone sodium phosphate & betamethasone	Celestone Soluspan Suspension	Schering Corporation	Suspension	multidose vial
dibasic sodium	0.558	7.2 - 7.4	IM - intramuscular	pegademase bovine	Adagen ®	Enzon	Solution	single dose vials
dibasic sodium	0.530 - 0.585	7.3	IM - intramuscular	pegaspargase	Oncaspar ®	Rhone-Poulenc Rorer	Solution	single dose vials
dibasic sodium	0.044 - 0.44		IM - intramuscular	chorionic gonadotropin for injection, USP	Pregnyl ®	Organon	Powder	multidose vials
dibasic sodium	0.16 - 0.8		IM - intramuscular	human chorionic gonadotropin (HCG) for	Profasi	Serono Laboratories, Inc.	Lyophilized	multidose vial
dibasic sodium	0.089	7.2 - 7.8	IV - intravenous	aldesleukin (recombinant human	Proleukin ®	Chiron Therapeutics	Lyophilized	single use vial
dibasic sodium	0.18	6.7 - 7.3	IV - intravenous	ranitidine hydrochloride	Zantac Injection Premixed	Glaxo Wellcome	Solution	flexible plastic
dibasic sodium	0.003		IV - intravenous	sermorelin acetate for injection	Geref ®	Serono Laboratories, Inc.	Lyophilized	ampule

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
dibasic sodium	0.072	7.9	IV - intravenous	sodium tetradecyl sulfate injection	Sotradecol ®	Elkins-Sinn Inc.	Solution	ampul
dibasic sodium	0.87 - 1.75	7.0 - 8.0	IM - intramuscular	methylprednisolone sodium succinate, USP	Solu-Medrol Sterile Powder	The Upjohn Company	Powder	Act-O-vial
dibasic sodium	0.137-0.144	3.5 - 7.0	IM - intramuscular	Methylprednisolone acetate	Depo-Medrol	The Upjohn Company	Suspension	single dose vial
diethanolamine	0.3	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra I.V. Infusion	Glaxo Wellcome	Solution	multidose vials
diethanolamine	0.3	~10.0	IV - intravenous	trimethoprimand sulfamethoxazole	Septra IV Infusion	Glaxo Wellcome	Solution	vial
diethanolamine	0.3	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra IV Infusion ADD	Glaxo Wellcome	Solution	vial
dimethylsulfoxide	<0.06		IV - intravenous	anistreplase	Eminase ®	Roberts Pharmaceutical	Lyophilized	vial
disodium edetate	0.05	5.0 - 7.5	IM-intramuscular	dexamethasone acetate	Decadron-LA	Merck & Company	Suspension	vials
disodium edetate	0.05	6.5 - 6.9	LI - local injection	dexamethasone sodium phosphate-lidocai	Decadron Phosphate with Xylocaine Injection	Merck & Company	Solution	vials
disodium edetate	0.01	~5.0	IM - intramuscular	trimethobenzamide HCl	Tigan ®-syringe	Roberts Pharmaceuticals	Solution	disposable
disodium edetate	0.01	~3.0	IV - intravenous	midazolam hydrochloride	Versed	Hoffman - LaRoche Inc.	Solution	vials
disodium edetate	0.05		IV - intravenous	methyldopate HCl	Aldomet Ester Hydrochloride	Merck & Company	Solution	vials
disodium edetate	0.05		IM - intramuscular	clindamycin phosphate	Cleocin Phosphate Sterile Solution	The Upjohn Company	Solution	vials
disodium edetate	0.004		IV - intravenous	clindamycin phosphate	Cleocin Phosphate IV Solution	The Upjohn Company	Premixed	Galaxy (R) plastic
disodium edetate	0.05	7.0 - 8.0	IM - intramuscular	prednisolone sodium phosphate	Hydeltrasol	Merck & Company	Solution	vial
disodium edetate USP	0.065	~4.5	IM - intramuscular	methotrimeprazine as the hydrochloride salt	Levoprome	Immunex Corporation	Solution	vials
disodium EDTA	0.011	2.7 - 4.0	IF - infiltration &	chloroprocaine hydrochloride	Nesacaine Injection	Astra USA, Inc.	Solution	multidose vials
disodium EDTA	0.011	2.7 - 4.0	IF - infiltration &	chloroprocaine hydrochloride	Nesacaine-MPF Injection	Astra USA, Inc.	Solution	single dose vials
disodium hydrogen	0.34	~6.1	IV - intravenous	imiglucerase	Cerezyme ™	Genzyme Corporation	Lyophilized	vial
disodium hydrogen	0.25		IVS - intravesical	BCG Live (intravesical)	TheraCys ®	Connaught Laboratories	Freeze-dried	vial
disodium hydrogen	0.028	7.0 - 7.5	ITO - intraocular	sodium hyaluronate	Healon ®	Pharmacia, Inc. Ophthalmics Inc.	Viscoelastic	Disposable glass
disodium hydrogen	0.028	7.0 - 7.5	ITO - intraocular	sodium hyaluronate 7000	Healon GV	Pharmacia Inc. Ophthalmics	Viscoelastic	disposable glass
disodium phosphate		7.0	IV - intravenous	plicamycin	Mithracin	Bayer Corporation-Pharma	Freeze-dried	vials
disodium phosphate	0.013	7.0 ± 0.3	IM - intramuscular	typhoid Vi polysaccharide vaccine	Typhim Vi ™	Connaught Laboratories	Solution	syringe

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
disodium phosphate	0.0265	~6.7	SC - subcutaneous	somatropin (rDNA origin) for injection	Genotropin ™	Pharmacia Inc.	Lyophilized	Intra-Mix two
disodium phosphate	0.027	~6.7	SC - subcutaneous	somatropin (rDNA origin) for injection	Genotropin ™ Injection	Pharmacia, Inc.	Lyophilized	Intra-Mix two
disodium phosphate	0.0125 - 0.025		IM - intramuscular	menotropins for injection	Humegon™	Organon Inc.	Lyophilized	vial
disodium phosphate	0.098		IM - intramuscular	hepatitis B vaccine (recombinant)	Engerix-B	SmithKline Beecham Pharmaceuticals	Suspension	single dose vial
DL-lactic acid &	3.31		IM - intramuscular	leuprolide acetate	Lupron Depot 3.75	TAP Pharmaceuticals	Lyophilized	single dose vial
DL-lactic acids &	6.62		IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals	Lyophilized	single dose vials
DL-lactic acids &	6.62-13.24		IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
E-aminocaproic acid	0.026		IV - intravenous	anistreplase	Eminase ®	Roberts Pharmaceutical	Lyophilized	vial
edetate calcium	0.01	3.4 - 4.5	various	bupivacaine hydrochloride and epinephrine	Marcaine Hydrochloride with Epinephrine	Sanofi Winthrop	Solution	single dose vials
edetate disodium	0.05	5.0 - 7.5	IM-intramuscular	Dexamethasone Acetate Suspension	Dalalone D.P. ®	Forest Pharmaceuticals	Suspension	vials
edetate disodium	0.01	3.0 - 6.5	IM - intramuscular	tobramycin sulfate	Tobramycin Sulfate Injection, USP	Elkins-Sinn	Solution	multidose vials
edetate disodium	0.01	3.0 - 4.0	IV - intravenous	labetalol hydrochloride	Trandate Injection ®	Glaxo Wellcome	Solution	vials
edetate disodium	0.01	3.5 - 6.0	IM - intramuscular	netilmicin sulfate, USP	Netromycin Injection	Schering Biochem. Corporation	Solution	vials
edetate disodium	0.01	3.0 - 4.0	IV - intravenous	labetalol HCl	Normodyne	Schering Corporation	Solution	multidose vial
edetate disodium	0.05		IM - intramuscular	hydromorphone hydrochloride	Dilaudid-vials	Knoll Laboratories	Solution	multidose vials
edetate disodium	0.01	~7.0	IM - intramuscular	bumetanide	Bumex ®	Roche Laboratories	Solution	ampuls
edetate disodium	0.01	6.8 - 7.2	ID - intradermal	betamethasone sodium phosphate & betamethasone	Celestone Soluspan Suspension	Schering Corporation	Suspension	multidose vial
edetate disodium	0.05		IM - intramuscular	mesoridazine besylate USP	Serentil ®	Boehringer Ingelheim	Solution	ampuls
edetate disodium	0.025	6.5 - 8.5	IV - intravenous	mesna	Mesnex Injection	Bristol-Myers Squibb-Oncology	Solution	multidose vial
edetate disodium	0.01	~4.0	IV - intravenous	flumazenil	Romazicon ™	Roche Laboratories	Solution	vials
edetate disodium	0.01		IM - intramuscular	tobramycin sulfate injection	Nebcin ®	Eli Lilly & Company	Solution	multidose vials
edetate disodium	0.005		IM - intramuscular	papverine hydrochloride	Papverine Hydrochloride Injection, USP	Eli Lilly & Company	Solution	multidose vials
edetate disodium	0.01		IM - intramuscular	promethazine hydrochloride	Phenergan Injection (ampuls)	Wyeth-Ayerst	Solution	ampuls
edetate disodium	0.01		IM - intramuscular	promethazine hydrochloride	Phenergan Injection	Wyeth-Ayerst	Solution	sterile cartridge

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EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
edetate disodium	0.01		IM - intramuscular	meperidine hydrochloride & promethazine	Mepergan	Wyeth-Ayerst	Solution	sterile cartridge
edetate disodium	0.01		IM - intramuscular	gentamicin sulfate USP	Garamycin Injectable	Schering Corporation	Solution	vial
EDTA	trace		SC - subcutaneous	Varicella Virus Vaccine Live (Oka/Merck)	Varivax	Merck & Company	Lyophilized	single-dose vial
egg lecithin	1.2	7.0 - 8.5	IV - intravenous	propofol	Diprivan ® Injection 1%	Zeneca Pharmaceuticals	Emulsion	ampules
ethanol	10.0 (v/v)	5.6 - 6.0	IV - intravenous	sterile carmustine (BCNU)	BiCNU	Bristol-Myers Squibb-Oncology	Lyophilized	single dose vials
ethanol	70.0 (v/v)		IV - intravenous	nitroglycerin injection, USP	Nitro-Bid ®	Marion Merrell Dow Inc.	Solution	vials
ethanol (96%)	5.2 (v/v)		IV - intravenous	melphalan hydrochloride	Alkeran for Injection	Glaxo Wellcome	Freeze-dried	single use vial
ethyl alcohol	10.0	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra I.V. Infusion	Glaxo Wellcome	Solution	multidose vials
ethyl alcohol	10.0		IM - intramuscular	diazepam	Valium Injectable	Roche Products	Solution	ampuls
ethyl alcohol	10.0	~10.0	IV - intravenous	trimethoprimand sulfamethoxazole	Septra IV Infusion	Glaxo Wellcome	Solution	vial
ethyl alcohol	10.0	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra IV Infusion ADD	Glaxo Wellcome	Solution	vial
fetal bovine serum	trace		SC - subcutaneous	Varicella Virus Vaccine Live (Oka/Merck)	Varivax	Merck & Company	Lyophilized	single-dose vial
formaldehyde	≤0.02		IM-intramuscular	Diphtheria and Tetanus Toxoids and Acellular	Acel-Imune	Lederle Laboratories	Suspension(afi	multidose vial
formaldehyde	≤0.02	~ 7.4	IM-intramuscular	Diphtheria & Tetanus Toxoids and Acellular	Tripedia ™	Connaught Laboratories, Inc.	Solution/Suspe	vial
formaldehyde	<0.0125		ID - intradermal	Mumps Skin Test Antigen (suspension killed	MSTA ™	Connaught Laboratories, Inc.	Suspension	vial
formaldehyde	<0.001		IM - intramuscular	combination of purified tetanus & diphtheria	Diphtheria & Tetanus Toxoids & Pertussis	SmithKline Beecham Pharmaceuticals	Suspension	vials
formaldehyde	≤0.02		IM - intramuscular	combines diphtheria & tetanus toxoids	Diphtheria & Tetanus Toxoids & Pertussis	Connaught Laboratories, Inc.	Turbid Liquid	vial
formaldehyde	≤0.02		IM - intramuscular	Diphtheria & Tetanus Toxoids and Pertussis	Tetramune, (DTP-HbOC)	Lederle Laboratories	Suspension(afi	vial
formaldehyde	0.0027		SC - subcutaneous	poliovirus vaccine inactivated; type 1 (Mahoney), type 2	Poliovax ®	Connaught Laboratories, Inc.	Suspension	ampoules
formaldehyde			IM - intramuscular	hepatitis B vaccine (recombinant)	Recombivax HB	Merck & Company	Suspension	single dose vial
formaldehyde	≤0.04		SC - subcutaneous	combination of type 1 (Mahoney), type2 (MEF-1),	Ipol ™	Connaught Laboratories	Suspension	syringe
formaldehyde	<0.01		SC - subcutaneous	Japanese encephalitis virus vaccine	Jc-Vax ™	Connaught Laboratories, Inc.	Lyophilized	vial
fractionated egg yolk	1.2	~8.0	IV - intravenous	diazepam emulsified injection	Dizac	Ohmeda PPD, Inc.	Emulsion	single dose vial
fractionated soybean	15.0	~8.0	IV - intravenous	diazepam emulsified injection	Dizac	Ohmeda PPD, Inc.	Emulsion	single dose vial

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ATTACHMENT F - COMPILATION

TAB 11

definite bearing on the usefulness of any column packing prepared. The performances of the seven supports mentioned previously were examined under the same operating conditions. The supports that can be used for lightly loaded packings are: glass beads, Gas Chrom-P, and Chromosorb W-HMDS. The other four supports cannot be used for lightly loaded column packing since their interaction with the antihistamines causes excessive peak tailing.

The hydrogen flame detector used in conjunction with the 0.010-in. stainless capillary column would not respond to compounds with boiling points above 330°. This limitation prevented evaluation of this column for the analysis of these antihistamines.

The 100-ft. 0.065-in. copper open tubular column was coated with XF-1150 and evaluated using the above group of antihistamines. The Sr^{90} ionization detector was used with a column flow of 36 ml./minute. The retention times obtained were comparable to the 6-ft.-XF-1150 packed column, but the peak base widths were considerably wider. Because of this increase in base width, the 0.065-in. column was less efficient than the 6-ft. packed column.

A 250-ft. 0.065-in. column wound on a $1^1/_4$-in. diameter mandrel has been reported to be more efficient than a packed column (15). There are two possible reasons why efficiency was less than previously reported: (*a*) the column was shorter (100 ft.), and (*b*) the winding configuration was markedly different. The column was wound on a $1^1/_4 \times {}^1/_4$-in. bar which resulted in a definite flattening of the tube around the edge of the bar.

CONCLUSIONS

The antihistamines investigated, except for meclizine, can be separated, identified, and concentration estimated using the Carbowax 20M, PDEAS, and XF-1150 columns described. The PDEAS column is the most efficient of the three for the analysis of antihistamines.

The usefulness of the 0.010-in. capillary and the 0.065-in. open tubular columns cannot be properly evaluated until the mentioned limitations are removed.

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Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones

By C. RIFFKIN, R. HUBER, and C. H. KEYSSER

Steroid hormones may be administered parenterally in high concentrations as oil solutions. In this form they exhibit a prolonged action and reduce the number of injections required. To accommodate the demand for increasingly greater concentrations of hormones in solution, castor oil in combination with other suitable oil-miscible solvents, has been found to fulfill a need. The development of several formulations together with the results of animal testing, as well as clinical trials in humans, attest to the acceptability of this oil for the purposes intended.

FIXED OILS are included in the "United States Pharmacopeia XVI" as nonaqueous vehicles for injection and are characterized as being of vegetable origin, essentially odorless, and without suggestion of rancidity. They must also comply with certain measurable physical limits specified for the saponification, acid, and iodine values.

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After subcutaneous injection, Deanesly and Parkes (1) observed the persistence of olive oil and castor oil in animal tissue. Comparing other oils Brown, *et al.* (2), reported that sesame and corn oils were superior to cottonseed and peanut oils because they were less irritating, less antigenic, more quickly released from tissue, and possessed superior physical properties.

More recently the use of steroid hormone medication has expanded considerably. Due to limited water solubility, hormones have been administered as aqueous suspensions or solutions in oil. It has been claimed that the latter provided the slow release preferred in cyclical

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TABLE I.—ANALYSIS OF COMMERCIAL OILS AND COMPARISON TO U.S.P. XVI SPECIFICATIONS

Oil	Lot No.	ml. 0.02 *N* NaOH Equiv. to Free Fatty Acid in 10-Gm. Sample	Sapon. Value	Iodine Value
Castor Oil	U.S.P. specs.	35.0[a]	179–185	83–88
	23946	14.0	183.3	84.8
	25589	4.6	179.8	87.0
	23463	7.9	182.7	84.5
	33742	9.2	180.4	84.2
Sesame Oil	U.S.P. specs.	3.0	188–195	103–116
	23549A	0.5	189.6	106.9
	26953	1.4	194.0	111.8
	33646	0.75	189.6	104.7
	29981	0.45	191.7	108.2
Cottonseed Oil	U.S.P. specs.	2.0	190–198	109–116
	49684	...	195.9	111.8
	44441	...	196.3	113.1
Corn Oil	U.S.P. specs.	2.0	187–193	102–128
	52148	1.0	194.5	119.1
	36716	1.2	191.4	124.4
	33436	1.2	189.3	125.0
	33715	1.0	189.3	123.0
Peanut Oil	U.S.P. specs.	2.0	185–195	84–100
	22160	1.2	192.0	94.4
	20993	1.4	191.7	93.2
	33622	0.8	193.1	87.8
	26147	1.2	190.4	93.9

[a] The U.S.P. specifies that the titration of free fatty acids in oral grade castor oil shall not exceed 7 ml. of 0.1 *N* NaOH which is equal to 35.0 ml. of 0.02 *N* NaOH.

TABLE II.—SOLUBILITY OF STEROIDS IN U.S.P. OILS AT 25°

Steroid	mg./ml. Castor Oil	Sesame Oil	Peanut Oil
17-Hydroxyprogesterone caproate	55.6	23.4	27.9
Testosterone	38.6	5.4	8.1
Estradiol valerate	60.6	16.1	18.8
Progesterone	52.0	22.9	23.5

therapy (3). Using withdrawal bleeding in human females as the criterion, Master, *et al.* (4), compared the duration of action of an aqueous suspension of progesterone with an oil solution, and confirmed the superiority of the latter. The prolongation of activity was generally related to storage in the fatty depots of the body (5).

In 1952 Junkmann (6) determined that a testosterone ester dissolved in sesame oil prolonged the androgenic effects in castrated rats. Davis and Wied (7) demonstrated that prolonged activity was also obtained in humans when oil solutions of a progesterone derivative were injected. There was still a limiting factor, however, in that only a relatively small amount of hormone could be dissolved in the traditional oils. To increase the solvent power of the oil it was necessary to add compatible and nonirritating cosolvents. Such additions consisted of benzyl benzoate, benzyl alcohol, ethyl lactate, ethyl oleate, etc. The U.S.P. recognized the need for such "other vehicles," with the restrictions that they must be safe in the volume of injection administered, and that they should not interfere with the therapeutic efficacy of the preparation or its testing.

Demand for increased hormone concentrations per dose, furthered the search for an acceptable oil with greater solubilizing power *per se*. Boschann (8) in 1954, observed that 17-hydroxyprogesterone caproate in a castor oil–ethyl lactate vehicle was well tolerated. In addition, private communications from clinicians in West Germany[1] reported good tolerance to Proluton-Depot containing a castor oil–benzyl benzoate vehicle. Since then other hormones have been used as solutions in ricinoleic acid esters, as well as in castor oil (9–11). Accordingly, an investigation was undertaken into the suitability of castor oil as a vehicle for parenteral administration of steroid hormones.

METHODS AND RESULTS

Representative samples of U.S.P. oils obtained from commercial sources were tested in accordance with the official method for free fatty acid content, saponification, and iodine values. The results are listed in Table I along with the U.S.P. XVI specifications for these oils.

Solubility of selected steroids in various oils was determined in the following manner. An excess of steroid was stirred for 4 hours at room temperature (25°) in the test oil, after which the undissolved solids were removed by filtration, and the clear solution assayed for steroid content. Table II shows the results obtained.

An attempt was made to reduce the free fatty acids in castor oil by treatment with alumina and anhy-

[1] Dr. Napp, Universitats-Krankenhaus, Hamburg; Dr. Pots, Humboldt-Universitat-Charite Frauenklinik, Berlin; Dr. Prill, Universitats-Frauenklinik, Wurzburg; and Dr. Rauscher, Universitats-Frauenklinik, Vienna.

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TABLE III.—ABSORPTION OF OIL FROM ANIMAL MUSCLE[a]

Days after Injection	Oil	ml. 0.02 N NaOH Equiv.	Residual Oil in Muscle (estd.)
1–3	Castor oil (aged)	50	1 day —50% 3 days—20%
1–3	Castor oil U.S.P.	13	1 day —30% 3 days—10%
1–3	Sesame oil U.S.P.	1.4	1 day —30% 3 days—30%
7–60	All oils	...	Declining 10 to 2%

[a] 1 ml. injected into back muscle of rabbit.

drous sodium sulfate. Three grams of dried, powdered, amorphous aluminum oxide (Merck No. 1097) and 6 Gm. of anhydrous sodium sulfate, reagent grade, were suspended in 120 ml. of oil and heated at 80° under a blanket of nitrogen for 1.5 hours. After allowing the oil to cool to room temperature, the solids were filtered off and the acids titrated in the usual manner. A significant reduction in free fatty acid was not obtained.

The absorption characteristics of oils with varying fatty acid content were examined and compared on a biological basis. Aged castor oil with a high free fatty acid content was compared to fresh U.S.P. castor oil with a low acid content and U.S.P. sesame oil by injecting 1 ml. of oil into the back muscles of rabbits, approximately 2 in. from the iliac crest. A rotational pattern of injection was used and the oil samples were stained to aid visibility in the tissues. The animals were sacrificed and the muscles excised and examined grossly. The results were averaged and appear in Table III.

The test disclosed that oil migrated or was carried to the fascia, and very small amounts remained for 60 days. Localized degeneration produced by the high acid value castor oil was essentially healed in 7 days, and the low acid value castor oil appeared to be no more irritating than sesame oil.[3]

In a specific test for irritation 0.25 ml. of the above oil samples were also injected into the *vastus lateralis* muscles of rabbits. After 2 days the animals were sacrificed and the injected muscles examined grossly for evidence of irritation. It was found that the castor oil containing a high level of free fatty acid produced a lesion size measuring approximately 121 mm.[2]. The lesion itself was characterized mainly by degeneration of local tissue without necrosis. Castor oil with low free fatty acid and sesame oil, on the other hand, produced no measurable lesion at the injection site.

Combinations of benzyl alcohol and benzyl benzoate with both castor oil and sesame oil were also injected into the *vastus lateralis* muscles of rabbits and Table IV lists the lesion sizes produced.

Solutions which were formulated for clinical trials in humans were prepared by dissolving the steroid hormones in appropriate vehicles at 60° under nitrogen. The solutions were then filtered through a coarse sintered-glass filter with the aid of nitrogen pressure, filled into vials, and sterilized by autoclaving for 2 hours at 121° (15 lb. steam pressure). The products were then submitted for assay, safety, and animal muscle irritation testing prior to release for clinical investigation.

[3] Due to the apparent increase in free fatty acids with aging, subsequent work utilized fresh oils which required for neutralization less than 3 ml. of 0.1 N NaOH (15 ml. of 0.2 N NaOH) per 10 Gm. of sample.

DISCUSSION

Throughout the investigation it was desirable to have a reference oil to serve as a basis for comparison. Since sesame oil is universally accepted as a parenteral oil vehicle, it was chosen as the "standard" vegetable oil to be compared to castor oil, with and without other cosolvents. The physical, chemical, and biological properties of sesame oil are well documented and require no comments here.

Chemically, castor oil consists of the triglycerides of ricinoleic acid, together with small quantities of glycerides of other acids. The quantitative composition is given by Eckey (12) as follows: ricinoleic acid 87%, oleic acid 7.4%, linoleic acid 3.1%, dihydroxyricinoleic acid 0.6%, and miscellaneous acids 2.4%. Two grades are commonly recognized in this country—U.S. No. 1 which is cold pressed oil, and U.S. No. 3 which is oil extracted from the pressed cake. Only the former is used for medicinal purposes.

The high viscosity of castor oil compared to other vegetable oils is undoubtedly related to hydrogen bonding and it is probably the hydroxy groups which contribute to the greater polarity and superior solvent power of the oil. As indicated in Table I, the saponification and iodine values of commercial castor oil appear to be slightly lower than the U.S.P. XVI limits for oils used for injection. On the other hand, the content of free fatty acids even in fresh oil, varies considerably and exceeds the traditional limits for injectable oils. The significance of this is somewhat obscure, although "Remington's Practice of Pharmacy, 12th edition," page 387, states "a low free fatty acid content is essential since it indicates a fresh and pure product and not one that is likely to have become old and heavily contaminated with bacterial products."

Despite better solubility of steroids in castor oil, other cosolvents were necessary to dissolve the

TABLE IV.—LOCAL IRRITATION PRODUCED IN RABBIT MUSCLE BY INJECTION OF VARIOUS OIL VEHICLES[a]

Identification	Composition	Lesion size, mm.[2]
SHY-47-2	Sesame oil 98% Benzyl alcohol 2%	61
SHY-47-4	Castor oil 98% Benzyl alcohol 2%	Too small to measure
SHY-47-3	Sesame oil 95% Benzyl alcohol 5%	506
SHY-47-5	Castor oil 95% Benzyl alcohol 5%	106
SHY-14-2	Sesame oil 65% Benzyl benzoate 35%	291
SHY-14-5	Castor oil 65% Benzyl benzoate 35%	184
SHY-47-6	Sesame oil 63% Benzyl benzoate 35% Benzyl alcohol 2%	207
SHY-47-7	Castor oil 63% Benzyl benzoate 35% Benzyl alcohol 2%	262
SHY-14-3	Sesame oil 50% Benzyl benzoate 50%	291
SHY-14-6	Castor oil 50% Benzyl benzoate 50%	158

[a] A 0.25-ml. quantity of the oil vehicle was injected into the *vastus lateralis* muscle of the rabbit. Two days later the muscle was excised and the lesion size measured in mm.[2].

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increasingly higher concentrations required by therapeutic regimens. Often these materials contributed additional advantages. For example, the addition of benzyl alcohol or benzyl benzoate to castor oil resulted in a lower and more favorable viscosity, making it easier to inject. Also, benzyl alcohol was an effective preservative and local anesthetic.

The nature of the irritative response depended on the particular hormone, its concentration in the formulations, and/or the composition of the vehicle. Although rabbit muscles are more sensitive than human muscles, they were selected primarily because local changes in the muscle were observed easily. It was not always possible, however, to correlate muscle irritation in animals to that of humans.

A numerical assignment to lesion size was used solely as a convenience for grading response. The numbers alone do not adequately describe the nature of the response, however. More completely it is characterized by the amount of hemorrhage and edema and the incidence, degree, and extent of local degeneration produced by the injection. A slight, reversible irritative response may cover a large area and a severe irreversible one may be comparatively small. A decrease in the size of the degenerated area indicates a reversible condition. The presence of necrosis, which is the most damaging situation, means that the cellular structure was destroyed and repair must take place. The debris must be removed and the original cellular mass in the area replaced with fibrous connective tissue. The extent of this fibrosis or formation of scar tissue gives an index of the amount of irreversible damage. Fortunately necrosis was not encountered, indicating the lack of permanent muscle damage. Since these changes take time, final assessment of the effects of an injection in the muscle frequently required observation for 7 days or longer.

It is unfortunate that pain cannot be measured by any known method of animal testing. The animal usually does not respond unless the painful stimulus is marked. Furthermore, the pain caused by injection into human muscle is not usually proportionate to the irritation produced either in animal muscle or in human muscle. Realizing that these limitations are inherent in animal test methods, it remained for final acceptability to be determined in man.

When it was discovered that 17-hydroxyprogesterone caproate possessed high progestational activity, potencies of the order of 65 mg./ml. were used. By increasing the dose, additional prolongation of action was obtained, and eventually concentrations of the order of 250 mg./ml. were required. Such a solution in sesame oil produced acceptable animal muscle tolerance, but the pain and local reaction in humans was so great as to prohibit the adoption of the formulation as a commercial product (see Table V, Lot Pr. 142-53/15-10).[8] Solutions were also prepared using castor oil as the vehicle, and Table V lists the formulations tested and the results obtained. Information obtained from the clinical trials (14–21) attested to the acceptability and safety of the adopted formulations.

Inherent in the development of an acceptable formulation of 17-hydroxyprogesterone caproate was the required development of a suitable assay method. This was accomplished by Roberts and Florey (13) using paper-strip chromatography.

Since estrogens are more potent than progestogens and require less per dose, an acceptable formulation of estradiol valerate was easier to prepare. Besides use in estrogen therapy, estradiol valerate has found utility in the treatment of carcinoma, and for that purpose high dosages were required. Concentrations were increased from 10 to 40 mg./ml. and

[8] Reactions in excess of 5–6% were considered unacceptable.

TABLE V.—EVALUATION OF 250 mg./ml. 17-HYDROXYPROGESTERONE CAPROATE SOLUTIONS IN VARIOUS OIL VEHICLES

Vehicle Composition	Animal Muscle Lesion Size, mm.[a]	Lot Number and Remarks on Clinical Testing
Sesame oil 50% Benzyl benzoate 50%	1049	Pr.142-53/15-7—238 injections, 20.6% reactions, rejected
Castor oil 58% Benzyl benzoate 40% Benzyl alcohol 2%	691	Pr.142-53/15-8—270 injections, 23.2% reactions, rejected
Sesame oil 60% Benzyl benzoate 35% Benzyl alcohol 5%	697	Pr.142-53/15-10—189 injections, 10.7% reactions, rejected
Castor oil 54% Benzyl benzoate 46%	258	Pr.142-53/15-11—503 injections, 4.2% reactions, accepted
Castor oil 52% Benzyl benzoate 46% Benzyl alcohol 2%	633	Pr.142-53/15-13—924 injections, 1.3% reactions, accepted

[a] Injection of 0.25 ml. into *vastus lateralis* muscle of rabbits and lesion size determined 2 days after injection.

TABLE VI.—EVALUATION OF ESTRADIOL VALERATE IN VARIOUS OIL VEHICLES

Composition	Animal Muscle Lesion Size, mm.[a]	Lot Number and Remarks
20 mg./ml. in Castor oil 78%, Benzyl benzoate 20%, Benzyl alcohol 2%	197	Es.31-53/15-B—Commercially available
30 mg./ml. in Sesame oil 60%, Benzyl benzoate 40%	306	DEK-98-2—Not tested clinically; dosage increased to 40 mg./ml.
30 mg./ml. in Castor oil 80%, Benzyl benzoate 20%	194	Es.31-53-V—Not tested clinically; dosage increased to 40 mg./ml.
40 mg./ml. in Sesame oil 65%, Benzyl benzoate 30%, Benzyl alcohol 5%	803	SHX-94-4—Too irritating; not tested clinically
40 mg./ml. in Sesame oil 58%, Benzyl benzoate 40%, Benzyl alcohol 2%	496	Es.31-53-8—201 injections, 23.2% reactions, rejected
40 mg./ml. in Castor oil 58%, Benzyl benzoate 40%, Benzyl alcohol 2%	250	Es.31-53-A—826 injections, 2.67% reactions (all mild), accepted

[a] Injection of 0.25 ml. into *vastus lateralis* muscle of rabbits and lesion size determined 2 days after injection.

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again formulations containing castor oil in the vehicle proved to be less irritating than similar preparations containing sesame oil. Physically and chemically both oil solutions were stable. Based on acceptable preliminary data, formulations such as those listed in Table VI were prepared and tested. Acceptability in humans was confirmed by clinicians and described in the literature (22, 23) and in case reports.[4]

SUMMARY

1. The development and testing of parenteral steroid hormone formulations has been described, using castor oil as a vehicle.

2. After ascertaining stability and animal muscle irritation, selected formulations were evaluated in humans. They exhibited a prolonged action, were effective and well tolerated.

3. Examples of commercially available products are the estrogen, estradiol valerate[5] at 20 mg./ml. and 40 mg./ml., and the progestogen, 17-hydroxyprogesterone caproate[6] at 250 mg./ml.

[4] Case reports: estradiol valerate, 20 mg./ml., in castor oil 78%, benzyl benzoate 20%, benzyl alcohol 2%—90 injections in 46 patients. Two mild local reactions. Estradiol valerate 40 mg./ml. in castor oil 58%, benzyl benzoate 40%, benzyl alcohol 2%—51 patients. Number of injections not completely tabulated. One report is in press.

[5] Marketed as Delestrogen by E. R. Squibb & Sons, New York, N. Y.

[6] Marketed as Delalutin by E. R. Squibb & Sons, New York, N. Y.

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Isolation of Marrubiin, a Sterol, and a Sesquiterpene from *Marrubium vulgare*

By HAROLD J. NICHOLAS*

A simple column chromatographic method for isolating the bicyclic diterpene marrubiin from acetone and ethanol extracts of *Marrubium vulgare* L. is described. An unsaturated sterol of the stigmastanol series, present in esterified form, and a sesquiterpene ($C_{15}H_{22}O_2$) have been isolated from the extracts.

IN PREPARATION for radioactive tracer work on the biosynthesis of marrubiin it was necessary to examine extracts of the plant for associated terpenoid substances. A convenient column chromatographic method was therefore devised for separating relatively pure marrubiin from crude acetone extracts. Two new terpenoid substances were detected in the extracts.

EXPERIMENTAL

Materials and Methods.—Ground *M. vulgare* L. was obtained from the Wunderlich-Diez Corp., Hasbrouck Heights, N. J.[1] This material was exhaustively extracted with hot acetone or hot ethanol. Either solution on removal of solvent by distillation (the last stages *in vacuo*) yielded black, viscous material which was used for further examination. Melting points were determined on a Fisher-Johns melting point apparatus. Optical rotations (in $CHCl_3$) and C—H analyses were determined by Drs. G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England. An infrared spectrum of the unidentified diterpene was determined on a Perkin-Elmer spectrophotometer by the KBr disk method.[2] An infrared spectrum of the sterol was determined in chloroform solution in a 0.1-mm. sealed cell, compensated with $CHCl_3$, on a Beckman IR-4 recording infrared spectrophotometer,[3] and by the KBr disk method. The

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[1] This firm has given assurance that the material investigated was *M. vulgare* or white horehound, not *Ballota hirsuta* (black horehound).

[2] We are indebted to the Department of Pathology, University of Kansas, for this determination.

[3] Determined by Sadtler Research Laboratories, Philadelphia, Pa.

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ATTACHMENT F - COMPILATION

TAB 12

Parenteral Formulations of Small Molecules Therapeutics Marketed in the United States (1999)—Part I

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Overview

The chemical structure of a molecule determines the potential successful formulation approaches available to the parenteral scientist. However, there is no comprehensive listing of parenteral products with the chemical structure and formulation. A review of domestically marketed injectable product formulations of small molecule therapeutics is presented herein with the intent of compiling a comprehensive source of public information for the formulation scientist. The compilation lists the drug name, marketed name, chemical structure of the drug, marketed injectable formulation, preadministration preparation, route of administration, company and the clinical indication (1–7).

One purpose of this compilation is to assist the formulation scientist in being able to look at a drug's chemical structure and then be able to determine possible formulation approaches. This compilation will also be useful for those interested in knowing what additives are currently used in injectable products and at what concentrations they are administered in practice. This compilation only focuses on marketed formulations and does not delve into the subject of preclinical or drug discovery formulations associated with early-stages pharmacokinetics or proof-of-concept pharmacodynamics, where the formulation scientist is not bound by regulatory constraints.

There are a few published reviews on parenteral formulations (8) and in an excellent review article (9) Lilly scientists, Sweetana and Akers, discuss the various formulation approaches with detailed tables of examples. In a compendium of excipients for parenteral formulations (10) Genentech scientists, Powell, Nguyen and Baloian, list the acceptable excipients as well as their percent's within the formulations, route of administration and pH. The compilation herein is an additional resource to the parenteral scientist by presenting the chemical structure and the formulation in a side-by-side fashion. An examination of this compilation reveals many examples of injectable formulation techniques to improve solubility or provide a sustained release. The next few sections highlight various formulation approaches with specific examples and tables, as well as general discussions of parenteral formulations.

Editor's Note: This review article on Injectable Products is being published in several parts. The next installment(s) will appear in subsequent issues of the *Journal*.

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Introduction

The word "parenteral" is Latin for "other than intestine," thus by definition the parenteral sciences not only includes injectable products but also transdermal, pulmonary, nasal, ophthalmic, and buccal routes of administration. However, in practice, parenteral usually refers to injectable products. Recently we have seen the commercialization of previously academic pursuits such as controlled-release formulations using microspheres, liposomes and polymeric gels, longer *In vivo* circulating times using PEGylated liposomes (also known as stealth liposomes) and PEGylated proteins, and new excipients such as cyclodextrin derivatives used as complexing agents for increasing water solubility of poorly soluble drugs. We have also seen the commercialization of injection devices such as prefilled syringes, dual chamber syringes containing solid drug and a liquid for reconstitution, and will likely soon see needle-free injectors and pocket-size infusion pumps.

Injectable Formulations

Two key aspects of any successful injectable formulation are: 1) to achieve the required drug concentration, and 2) the drug must be chemically and physically stable in order to have a sufficient shelf-life, which is generally considered to be the time for 10% degradation. The ideal injectable formulation, from an *in vivo* tolerability point-of-view, is isotonic with physiological fluids and a neutral pH (i.e., PBS: phosphate buffered saline, 0.01M sodium phosphate with 0.135M NaCl and 0.003M KCl, pH 7.4). However, in many instances the drug does not have sufficient water solubility at pH 7.4, and thus the formulation scientist must use a wide variety of solubilization techniques. If stability is insufficient to provide a two-year shelf-life, then the formulation scientist must either change the solution conditions to achieve both the solubility and stability requirements or develop a lyophilized product. This manuscript focuses on solubilization techniques for small molecules, and will not focus on stability or stabilization techniques.

I. Solubilization Techniques

1. pH Adjustment and Salts

If the drug molecule is ionizable, then pH adjustment can be utilized to increase water solubility since the ionized molecular species has higher water solubility than its neutral species. Indeed, the most common solubilization technique is pH adjustment and weak acids are normally formulated at

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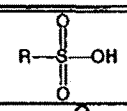
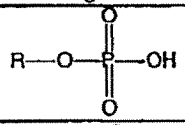
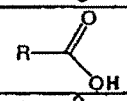
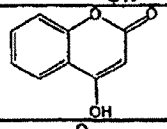
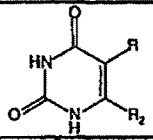
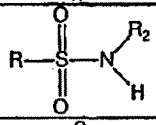
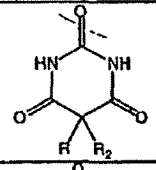
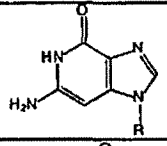
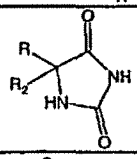
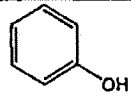
Table I. Examples of Weak Acid Chemical Functional Groups, Their Approximate pKa's and Formulation pH's.

Functional Group Name	Functional Group Structure	Functional Group pKa	Formulation pH	Selected Examples
Sulfonic acid		<1	Neutral	Aztreonam
Phosphate ester		2	Neutral	Fosphenytoin Bethamethasone Dexamethasone Fludarapine
Carboxylic acid		2.5-5	5-8	Penicillin Ketorolac
4-Hydroxy coumarin		~ 8	8.3	Warfarin
Uracil		~ 8	9.2	Flurouracil
Sulfonamide		7-9	9-11.6	Acetazolamide Clorothiazide Diazoxide
Barbituric acid		7-9	9.5-11	Methohexital Pentobarbital Phenobarbital Secobarbital
Guanine		2.2, 9.4	11	Acyclovir Gancyclovir
Hydantoin		~ 10	10-12	Phenytoin
Phenol		8-10	10.5 emulsion organic organic	Liothyronine Propofil Etoposide Teniposide

pH > 5 (Table I), weak bases at pH < 7 (Table II). Zwitterionic molecules have multiple ionizable groups and can be either cationic, anionic or neutral (positive and negative charges cancel each other, for an overall net neutral molecule) and are usually formulated at a pH in which the drug is ionic (Table III). For example, both ciprofloxacin and sufentanil have a carboxylic acid and an amine, but are formulated as the cation at pH < 7. On the other hand, both ampicillin and cephapirin have a carboxylic acid and an amine or pyridine, but are formulated as the anion at pH > 5.

The range in pH is quite broad and is between pH 2–12, and thus any molecule with a pKa between 3–11 can be potentially solubilized by pH adjustment. However, when using extremes in pH, care must be taken to minimize buffer capacity in order for the formulation to be *in vivo* compatible. When given intravenously, the formulation components are quickly diluted by the flow of blood and neutralized by the buffer capacity of blood. When given via intramuscular injection, the rate of dilution is reduced but rapid enough to still be able to inject in the range pH ~ 3–11. However,

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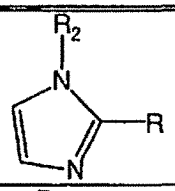
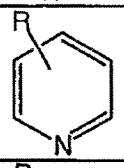
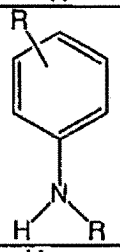
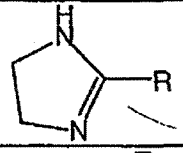
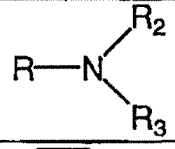
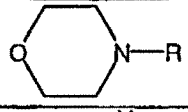
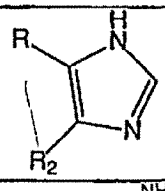
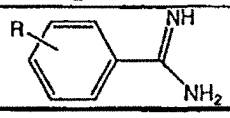
Table II. Examples of Weak Base Chemical Functional Groups, Their Approximate pKa's and Formulation pH's.

Functional Group Name	Functional Group Structure	Functional Group pKa	Formulation pH	Selected Examples
1H-Imidazole		~ 4-6	< 6	Miconazole Ondansetron
Pyridine		~ 5	2-4	Amronone Milrinone Papaverine Pyridoxine
Aniline		~ 5	2-6	Metoclopramide Minocycline (Procaine Procainamide also have a tertiary amine)
4,5-Imidazoline		~ 6	3-4	Tolazoline
Amine		7-10	3-7	Atenolol Codeine Daunorubicin Morphine Verapamil
N-Alky morpholine		7.4	< 5	Doxapram
Imidazole		~ 7	3-6.5	Cimetidine Dacarbazine Phentolamine
Amidine		~ 9-11	< 8	Pentamidine

when given subcutaneously the rate of dilution is reduced further with more potential for irritation at the injection site and thus the range is pH 3–6. For example, chlordiazepoxide is administered intravenously or intramuscularly and formulated at pH 3 with 20% propylene glycol and 4% TWEEN 20. Phenytoin sodium is administered either intravenously or intramuscularly and formulated at pH 10–12 with 40% propylene glycol and 10% ethanol. Subcutaneous formulations are slightly acidic such as methadone at pH 3–6, and levorphanol at pH 4.3.

Water-soluble salt forms (i.e., sodium salts of weak acids, or hydrochloride salts of weak bases) utilize the same principle of ionization, and are often the marketed form of the drug (Table IV). The most common cationic counterion is sodium which accounts for > 90% of the cations, and there are three meglumine salts, while only one salt each of

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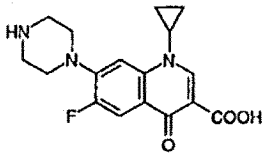
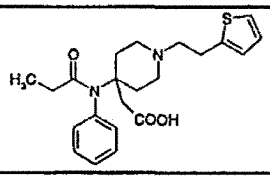
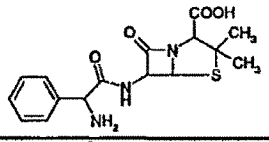
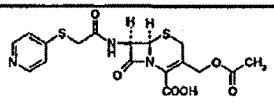
Table III. Examples of Zwitterionic Drugs, Approximate pKa's and Formulation pH's.				
Selected Example	Chemical Structure	Acidic Functional Group Name and pKa	Basic Functional Group Name and pKa	Formulation pH (ionic state)
Ciprofloxacin		Carboxylic acid ~4	Aniline ~4 Amine ~9	3-4 (Cationic)
Sufentanil		Carboxylic acid ~4	Amine ~8	3.5-6 (Cationic)
Ampicillin		Carboxylic acid ~4	Amine ~8	8-10 (Anionic)
Cephapirin		Carboxylic acid ~3	Pyridine ~5	6-8 (Anionic)

the cations potassium, tromethamine and calcium. There are many more anionic counterions and the most common is the hydrochloride salt followed by sulfate, mesylate, maleate and tartrate. When a salt is dissolved in non-buffered water, the resulting pH is generally ~2 pKa units away from the pKa, because protons are either added to (salt of a weak base) or taken away from water (salt of a weak acid). For example, gancyclovir is a weak acid with $pKa_2 = 9.4$ and dissolving its sodium salt in water results in pH ~ 11.

In order to maintain a desirable pH range, many formulations that utilize pH adjustment also use buffers to control pH (Table V). Buffers span the range of pH 2.5–11 and

Table IV. List of Counter Ion in Salt Forms of Parenteral Drugs.			
Cation	Number of instances	Anions	Number of instances
Sodium	55	Hydrochloride	64
Meglumine	3	Sulfate	16
Potassium	1	Mesylate	8
Calcium	1	Chloride	7
Tromethamine	1	Maleate	6
		Tartrate	6
		Citrate	5
		Bromide	5
		Lactate	5
		Acetate	2
		Phosphate	2
		Besylate	1
		Hydrobromide	1
		Fumarate	1
		Gluceptate	1
		Gluconate	1
		Glucuronate	1
		Lactobionate	1
		Salicylate	1
		Tosylate	1

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Table V. List of Buffers Used in Parenteral Formulations				
pH	Buffer (pKa's)	Concentration in Formulation, Molarity	Concentration Administered, Molarity	Route of Administration
2.5-4.0	Tartartic acid (2.9, 4.2)	0.04	0.04	IM, IV
3	Maleic acid (1.9, 6.2)	0.14	0.14	IM
3	Glycine (2.3, 9.6)	0.2	0.05	IV infusion
3.0-4.5	Sodium lactate/ Lactic acid (3.8)	0.17 0.02	0.17 0.085 0.02	IV IV infusion, SC
3-5	Ascorbic acid (4.2, 11.6)	0.02	0.01 0.02	IM IV
3.0-7	Sodium citrates/ Citric acid (3.1, 4.8, 6.4)	0.6 0.1	0.6 0.1	IM, IV, IV infusion, SC
4-6	Sodium acetate/ Acetic acid (4.75)	0.01	0.01	IV, SC
4-6.5	Sodium bicarbonate/ Carbonic acid (6.3, 10.3)	0.08	0.08 0.001	IM IV, IV infusion
4.2-6	Sodium succinate/ Succinic acid (4.2, 5.6)	0.04	0.005 0.04	IV infusion, SC
6	Histidine (1.8, 6.0, 9.2)	0.005 0.05	0.0005 0.05	IV infusion IM
6-7	Sodium benzoate/ Benzoic acid (4.2)	0.5	0.5	IV
3-8	Sodium phosphates (2.2, 7.2, 12.4)	0.08	0.08	IV, IV infusion IM
7.4-9.0	Tris(hydroxy-methyl)amino-methane (8.3)	0.01	0.01	IM, IV infusion Intra-arterially, Intrathecal
8.7-11	Sodium bicarbonate/ Sodium carbonate (6.3, 10.3)	0.01	0.01	IV, IV infusion, Intravitreal (Fomiversen)

IM = intramuscular
IV = intravenous
SC = subcutaneous

include citrates, acetates, histidine, phosphate, tris(hydroxymethyl)aminomethane, and carbonates. The buffer concentration must be high enough to maintain the desired pH, but must be balanced by *in vivo* tolerability considerations, and thus it is good practice to minimize buffer capacity of the administered formulation.

2. Mixed Organic/Aqueous Formulations

If pH adjustment alone is insufficient in achieving the desired solution concentration, then a combination of pH and organic solvent(s) is often employed. If the drug molecule is not ionizable then pH has no effect on solubility,

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but solubility enhancement can often be accomplished by a combination of aqueous and organic solvents (i.e., a cosolvent). The currently used organic solvents used in mixed organic/aqueous formulations are propylene glycol, ethanol, polyethylene glycol 300 or 400, cremophor EL, TWEEN 80, sorbitol, glycerin and dimethylacetamide (DMA) (Table VI).

As with any formulation additive, the concentration that is administered should be minimized to avoid any *in vivo* complications such as local irritation or precipitation at the injection site. Many cosolvent formulations are marketed using rather high concentrations of organic solvent, and are usually but not always diluted prior to injection. For example, propylene glycol is 50% of the fenoldopam marketed formulation, but is diluted to <1% for IV infusion. However, propylene glycol is ~70% of the oxytetracycline marketed formulation and is injected intramuscularly without dilution.

Similar to formulations using pH adjustment, of the three main routes of administration (i.e., intravenous, intramuscular and subcutaneous), the subcutaneous route has the most constraints when using cosolvent due to the reduced volume flow away from the injection site compared to intravenous and intramuscular. As a result, only three cosolvent products are administered subcutaneously and the amount of organic solvent is limited to ethanol 6% (dihydroergotamine), glycerin 32% (epinephrine), and propylene glycol 10% (hydralazine). Whereas, the intravenous bolus route can use ethanol up to 20% (paricalcitrol), PEG 300 up to 50% (methocarbamil), and propylene glycol up to 68% (phenobarbitol). The intramuscular route has similar *in vivo* constraints to the intravenous route, but can tolerate even more organic solvent (see section I.3, Totally Organic Solution Formulations).

Surfactant formulations seem to be on the increase with excipients Cremophor EL and TWEEN 80 leading the way. These formulations, in general, are supersaturated upon dilution and must be used soon after dilution into IV compatible fluids. For example, cremophor EL is 11% of the miconazole marketed formulation, but is diluted to 1% for IV infusion. Also, TWEEN 80 is 10% of the amiodarone marketed formulation, but is diluted to 0.4% for IV infusion. However, cremophor EL at 10% or TWEEN 80 at 25% can be administered by IV infusion (see section I.3).

3. Totally Organic Solution Formulations

Molecules that are non-ionizable (have pKa < 2, or pKa > 11) and non-polar are water insoluble with no effect of pH on solubility, and thus are the most challenging for the formulation scientist. These water-insoluble molecules can be formulated in 100% organic solvent, which is then usually but not always diluted prior to administration (Table VII). For example, busulfan is marketed in 33% dimethylacetamide and 67% PEG 400, but is diluted 10-fold prior to IV infusion. The lorazepam marketed formulation is 80% propylene glycol, 18% ethanol and 2% benzyl alcohol, but is diluted 2-fold for IV bolus injection, but not diluted for intramuscular injection. Paclitaxel is marketed with 51% cremophor EL and 49% ethanol, but is diluted 5- to 20-fold for IV infusion. Docetaxel is marketed in 100% TWEEN 80, but is diluted to 25% for IV infusion.

4. Cyclodextrins

Some molecules can be solubilized by forming an inclusion complex with a cyclodextrin. Cyclodextrins have a hydrophilic exterior and a hydrophobic interior core of specific dimensions, and thus molecules with a non-polar, aromatic or heterocyclic ring can potentially fit inside the core. Increased water solubility through molecular complexation with cyclodextrins has advantages over the cosolvent approach since upon dilution a 1:1 complex between cyclodextrin and drug will not precipitate, but a drug dissolved in a cosolvent often precipitates upon dilution. Two cyclodextrins have been accepted for human injectable use with the approval of alprostidol alfadex and itraconazole. Alprostidol alfadex is marketed as a lyophilized powder with α-cyclodextrin and is administered intracavernosally. Itraconazole was approved in April 1999 as a solution with 40% hydroxypropyl-β-cyclodextrin and is administered by intravenous infusion after a 2-fold dilution with saline (6). The next cyclodextrin likely to be approved is sulfobutylether-β-cyclodextrin, which is in the clinical formulation of ziprasidone for intramuscular injection (11).

5. Emulsions

Oil-soluble molecules are generally neutral uncharged and non-polar molecules, but can be formulated for intravenous administration by the use an oil-in-water emulsion. Emulsions can solubilize oil-soluble drugs since the drug partitions into the oil phase. A typical emulsion is composed of water with 10–20% soybean and/or safflower oil, 2% glycerol, 1% egg lecithin and pH 7–8, and is injected by either IV bolus or IV infusion. The only marketed emulsion formulation is propofol, which is in a typical emulsion composed of 10% soybean oil containing 10 mg/mL drug. The total parenteral nutrition (TPN) formulations are the lipid emulsions Intralipid and Liposyn, which are administered by intravenous infusion as nutritional supplements.

6. Prodrugs

Molecules which contain an alcohol, phenol, carboxylic acid, amine, hydantoin functional group can potentially be derivatized as a prodrug. Once the prodrug is administered *in vivo*, the promoiety is hydrolyzed by either esterases or phosphatases releasing the parent drug. Although prodrugs are normally associated with orally administered products for better oral bioavailability, many parenteral products are prodrugs (Table VIII).

The versatility of the prodrug approach is demonstrated with prodrugs that in design either increase or decrease water solubility. A water-soluble prodrug has an electronically charged promoiety, while a water insoluble prodrug has been derivatized to be a neutral molecule (see section II.7b). Recently, a few water-soluble phosphate ester prodrugs have been developed and marketed in order to replace the original formulations that contain high concentrations of organic solvent. The phenol-containing etoposide (etoposide phosphate) is derivatized as a water-soluble phosphate ester. Water-soluble phosphate esters are also prodrugs for alcohol-containing betamethasone, clindamycin, dexamethasone, fludarabine, hydrocortisone, and prednisolone. The hydan-

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Table VI. List of Cosolvents Used in Parenteral Formulations.				
Solvent	% in Marketed Formulation	% Administered	Route of Administration	Examples
Cremophor EL	11	1	IV infusion	Miconazole
	20	0.02-0.08	IV infusion	Tacrolimus
	50	0.1-1	IV infusion	Tenoposide
	50	18	Intravesical	Valrubicin
	51	2.5-10	IV infusion	Paclitaxel
	65	0.65-3.3	IV infusion	Cyclosporin
Dimethyl-acetamide (DMA)	6	0.012-0.12	IV infusion	Tenoposide
	33	3	IV infusion	Busulfan
Ethanol	5 (diluent for LP)	0.5	IV infusion	Medroxy-progesterone
	6	6	IM, SC, IV	Dihydroergotamine
	10	10	IM, IV	Diazepam
	10	2.5-10	IV	Digoxin
	10	10	IM, IV	Ketorolac
	10	10	IM, IV	Pentobarbital
	10	10	IM, IV	Phenobarbital
	10	10	IM, IV	Phenytoin
	13 (diluent)	10 (diluent)	IV infusion	Docetaxel
	20	20	IV	Paricalcitol
	25	1	IV infusion	Esmolol
	30	0.3-0.6	IV	Etoposide
	35	0.35-1.7	IV infusion	Cyclosporin
	42	0.084-0.84	IV infusion	Teniposide
	49	2.5-10	IV infusion	Paclitaxel
	50	18	Intravesical	Valrubicin
	80	0.08-0.32	IV infusion	Tacrolimus
	100 (diluent for LP)	10	IV infusion	Carmustine
Glycerin	15	15	IM, SC, IV	Dihydroergotamine
	25	25	IV infusion	Idarubicin
	32	32	SC	Epinephrine
N-methyl-2-pyrrolidone (Pharmasolve)	100 (diluent for LP)	100	Subgingival	Doxycycline
Monothio-glycerol	10	10	IM	Oxytetracycline
PEG 300	50	50	IM, IV	Methocarbamil
	60	0.6-1.2	IV	Etoposide
PEG 400	18	18	IM	Lorazepam
	18	9	IV	Lorazepam
	67	6-7	IV infusion	Busulfan

toin-containing phenytoin prodrug (fosphenytoin) is derivatized in a unique fashion as a water-soluble hydroxymethyl phosphate ester, which after *in vivo* enzymatic phosphate ester cleavage, the resulting hydroxymethyl intermediate quickly dissociates to phenytoin and formaldehyde (12). Other water solubilizing prodrug approaches are a succinate ester of the alcohol methylprednisolone, and a piperidine carbamate in irinotecan a prodrug for a phenol drug.

Prodrugs can also be used for stability reasons. For example, alatrofloxacin is the alanine-alanine dipeptide prodrug for the primary amine trovafloxacin which is unstable in solution. The prodrug alatrofloxacin is marketed as a solution at pH 3.4–4.3.

II. Sustained-Release Technlques

The research in controlled release during the 1970s has in the 1990s become a commercial realization with the approval of liposomal, polymeric microsphere and polymeric gel formulations. However, traditional approaches are still in use such as suspensions, prodrugs and oil depots.

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Table VI (cont.). List of Cosolvents Used in Parenteral Formulations.				
Solvent	% in Marketed Formulation	% Administered	Route of Administration	Examples
Propylene glycol (PG)	10	10	IM, SC	Hydralazine
	20 (diluent for LP)	20	IM	Chlordiazepoxide
	25	1	IV infusion	Esmolol
	30	30	IV	Paricalcitol
	35	35	IV	Etomidate
	40	40	IM, IV	Diazepam
	40	10-40	IV	Digoxin
	40	40	IM, IV	Pentobarbital
	40	40	IM, IV	Phenytoin
	50	50	IM	Dimenhydrinate
	50	5	IV infusion	Dimenhydrinate
	50	0.2	IV infusion	Fenoldopam
	60 (diluent for LP)	6	IV infusion	Medroxy-progesterone
	67-75	67-75	IM	Oxytetracycline
	68	68	IM, IV	Phenobarbital
	80	80	IM	Lorazepam
	80	40	IV	Lorazepam
Sorbitol	2	2	IM	Thiethylperazine
	4.5	0.1	IV infusion	Irinotecan
	5	0.2	IV infusion	Nicardipine
	7	0.7-2	IV	Diltiazem
	50	50	Intra-articular, Intralesional	Triamcinolone
TWEEN 80 (Polysorbate 80)	0.075	0.075	IM	Dexamethasone Acetate
	0.4	0.4	IV bolus	Calcitriol
	4 (diluent for LP)	4	IM	Chlordiazepoxide
	8	0.08-0.16	IV	Etoposide
	10	0.4	IV infusion	Amiodarone
	100	25	IV infusion	Docetaxel

IM = intramuscular
IV = intravenous
LP = lyophilized powder
PEG = polyethyleneglycol
SC = subcutaneous

7a. Suspension Formulations

Suspension formulations provide a sustained-release depot at the injection site that releases prodrug by dissolution. Suspensions used for sustained delivery are composed of a drug dispersion in either an aqueous or oil-based suspension (Table IX).

Almost all suspensions are administered intramuscularly, intralesionally or intra-articularly. The only subcutaneously administered suspension of a small molecule (many proteins are administered subcutaneous, e.g., human insulin) is epinephrine, which is administered every 6 hours and is formulated in 32% glycerin providing both rapid (drug in solution) and sustained activity (crystalline drug in suspension). The only sesame oil suspension is the anti-rheumatic aurothioglucose, which is administered intramuscularly every 1–4 weeks.

7b. Prodrugs in Suspension Formulations

Most of the other suspension formulations are aqueous-based and contain water-insoluble prodrugs which are lipophilic esters of alcohols. For example, hydrocortisone acetate and dexamethasone acetate are acetate esters of their alcohol-containing parent drug, and are administered intramuscularly, intralesionally or intra-articularly once every 1–3 weeks. The contraceptive medroxyprogesterone acetate is administered intramuscularly once every 13 weeks. Aqueous-based suspensions typically contain TWEEN 80 at ~0.75–4 mg/mL (0.4%) along with a suspending agent such

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Table VII. List of Non-Aqueous Solution Formulations for Parenteral Administration.

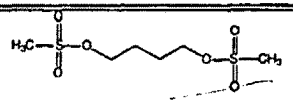
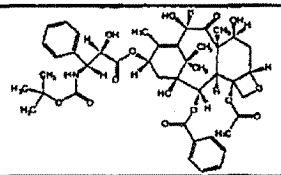
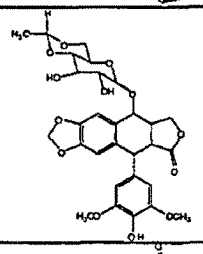
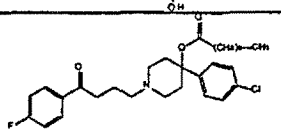
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Busulfan/ Busulfex		6 mg/mL N, N-dimethylacetamide **(DMA) 33%, PEG 400 at 67%**	Dilute with saline or dextrose 5% to 0.6 mg/mL.	IV infusion	Orphan Medical, Neoplastic
Cyclosporin/ Sandimmune	Cyclic peptide (11 amino acids), MW ~ 1200	50 mg/mL **Cremophor EL 65%, Ethanol 35%,** blanketed with nitrogen	Dilute with saline or dextrose 5% to 1-2.5 mg/mL (1 mL into 20-100 mL)	IV infusion over 2-6 hours	Novartis, Immuno-suppressant
Docetaxel/ Taxotere		40 mg/mL in **TWEEN 80** Provided **diluent of Ethyl alcohol 13%** in water	Dilute with provided diluent (13% ethyl alcohol) to 10 mg/mL.	IV infusion over 1 hour	Rhone-Poulenc Rorer , Antineoplastic
Etoposide/ Etoposide injection and VePesid		20 mg/mL **PEG 300 60%, Ethyl alcohol 30%, TWEEN 80 at 8.0%,** Benzyl alcohol 3.0 %, Citric acid 2 mg/mL pH = 3-4	Dilute with saline or dextrose 5% to 0.2-0.4 mg/mL.	IV infusion over 30-60 minutes	Astra and Bristol-Myers Squibb, Antineoplastic
Haloperidol Decanoate/ Haldol decanoate		50-100 mg/mL in **Sesame Oil** Benzyl alcohol 1.2%	None	IM	Ortho-McNeil, psychotic disorders, Tourette's Disorder

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Table VII (cont.). List of Non-Aqueous Solution Formulations for Parenteral Administration.

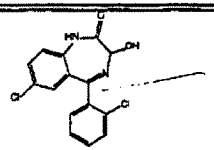
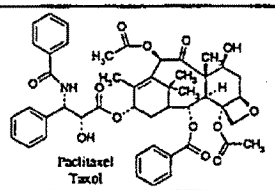
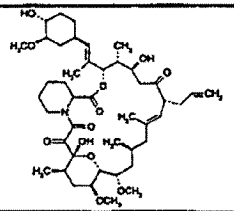
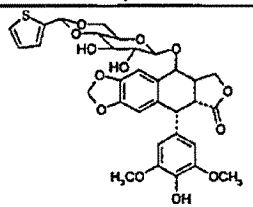
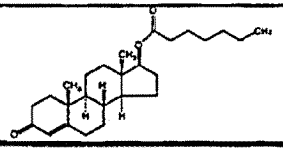
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Lorazepam/ Ativan		2-4 mg/mL **PEG 400 at 18%, in Propylene glycol** Benzyl alcohol 2%	None for IM. For IV dilute with equal volume of saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus at ≤ 2 mg/min	Wyeth-Ayerst, Anxiolytic; sedation; status epilepticus
Paclitaxel/ Taxol		Solution 6 mg/mL **Cremophor EL 51%; Ethyl alcohol 49% (v/v)**	Dilute with saline, dextrose 5% or lactated Ringer's to 0.3-1.2 mg/mL.	IV infusion	Bristol-Myers Squibb, Antineoplastic
Tacrolimus (FK 506)/ Prograf		5 mg/mL **Cremophor EL 20%, Ethyl alcohol 80%**	Dilute 250 or 1000-fold into saline or dextrose 5% to 0.004-0.02 mg/mL	IV infusion	Fujisawa, Immuno-suppresent (transplant rejection)
Teniposide (VM-26)/ Vumon		50 mg/mL **Cremophor EL 50%, Ethyl alcohol 42%, Dimethylacetamide 6%,** Benzyl alcohol 30 mg/mL pH 5 (Maleic acid)	Dilute with saline or dextrose 5% to 0.1-1 mg/mL	IV infusion over 30-60 minutes	Bristol-Myers Squibb, Antineoplastic
Testosterone Enanthate/ Delatestryl		200 mg/mL **Sesame oil,** Chlorobutanol 5 mg/mL	None	IM	BTG

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Table VIII. List of Prodrugs for Parenteral Administration.

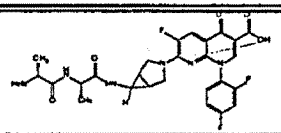
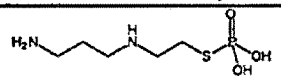
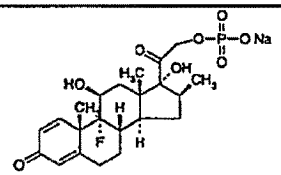
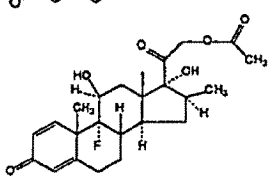
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Ala-trofloxacin mesylate/ Trovan		Solution 5 mg/mL pH 3.4-4.3	Amide	Dilute to 1-2 mg/mL with 5% dextrose	IV infusion over 60 minutes
Amifostine/ Ethyol		Lyophilized powder 500 mg	Phosphor-ylated thiol	Reconstitute with saline to 50 mg/mL (stable at room temperature for 5 hours). May be further diluted to 5 mg/mL with saline.	IV infusion over 15-30 minutes
Betametha-sone Phosphate sodium and Betametha-sone Acetate/ Celestone soluspan	 	**Suspension** Betamethasone sodium phosphate 3 mg/mL, Betamethasone acetate 3 mg/mL, Sodium phosphate dibasic 7.1 mg/mL, Sodium phosphate monobasic 3.4 mg/mL, EDTA 0.1 mg/mL, Benzalkonium chloride 0.2 mg/mL, pH 6.8-7.2	Water soluble phosphate ester and Water insoluble acetate ester	None	IM

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Table VIII (cont.). List of Prodrugs for Parenteral Administration.

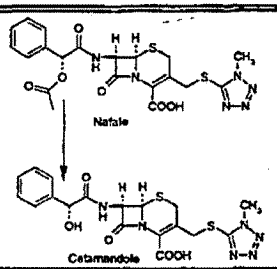
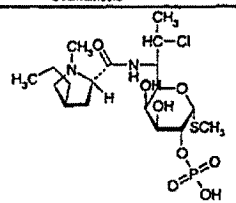
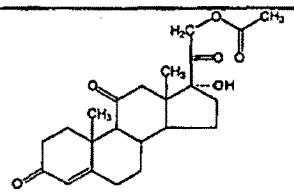
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Cefamandole /Mandol		Solid 1-10 g Sodium carbonate 63 mg/gram cefamandole, pH 6-8.5	Formate ester - rapid hydrolysis after dissolution	Reconstitute to 100-285 mg/mL with WFI, saline or dextrose 5%.	IM/ IV bolus over 3-5 minutes/ IV infusion over 15-30 minutes
Clindamycin Phosphate/ Cleocin phosphate		**1)** Solution 150 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9.4 mg/mL pH = 5-6. 2) Ready to use solution 0.5-18 mg/mL Dextrose 5%, EDTA 0.04 mg/mL.	Water soluble phosphate ester	Dilute concentrated solution with saline or lactated Ringer's to ≤ 18 mg/mL.	IV infusion at 30 mg/hour
Cortisone Acetate/ Cortone		**Suspension** 50 mg/mL, Sodium carboxymethylcellulose 5 mg/mL, TWEEN 80 at 4 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL	Water insoluble acetate ester	None	IM only

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Table VIII (cont.). List of Prodrugs for Parenteral Administration.

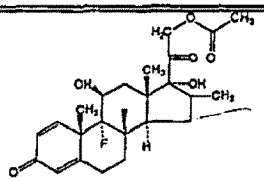
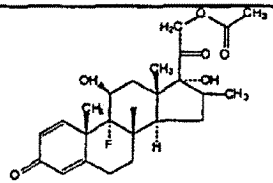
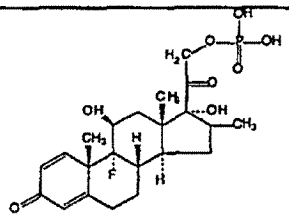
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Dexamethasone Acetate/ Decadron-LA		**Suspension** 8 mg/mL TWEEN 80 at 0.75 mg/mL, Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Water insoluble acetate ester	Gentle swirl contents to resuspend settled particles.	IM/ Intralesional/ Intra-articular/ Soft tissue
Dexamethasone Acetate/ Dalalone D.P.		**Suspension** 16 mg/mL Sodium carboxymethylcellulose 5 mg/mL, TWEEN 80 at 0.75 mg/mL, Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Water insoluble acetate ester	Gentle swirl contents to resuspend settled particles.	IM/ Intra-articular/ Soft tissue (Not intralesional)
Dexamethasone Phosphate sodium/ Decadron		**Solution** 4 and 24 mg/mL w/wo Lidocaine 10 mg/mL, Creatinine 8 mg/mL, Sodium citrate 10 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5 under nitrogen	Water soluble phosphate ester	For IV infusion dilute with saline or dextrose 5%.	IV bolus/ IV infusion/ IM/ Intralesional/ Intra-articular/ Soft tissue

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Table VIII (cont.). List of Prodrugs for Parenteral Administration.

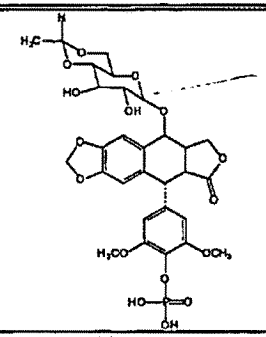
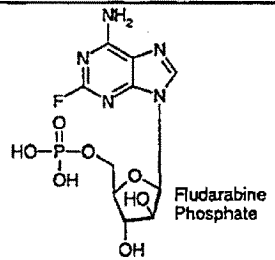
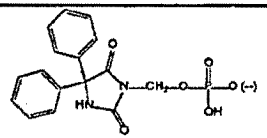
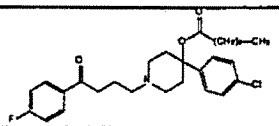
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Etoposide Phosphate/ Etopophos		Lyophilized powder 100-1000 mg, Sodium citrate 32-327 mg/mL, Dextran 40 at 300-3000 mg	Water soluble phosphate ester	Reconstitute with WFI, saline or dextrose 5% to 10-20 mg/mL which is further diluted with saline or dextrose 5% to 0.2-0.4 mg/mL.	IV infusion over 30-60 minutes
Fludarabine Phosphate		Lyophilized powder 50 mg, Mannitol 50 mg pH 7-8	Water soluble phosphate ester	Reconstitute with 2 mL WFI to 25 mg/mL then further diluted with 100-125 mL saline or dextrose 5% to ~ 0.5 mg/mL.	IV infusion over 30 minutes
Fos-phenytoin/ Cerebyx		Solution 75 mg/mL Tromethamine, pH = 8.6-9.0	Water soluble hydroxy-methyl phosphate ester	None for IM. For IV infusion dilute with saline or dextrose 5% to 1.5-25 mg PE/mL.	IM/ IV infusion at ≤ 150 PE/minute
Haloperidol Decanoate/ Haldol decanoate		**Non-aqueous solution** 50-100 mg/mL in **Sesame Oil** Benzyl alcohol 1.2%	Water insoluble deconate ester	None	IM

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Table VIII (cont.). List of Prodrugs for Parenteral Administration.

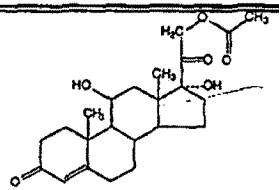
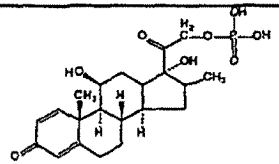
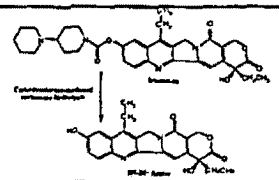
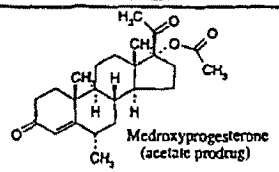
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Hydro-cortisone Acetate/ Hydro-cortone Acetate		**Suspension** 50 mg/mL TWEEN 80 at 4 mg/mL, Sodium carboxymethylcellulose 5 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL/	Water insoluble acetate ester	None	IM/ Intralesional/ Intra-articular
Hydro-cortisone Phosphate sodium/ Hydro-cortone Phosphate		Solution / 50 mg/mL Creatinine 8 mg/mL, Sodium citrate 10 mg/mL, Sodium bisulfite 3.2 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL, pH 7.5-8.5	Water soluble phosphate ester	None or dilute with saline or dextrose 5%.	SC/ IM/ IV bolus/ IV infusion
Irinotecan HCl/ Camptosar		Solution 20 mg/mL, Sorbitol 45 mg/mL, Lactic acid 0.9 mg/mL pH 3.0-3.8	Water soluble carbamate	Dilute with dextrose 5% or saline to 0.12-1.1 mg/mL.	IV infusion over 90 minutes
Medroxypro gesterone Acetate/ Depo-Provera	 Medroxyprogesterone (acetate prodrug)	**Suspension** 150-400 mg/mL, PEG 3350: 20-29 mg/mL, TWEEN 80 at 2.4 mg/mL, Sodium chloride: 8.7 mg/mL, Methylparaben: 1.4 mg/mL, Propylparaben: 0.15 mg/mL		None	IM once every 3 months

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Table VIII (cont.). List of Prodrugs for Parenteral Administration.

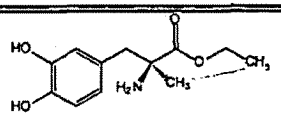
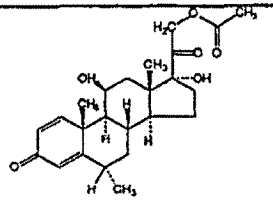
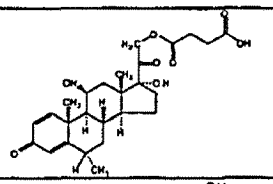
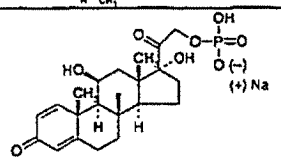
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Methyl-dopate HCl/ Aldomet Ester HCl		Solution 50 mg/mL Citric acid 5 mg/mL, Sodium bisulfite 3.2 mg/mL, Monothioglycerol 2 mg/mL, EDTA 0.5 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL pH 3-4.2	Ethyl ester	Dilute with dextrose 5% to 10 mg/mL.	IV infusion over 30-60 minutes
Methyl-prednisolone Acetate/ Depo-Medrol		**Suspension** 20-80 mg/mL PEG 3350 3%, TWEEN 80 at 2 mg/mL, Sodium phosphates 2 mg/mL, Benzyl alcohol 9 mg/mL, Sodium chloride (isotonic), pH 3.5-7.0	Water insoluble acetate ester	None	IM/ Intrasynovial/ Soft tissue or Intralesional
Methy-prednisolone Succinate sodium / Solu-Medrol		Lyophilized powder 40-2000 mg Sodium phosphates 18 mg/mL w/wo Lactose 25 mg/mL, Benzyl alcohol 9 mg/mL pH 7-8	Water soluble succinate ester	Reconstitute with WFI to 40-65 mg/mL. For IV infusion further dilute with saline or dextrose 5%.	IM/ IV bolus/ IV infusion
Prednisolone Phosphate sodium/ Hydeltrasol (Not in 1999 PDR as injectable)		Solution 20 mg/mL **Niacinamide 25 mg/mL**, EDTA 0.5 mg/mL, Sodium bisulfite 1 mg/mL, Phenol 5 mg/mL pH 7-8	Water soluble phosphate ester	None or for IV infusion dilute with 50-1000 mL saline or dextrose 5%.	IM/ IV bolus/ IV infusion/ Soft tissue/ Intra-articular/ Intralesional

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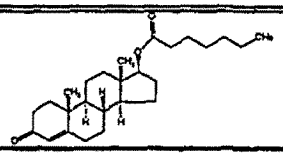
Table VIII (cont.). List of Prodrugs for Parenteral Administration.

Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Testosterone Enanthate/ Delatestryl		**Non-aqueous solution** 200 mg/mL **Sesame oil,** Chlorobutanol 5 mg/mL	Water insoluble heptanate ester	None	IM

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as sodium carboxymethylcellulose at ~5 mg/mL (i.e., dexamethasone acetate), PEG 3350 at 30 mg/mL (i.e., methylprednisolone acetate) or sorbitol at 50% (i.e., triamcinolone hexacetonide).

8. Depots

Sesame oil formulations of oil-soluble drugs provide a sustained-release depot at the injection site that releases drug by diffusion-like uptake of oil. For example, the prodrugs haloperidol deconate and testosterone enanthate are formulated in 100% sesame oil and administered intramuscularly once a month.

9. Liposomes

An exciting new era of the parenteral sciences began with the approval of liposomal products. A liposome is a lipid bilayer and an aqueous-based multilayered spherical drug delivery system where the drug is encapsulated inside the liposome, and is released as the liposome is eroded *in vivo*. A typical liposome formulation contains water with lipid at ~5 mg/mL, an isotonicifier, a pH 5–8 buffer, and with or without cholesterol. These liposomes are injected either by IV infusion or intrathecally. Table X lists the six currently available liposomal products of the four drugs amphotericin B (3 liposome formulations), cytarabine, daunorubicin and doxorubicin. The amphotericin B liposomal products are administered by IV infusion and have an *in vivo* elimination half-life of 40–150 hours. The daunorubicin liposomal formulation has an *in vivo* half-life of 4.4 hours compared to 0.8 hours for the conventional formulation (1, pg. 1970). The cytarabine liposomal formulation, Depocyt, is administered intrathecally once every 2 weeks, while the conventional formulation is given twice per week.

To further increase the *in vivo* circulating times, liposomes can be covalently derivatized with polyethyleneglycol to produce PEGylated or stealth liposomes. The only commercially available PEGylated liposome is doxorubicin in Doxil and is administered by IV infusion and has a half-life of 50–55 hours (1, pg. 2985). The proteins adenosine deaminase (Adagen) and asparginase (Oncaspar) are also available as a PEGylated derivative.

10. Polymeric Microspheres

The era of controlled release using polymeric microspheres began with the approval of the peptide leuprolide as lupron depot. The drug is incorporated into a biocompatible polymer and transformed into lyophilized microspheres during the manufacturing process. The reconstituted microspheres are injected intramuscularly and slowly erode *in vivo*, releasing the drug. In the marketed formulation, leuprolide is in lyophilized microspheres with DL-lactic/glycolic acid copolymer (PLGA), gelatin and mannitol, which is then reconstituted prior to administration to a suspension using an aqueous solution of sodium carboxymethylcellulose, TWEEN 80 and mannitol. The microspheres provide a depot of drug and are administered once every 1–4 months, depending on the dose (3.75 mg/1 month, 30 mg/4 months). One of the leuprolide formulations uses a dual chamber syringe for ease of reconstitution and administration.

A polymeric PLGA microsphere formulation of human growth hormone (Nutropin Depot) finished Phase III clinical trials in 1999 (13). In this formulation, human growth hormone is made into an insoluble complex with zinc, and encapsulated into PLGA microspheres in a non-aqueous cryogenic process (14). The resulting free-flowing powder is reconstituted to a suspension prior to subcutaneous or intramuscular administration.

11. Polymeric Gels

Polymeric gels provide a depot of drug that is released over 1–4 weeks. The era of controlled release using polymeric gels began with the approval of doxycycline hyclate which is available as a 7-day controlled-release system that is a solution upon subgingival administration, but solidifies upon contact with the crevicular fluid. This product is marketed as Atridox® in a Atrigel Delivery System which is a two-syringe set-up where syringe A contains the polymer poly(DL-lactide) dissolved in N-methyl-2-pyrrolidone, and syringe B contains solid doxycycline. Upon coupling the two syringes, the liquid in syringe A is injected into syringe B and repeatedly mixed to complete dissolution, and then the yellow viscous liquid is administered subgingivally.

Local delivery directly into tumors of the anti-tumor cancer drugs fluorouracil and cisplatin, as well a subcutaneous injection of leuprolide are in clinical trials using a polymeric gel formulation.

III. Containers/Vials

Most injectable products are still marketed in traditional vials, ampules and infusion bags. However, there is increased use of more convenient containers such as prefilled syringes, dual chamber syringes and pen-type injectors. Prefilled syringes are especially useful in emergency situations such as in the use of the antithrombotics dalteparin, danaparoid and enoxaparin; the analgesics morphine, hydromorphone, fentanyl, lidocaine and sumatripan; the sedatives lorazepam and propofol; and the antihypertensive labetalol. Dual chamber syringes are used to avoid the usual manipulations involved in reconstitution of a lyophilized powder, and one syringe contains the solid drug while the second syringe contains the liquid diluent, which are mixed prior to administration. Products that use a dual chamber set-up include diltiazem, doxycycline and leuprolide. Pen-type injectors such as NovoPen® with insulin involve a 1–3 mL cartridge that goes into the pen-like delivery device, and the epinephrine autoinjector for intramuscular self-administration.

IV. Future

The future is promising for the formulation sciences, in general, and also for the parenteral formulation sciences. New parenteral achievements will likely include targeted delivery, more sophisticated controlled delivery, novel formulations and new excipients, which may utilize new technologies and be marketed in new devices. Biotechnology proteins and antibodies will likely continue to be at the forefronts of the parenteral sciences. The new and exciting field of gene therapy will likely rely on injectable and

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Table IX. List of Suspension Formulations for Parenteral Administration.

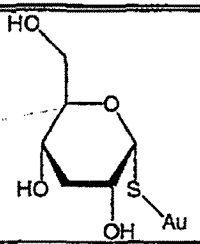
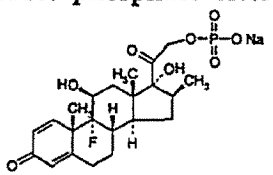
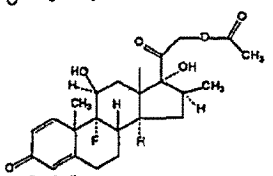
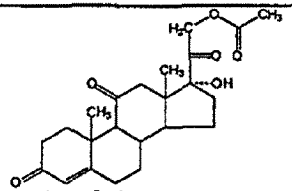
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration
Aurothio-glucose/ Solganal		50 mg/mL **in sesame oil** Aluminum monostearate 2%, Propylparaben 0.1%	None	**IM (oil)** Prolonged release due to slow absorption
Betametha-sone Phosphate sodium and Betametha-sone Acetate/ Celestone soluspan	**Water soluble phosphate ester prodrug**   **Water insoluble acetate ester prodrug**	Betamethasone phosphate 3 mg/mL, Betamethasone acetate 3 mg/mL, EDTA 0.1 mg/mL, Benzalkonium chloride 0.2 mg/mL, Sodium phosphates 10.5 mg/mL, pH 6.8-7.2	None	IM
Cortisone Acetate/ Cortone	 **Water insoluble ester prodrug**	50 mg/mL, TWEEN 80 at 4 mg/mL, Sodium CMC 5 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL	None	IM only

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Table IX (cont.). List of Suspension Formulations for Parenteral Administration.

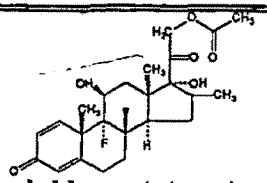
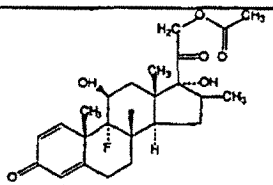
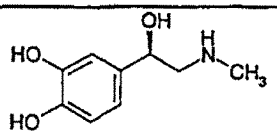
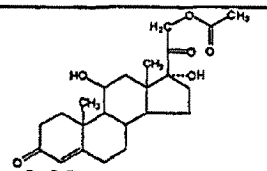
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration
Dexamethasone Acetate/ Decadron-LA	 **Water insoluble acetate ester prodrug**	8 mg/mL TWEEN 80 at 0.75 mg/mL, Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Gentle swirl contents to resuspend settled particles.	IM/ Intralesional/ Intra-articular/ Soft tissue
Dexamethasone Acetate/ Dalalone D.P.	 **Water insoluble acetate ester prodrug**	16 mg/mL TWEEN 80 at 0.75 mg/mL, Sodium CMC 5 mg/mL, Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Gentle swirl contents to resuspend settled particles.	IM// Intra-articular/ Soft tissue (Not intralesional)
Epinephrine HCl/ Susphrine		5 mg/mL **Glycerin 325 mg/mL,** **Thioglycolic acid 6.6 mg/mL,** Ascorbic acid 10 mg/mL, Phenol 5 mg/mL,	Shake contents of vial to disperse particles to uniformity.	SC
Hydrocortisone Acetate/ Hydrocortone Acetate	 **Water insoluble acetate ester prodrug**	50 mg/mL TWEEN 80 at 4 mg/mL, Sodium CMC 5 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL	None	IM/ Intralesional/ Intra-articular

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Table IX (cont.). List of Suspension Formulations for Parenteral Administration.

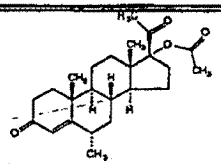
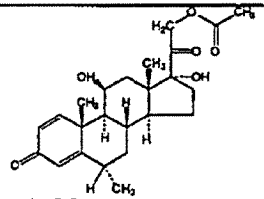
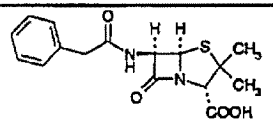
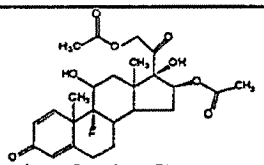
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration
Medroxyprogesterone Acetate/ Depo-Provera	 **Water insoluble acetate ester prodrug**	150-400 mg/mL, **PEG 3350: 2-3%** TWEEN 80 at 2.4 mg/mL, Sodium chloride 8.7 mg/mL, Methylparaben: 1.4 mg/mL, Propylparaben: 0.15 mg/mL	None	IM once every 3 months
Methyl-prednisolone Acetate/ Depo-Medrol	 **Water insoluble acetate ester prodrug**	20-80 mg/mL **PEG 3350 3%,** TWEEN 80 at 2 mg/mL, Sodium phosphates 2 mg/mL, Benzyl alcohol 9 mg/mL, Sodium chloride (isotonic), pH 3.5-7.0	None	IM/ Intrasynovial/ Soft tissue or Intralesional
Penicillin G benzathine and Penicillin G procaine / Bicillin		150,000-600,000 units each/mL CMC 0.55%, Lecithin 0.5% Povidone 0.1%, Methylparaben 0.1%, Propylparaben 0.01%, Sodium citrate pH 6-8.5	Shake vial before withdrawing the desired dose.	IM
Triamcinolone Diacetate/ Aristocorte	 **Water insoluble diacetate ester prodrug**	20-40 mg/mL PEG 3350 at 3%, TWEEN 80 at 0.2% Sodium chloride 8.5 mg/mL, Benzyl alcohol 9 mg/mL, pH ~ 6	None	IM/ Intra-articular/ Intrasynovial/ Intralesional

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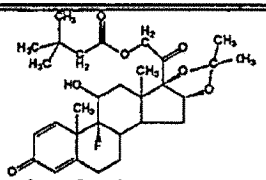
Table IX (cont.). List of Suspension Formulations for Parenteral Administration.

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration
Triamcinolone Hexacetonide/ Aristospan	 **Water insoluble ester prodrug**	5-20 mg/mL **Sorbitol 50%,** TWEEN 80 at 0.2-0.4% Benzyl alcohol 9 mg/mL, pH 4.5- 6.5	None	Intra-articular/ Intralesional

CMC = Carboxymethylcellulose

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Table X. List of Liposomal Formulated Parenteral Products for Parenteral Administration.

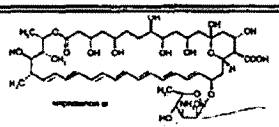
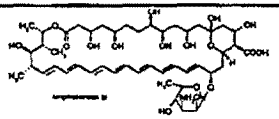
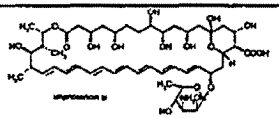
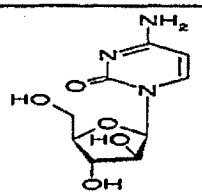
Drug Name/ Marketed Name	Structure	Formulation	Lipid-to-drug molar ratio	Preadministration preparation	Route of Administration
Amphoter-icin B/ Abelcet		**Opaque suspension** 5 mg/mL DMPC 3.4 mg/mL, DMPG 1.5 mg/mL, Sodium chloride 9 mg/mL pH = 5-7	1:1	Dilute to 1-2 mg/mL with 5% dextrose	IV infusion at 2.5 mg/kg/hr
Amphoter-icin B cholesteryl sulfate/ Amphotec		Lyophilized powder 50 -100 mg SCS 2.6 mg/mL, Lactose 95 mg/mL, TRIS 0.56 mg/mL, EDTA 0.037 mg/mL,	1:1	Reconstitute with WFI to a 5 mg/mL **colloidal dispersion,.** Dilute to 0.16 - 0.83 mg/mL with 5% dextrose.	IV infusion at 3-4 mg/kg/hr
Amphoter-icin B/ Ambisome		Lyophilized powder 50 mg HSPC 18 mg/mL, DSPG 7 mg/mL, Cholesterol 4 mg/mL, Alpha tocopherol 0.05 mg/mL, Sucrose 75 mg/mL, Disodium succinate 2 mg/mL pH 5.0-6.0	4:1	Reconstitute with WFI to a 4 mg/mL **translucent suspension,.** Dilute to 1-2 mg/mL with 5% dextrose.	IV infusion at 3-5 mg/kg/hr
Cytarabine (Ara-C)/ DepoCyte		**Suspension Multivesicular Lipid Particle** 5 mg/mL DOPC 5.7 mg/mL, DPPG 1 mg/mL, Cholesterol 4 mg/mL, Sodium chloride 9 mg/mL pH 5.5-8.5	1:1	None	Intrathecal

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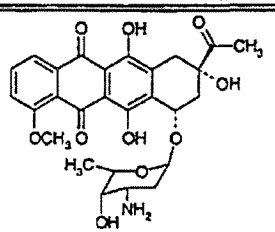
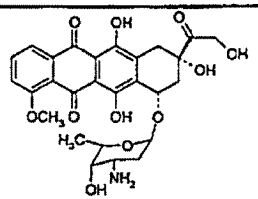
Table X (cont.). List of Liposomal Formulated Parenteral Products for Parenteral Administration.

Drug Name/ Marketed Name	Structure	Formulation	Lipid-to-drug molar ratio	Preadministration preparation	Route of Administration
Dauno-rubicin Citrate/ DaunoXome		Solution I 2 mg/mL, DSPC: Cholesterol in 2:1 molar ratio	18:1	Dilute 1:1 with dextrose 5% to 1 mg/mL.	IV infusion over 60 minutes
Doxorubicin HCl/ Doxil **(Pegylated stealth liposome)**		**Liposomal dispersion** 2 mg/mL, MPEG-DSPE 3.2 mg/mL, HSPC 9,6 mg/mL, Cholesterol 3.2 mg/mL, Ammonium sulfate 2 mg/mL, Histidine	1:1	Dilute the dose into 250 mL of dextrose 5%.	IV infusion over 30 minutes

DMPC = L-α-dimyristoylphosphatidylcholine

DMPG = L-α-dimyristoylphosphatidylglycerol
DOPC = Dioleoylphosphatidylcholine
DPPG = Dipalmitoylphosphatidylglycerol
DSPC = Distearoylphosphatidylcholine
DSPG = Distearoylphosphatidylglycerol
HSPC = Hydrogenated soy phosphatidylcholine
MPEG-DSPE = N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium
SCS = Sodium cholesteryl sulfate

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Table XI. Abbreviations Used in the Compilation	
Abbreviation	Meaning
ACE	angiotensin-converting enzyme
C, G, T (Fomiversen)	C = cytosine G= guanine T= thymine
CHF	congestive heart failure
CMV	Cytomegalovirus
EDTA	ethylenediamine tetraacetic acid
HCl	hydrochloride salt
IM	intramuscular
IP	intraperitoneal
IV	intravenous
LH-RH	leutenizing hormone-releasing hormone
PCI	percutaneous cardiovascular intervention
PDR	Physician's Desk Reference
PEG	polyethyleneglycol
PG	propylene glycol
PSVT	paroxysmal supraventricular tachycardia
SC	subcutaneous
TRIS	tris(hydroxymethyl)aminomethane
TWEEN	polysorbate
WFI	water for injection
w/wo	with or without

solution formulations for delivery of antisense oligonucleotides (15, 16), such as with the anti-sense ophthalmic product fomiversen (Vitravene). In general, formulation approaches along with drug design will be the means to achieve optimal drug delivery based upon therapeutic needs.

New approaches could include nanoparticles (17), submicron solid particles coated with either natural or semisynthetic phospholipids (18), mixed-micelles, microemulsions for injection (19), and soluble self-assembled block copolymers to either solubilize drug in a micelle-like structure [PEO-b-PAA-DOX, poly(ethylene oxide)-block-poly(aspartic acid)-doxorubicin] or covalently bind drug (20). "Smart" controlled-release systems that deliver drug when needed could be the next generation in controlled release, including pulsatile delivery to mimic human circadian rhythms or normal hormone production. The release of drug could be triggered by timed events or more sophisticated means, such as a chemical stimulus, photosensors, blood pressure sensors, or some type of biofeedback mechanism. New excipients will likely be approved, such as sulfobutyl ether β-cyclodextrin, tetraglycol, triglyme, transcutol, 2-pyrrolidone (Soluphor® P), glycerol formal, Solutol HS-15, and poloxamers which will expand the number of formulation additives available to the formulation scientist.

Devices such as needle-free injectors (already in use with vaccines) for both solutions and solids (21) could revolutionize the manner in which injectable drugs are administered. The increased emphasis on home health care will likely result in home infusion devices and set-ups such as battery operated and/or pocket-sized infusion pumps. We are likely to continue to see more applications of convenient injection devices, prefilled syringes, dual chamber devices and ready-to-use solutions.

Advanced technologies will likely be used in commercial production of future parenteral products; for example, the use of nanoparticles for injection of water-insoluble drugs. Supercritical fluid processing to form spherical microparticles (22) and perhaps a designed distribution of particle size has tremendous potential in future formulations and pharmaceutical manufacturing.

Combinations of novel formulations and novel delivery systems that are in active research (23) will certainly be developed. One can imagine the many combinations of needle-free injection of solutions or solids, controlled-release systems, "stealth" carriers, targeted delivery, vaccines, gene therapy, antibodies and specially designed small molecules. Yes, as the parenteral sciences continue to mature, future products will be science fiction come true!

Notes on the Compilation

A few comments on the compilation are in order to help the reader understand the table format, chemical structures, some occasional additional information, highlighted portions, and abbreviations.

1) The order of lines within the formulation box is:
   a) Solution or lyophilized powder
   b) Drug concentration or amount (i.e., mg/mL, mg, units/mL, etc.)
   c) Excipients and concentration or amount (i.e., mg/mL, %, mg, etc.)
      —organic solvent(s)
      —suspending agent(s)
      —bulking agent(s)
      —isotonicifier(s)

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—preservative(s)
—buffer
d) pH

2) Some drugs have the pKa listed, but this is not comprehensive and is added for informative purposes.
3) The chemical structures are drawn in most instances as the neutral species even though the market product may be a salt form.
4) In the drug name, the counter ion is in lower case, but a covalently bound prodrug moiety is capitalized.
5) Some entries were not found in the 1999 PDR at all or not as injectables, but were found in other references. In these cases "(Not in 1999 PDR)" is added under the marketed name.
6) Various portions of some entries are highlighted in **bold** typeface, in order to help the reader clearly notice key formulation aspect(s).
7) Some drugs are marketed in multiple formulations, and in these cases the formulations are numbered.
8) There are some peptide entries to highlight new formulation approaches.
9) Abbreviations used herein (Table XI).

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ATTACHMENT F - COMPILATION

TAB 13

REVIEW ARTICLE

Parenteral Formulations of Small Molecules Therapeutics Marketed in the United States (1999) Part II

ROBERT G. STRICKLEY

Axys Pharmaceuticals, Inc., South San Francisco, California

[Editor's Note: This review article on Injectable Products is being published in three parts. The introduction and summary appeared in the November/December 1999 issue. The final Part will appear in the March/April 2000 issue of the *Journal*.]

Injectable Products

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6. Food and Drug Administration internet website, http://www.fda.gov/, See human drugs, what's new, new and generics approvals.

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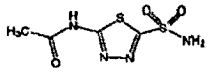
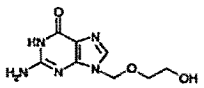
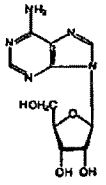
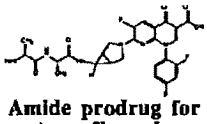
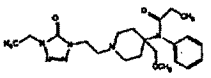
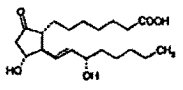
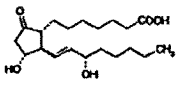
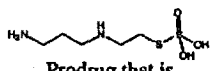
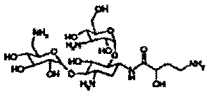
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Acetazolamide sodium/ Diamox	 pKa = 7.2	Solution 500 mg pH 9.2	Constitute with 5 mL WFI to ≤ 100 mg/mL.	IV bolus/ IV infusion; IM but may be painful due to alkaline pH	Lederle, Antiglaucoma; diuretic in treatment of mountain sickness
Acyclovir sodium/ Zovirax	 pKa ~ 10	Lyophilized powder 500 - 1000 mg **pH 10.5 - 11.6**	Reconstitute with WFI to 50 mg/mL; Dilute with dextrose 5% or saline to < 7 mg/mL.	IV infusion over 1 hour	Glaxo Wellcome, Antiviral
Adenosine/ Adenocard IV (bolus), Adenoscan (IV infusion)		Solution 3 mg/mL, Sodium chloride 9 mg/mL, pH 4.5-7.5	None	IV bolus/ IV infusion at 0.14 mg/kg/min for 6 minutes	Fujisawa, Conversion to sinus rhythm of PSVT (bolus). Adjunct for thallium-201 myocardial perfusion scintigraphy (infusion)
Alatrofloxacin mesylate/ Trovan	 **Amide prodrug for trovafloxacin**	Solution 5 mg/mL pH 3.4-4.3	Dilute with dextrose 5% to 1-2 mg/mL. (potentially incompatible with saline and lactated Ringer's)	IV Infusion over 60 minutes	Pfizer, Antibiotic
Alfentanil HCl/ Alfenta		Solution 0.5 mg/mL, Sodium chloride (isotonic) pH 4-6	None for bolus. For IV infusion dilute with saline, dextrose 5%, or lactated Ringer's to 0.025-0.080 mg/mL.	IV bolus/ IV infusion at 0.5-3.0 ug/kg/min	Taylor, Analgesic
Alprostadil (prostaglandinE1/ Caverject		Lyophilized powder 6-46 ug Lactose 172 mg, Sodium citrate 47 mg, Benzyl alcohol 8.4 mg	Reconstitute with 1.2 mL water preserved with benzyl alcohol 0.95% w/v. (~ 0.5-1.1 ug is lost due to adsorption to the vial and syringe.)	Intra-cavernosal	Pharmacia & Upjohn, Erectile dysfunction
Alprostadil **alfadex** (prostaglandinE1/ Edex	 complexed with **α-cyclodextrin**	Lyophilized powder 6-50 ug complexed with 200-1610 ug of **α-cyclodextrin** Lactose 56 mg pH 4-8	Reconstitute with 1.2 mL saline.	Intra-cavernosal	Schwarz Pharma, Erectile dysfunction
Amifostine/ Ethyol	 Prodrug that is dephosphorylated by alkaline phosphatase to active free thiol	Lyophilized powder 500 mg	Reconstitute with saline to 50 mg/mL (stable at room temperature for 5 hours). May be further diluted with saline to 5 mg/mL.	IV infusion over 15-30 minutes	Alza, Antineoplastic adjuvant [cytoprotective and radioprotective (reduces toxic effect of cisplatin)]
Amikacin sulfate		Solution 250 mg/mL, Sodium metabisulfite 0.66% Sodium citrate 2.8 % pH 3.5 - 5.5	For IV infusion dilute with saline or dextrose 5% to 2.5-5 mg/mL.	IM/ IV Infusion over 30 - 60 minutes	Elkins-Sinn, Antibiotic

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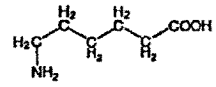
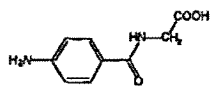
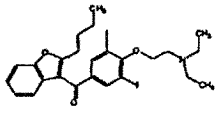
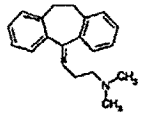
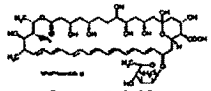
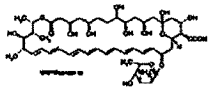
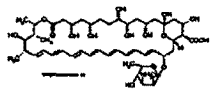
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Aminocaproic acid/ Amicar		Solution 250 mg/mL, Benzyl alcohol 0.9% pH 6.8	Dilute with saline or dextrose 5% to ~ 15-20 mg/mL.	IV infusion at 4 grams/hour	Immunex, Enhancing hemostasis when fibrinolysis contributes to bleeding
Amino-hippurate sodium "PAH"		Solution 200 mg/mL	None	IV infusion at 6-10 mg/kg and 10-24 mg/min	Merck, Measures effective renal plasma flow
Amiodarone HCL/ Cordarone		Solution 50 mg/mL, **TWEEN 80 at 10%,** Benzyl alcohol 2% pH 4.1	Dilute with dextrose 5% to < 2 mg/mL.	IV infusion at 5-15 mg/min dextrose	Wyeth-Ayerst, Antiarrhythmic, Antianginal
Amitriptyline HCl/ Elavil		Solution 10 mg/mL, Dextrose 44 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL pH 4-6	None	IM	Zeneca, Antidepressant
Amphoter-icin B/ Abelcet	 complexed 1:1 (drug-to-lipid molar ratio) with [L-α-dimyristoylphosphati-dylcholine (DMPC) and L-α-dimyristoylphosphati-dylglycerol (DMPG) in a 7:3 mole ratio]	**Liposome opaque suspension** 5 mg/mL DMPC 3.4 mg/mL, DMPG 1.5 mg/mL, Sodium chloride 9 mg/mL pH = 5-7	Dilute with dextrose 5% to 1-2 mg/mL.	IV infusion at 2.5 mg/kg/hr	The Liposome Company, Antifungal
Amphoter-icin B cholesteryl sulfate/ Amphotec	 complexed 1:1 molar with cholesteryl sulfate	Lyophilized powder 50 -100 mg After reconstitution with WFI to a 5 mg/mL **colloidal liposomal dispersion,** Sodium cholesteryl sulfate 2.6 mg/mL, EDTA 0.037 mg/mL, Lactose 95 mg/mL, TRIS 0.56 mg/mL	Reconstitute with WFI to 5 mg/mL. Dilute with dextrose 5% to 0.16 - 0.83 mg/mL.	IV infusion at 3-4 mg/kg/hr	Sequus (Purchased by AlzA), Antifungal
Amphoter-icin B/ Ambisome		Lyophilized powder 50 mg After reconstitution with WFI to a 4 mg/mL **translucent liposomal suspension,** Hydrogenated soy phosphatidylcholine 18 mg/mL, Distearoylphosphatidylglycerol 7 mg/mL, Cholesterol 4 mg/mL, Alpha tocopherol 0.05 mg/mL, Sucrose 75 mg/mL, Disodium succinate 2 mg/mL pH 5.0-6.0	Reconstitute with WFI to 4 mg/mL. Dilute with dextrose 5% to 1-2 mg/mL.	IV infusion at 3-5 mg/kg/hr	Fugisawa (developed by NeXstar, now Gilead), Antifungal

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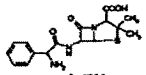
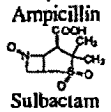
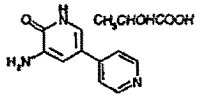
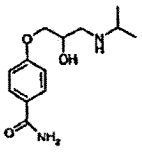
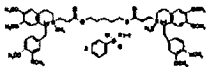
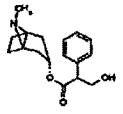
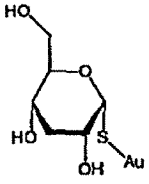
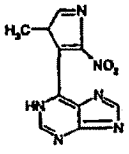
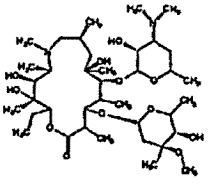
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Ampicillin and Sulbactam sodium/ Unasyn	 Ampicillin  Sulbactam	Powder 1-2 grams (ampicillin), 0.5-1.0 grams (sulbactam) pH = 8-10	Reconstitute with WFI to 250 mg/mL ampicillin and 125 mg/mL sulbactam. For IV dilute with saline or dextrose 5% to 3-45 mg/mL.	IM/ IV infusion over 10-30 minutes	Pfizer, Antibacterial (ampicillin)
Amrinone lactate/ Inocor (not in 1999 PDR)		Solution 5 mg/mL, Sodium metabisulfite 0.25 mg/mL, pH = 3-4	None or dilute with saline or half-saline to 1-3 mg/mL.	Slow IV bolus over 2-3 minutes IV infusion at 5-10 ug/kg/min	Sanofi Winthrop, Inotropic and vasodilator (short term management of CHF)
Atenolol/ Tenormin		Solution 0.5 mg/mL, Sodium chloride (to isotonic), Citric acid to pH = 5.5 - 6.2	None, or dilution with saline or dextrose 5%.	IV infusion at 1 mg/min	Zeneca, Antihypertensive and treatment of acute myocardial infarction
Atracurium besylate/ Tracrium		Solution 10 mg/mL w/wo Benzyl alcohol 0.9% pH = 3.2-3.6 (benzene sulfonic acid)	None for IV bolus For IV infusion dilute with saline or dextrose 5% to 0.2-0.5 mg/mL.	IV bolus/ IV infusion at 5-13 ug/kg/min	Glaxo Wellcome, General anesthesia (Skeletal muscle relaxant)
Atrophine sulfate		Solution 0.1-1.0 mg/mL, Sodium chloride 9 mg/mL, w/wo Benzyl alcohol 1.5% pH 3-6	None	SC/ IM/ IV bolus	Elkins-Sinn, Astra, and Baxter, Anticholinergic, Antispasmodic
Aurothio-glucose/ Solganal		**Suspension** 50 mg/mL **in sesame oil** Aluminum monostearate 2%, Propylparaben 0.1%	None	**IM (oil)** Prolonged release due to slow absorption	Schering Corp., Antirheumatic
Azathioprine sodium/ Imuran		Lyophilized power 100 mg **pH = 9.8-11**	Reconstitute with 10 mL WFI. For IV infusion dilute with saline or dextrose 5%.	IV bolus/ IV Infusion	Glaxo Wellcome, Immuno-suppressive anti-metabolite; management of severe rheumatoid arthritis
Azithromy-cin/ Zithromax		Lyophilized powder, 500 mg, Citric acid 414 mg	Reconstitute with 5 mL WFI, and dilute to 1-2 mg/mL with saline, dextrose 5%, or lactated Ringer's.	IV infusion of 500 mg at 1 mg/mL over 3 hours, or 2 mg/mL over 1 hour	Pfizer, Antibiotic

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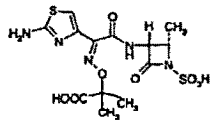
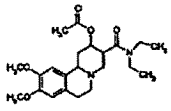
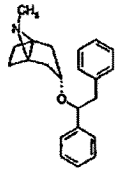
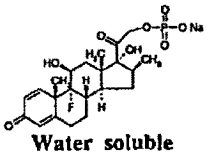
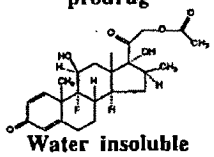
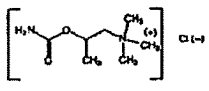
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Aztreonam/ Azactam		1) Lyophilized powder 0.5-2 g, L-arginine 780mg/gram aztreonam pH = 4.5-7.5 2) Frozen Solution 20-40 mg/mL Lactose 14-34 mg/mL, Arginine 16-32 mg/mL pH 4.5-7.5	For IM reconstitute with at least 3 mL WFI or saline to ~ 100-500 mg/mL. For IV bolus reconstitute with WFI to 50-200 mg/mL. For IV infusion reconstitute with 3 mL WFI, then dilute with saline, dextrose 5%, lactated Ringer's to ≤ 20 mg/mL.	IM/ IV bolus/ IV Infusion/	BMS, Antibiotic
Benzquinamide (Not in 1999 PDR)		Powder 50 mg pH = 3-4	Reconstitute with WFI to 25 mg/mL.	IM/ IV infusion	Pfizer, Prevent nausea with surgery anesthesia
Benztropine mesylate/ Cogentin		Solution 1 mg/mL, Sodium chloride 9 mg/mL pH = 5-8	None	IM/ (IV bolus is alright, but has no advantage over IM)	Merck, Anticholinergic used in psychotic patients with acute dystonic reactions, and in Parkinson's disease
Betamethasone Phosphate sodium and Betamethasone Acetate/ Celestone soluspan	 **Water soluble phosphate ester prodrug**  **Water insoluble acetate ester prodrug**	**Suspension** Betamethasone sodium phosphate 3 mg/mL, Betamethasone acetate 3 mg/mL, Sodium phosphate dibasic 7.1 mg/mL, Sodium phosphate monobasic 3.4 mg/mL, EDTA 0.1 mg/mL, Benzalkonium chloride 0.2 mg/mL, pH 6.8-7.2	None	IM	Schering, Anti-inflammatory and for allergies
Bethanechol chloride/ Urecholine		Solution 5.1 mg/mL, pH neutral	None	SC	Merck, Cholinergic

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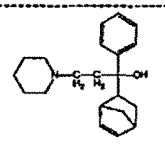
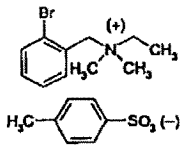
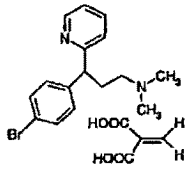
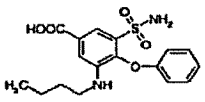
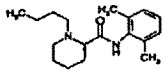
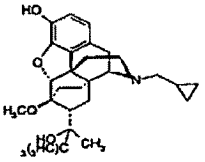
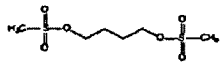
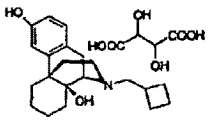
InnoPharma Exhibit 1046.0416

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Biperidan Lactate/ Akineton		Solution 5 mg/mL Sodium lactate 1.4%	None	IV/ IM	Knoll, Parkinson's Disease
Bretylium tosylate/ Bretylol		Solution 50 mg/mL pH 4.5-7	None for IV bolus or IM. For IV infusion dilute with saline, dextrose 5%, or lactated Ringer's to 10 mg/mL.	IM/ IV bolus/ IV infusion at 1-2 mg/min	Astra, Antidysrhythmic
Brom-pheniramine maleate (Liquid formulation not in 1999 PDR)		Solution 10 mg/mL, Methylparaben 0.18%, Propylparaben 0.02%, pH = 6.7-7.1	None for IM/SC/IV bolus. For IV infusion dilute with saline to 1 mg/mL.	SC/ IM/ IV bolus/ IV infusion/	Muro, Antihistamine
Bumetanide/ Bumex		Solution 0.25 mg/mL, Sodium chloride 8.5 mg/mL, Benzyl alcohol 10 mg/mL, EDTA 0.1 mg/mL, Ammonium acetate 4 mg/mL, pH 6.8-7.8	None for IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus over 1-2 minutes/ IV infusion at 1 mg/hr	Baxter, Diuretic
Bupivacaine HCl/ Sensorcaine	 pKa = 8.1	Solution 2.5-7.5 mg/mL Sodium chloride to isotonic, w/wo Epinephrine 9 ug/mL, Sodium metabisulfite 0.5 mg/mL, Methylparaben 1 mg/mL, Citric acid 0.2 mg/mL, pH 4-6.5	None	Epidural/ Spinal/ Sympathetic nerve/ Catheter into the area being anesthetized,~ 175-225 mg/ (not IV)	Astra, Local anesthesia
Buprenor-phine HCl (30-times more potent than morphine)/ Buprenex		Solution 0.3 mg/mL, Dextrose 50 mg/mL pH 3.5-5.5	None or dilute with saline, dextrose 5%, lactated Ringer's	Deep IM/ IV bolus over 2 minutes.	Reckitt-Coleman, Analgesic
Busulfan/ Busulfex		Solution 6 mg/mL **PEG 400 at 67% N, N-dimethylacetamide (DMA) 33%,**	Dilute with saline or dextrose 5% to 0.6 mg/mL.	IV infusion	Orphan Medical, Neoplastic
Butorphanol tartrate/ Stadol (Injectable not in 1999 PDR, the only product is a nasal formulation.)		**Injectable solution:** 1-2 mg/mL Sodium chloride 6.4 mg/mL Citrate buffer 0.045M pH 3-5.5. **Nasal spray solution:** 10 mg/mL, Sodium chloride, Citric acid, Benzethonium chloride, pH 5.0.	None	Nasal Spray (1 spray is ~ 1 mg in 0.1 mL)/ IM/ IV bolus (1-4 mg)	BMS, Analgesic

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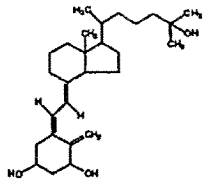
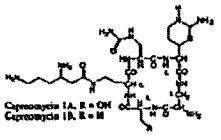
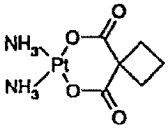
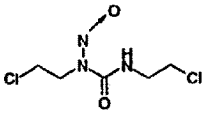
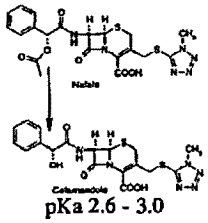
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Calcitonin - Salmon, Miacalcin	Polypeptide hormone 32 amino-acids (H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2)	Solution 200 I.U./mL, Phenol 5 mg/mL, Sodium chloride 7.5 mg/mL, Acetate buffer pH ~ 4	None	IM/ SC/ also Nasal spray of 2000 I.U./mL, and one spray contains 0.1 mL or 200 I.U.	Novartis, Treatment of postmenopausal osteoporosis; Paget's disease, and hypercalcemia
Calcitriol/ Calcijex		Solution 1-2 ug/mL, **TWEEN 20 at 4 mg/mL, Sodium ascorbate 10 mg/mL,** Sodium chloride 1.5 mg/mL, EDTA 1.1 mg/mL, Sodium phosphates 9.2 mg/mL, pH 6.5-8.0	None	IV bolus	Abbott, Management of hypocalcemia in patients undergoing chronic renal dialysis
Capreomycin sulfate/ Capastat		Powder 1000 mg	Reconstitute with 2 mL WFI or saline to 500 mg/mL (~ 3 minutes to dissolve). For IM no dilution, but may reconstitute with less water to 200-350 mg/mL For IV infusion dilute into 100 mL saline.	IM/ IV infusion over 60 minutes	Dura, Antibiotic
Carboplatin/ Paraplatin		Powder 50-450 mg, Mannitol equal mass as carboplatin. pH 5-7	Reconstitute with WFI, saline or dextrose 5% to 10 mg/mL. May be further diluted to 0.5 mg/mL with saline or dextrose 5%.	IV infusion of at least 15 minutes using 0.5-10 mg/mL.	BMS, Antineoplastic
Carmustine/ BiCNU		Lyophilized solid 100 mg pH 5-6	**Reconstitute with supplied 3 mL of ethanol,** then further dilute with 27 mL WFI to a final **10% ethanol.**	IV infusion over 1-2 hours, 150-200 mg/m^2	BMS, Antineoplastic
Cefamandole /Mandol (Formate ester **prodrug** - rapid hydrolysis after dissolution)	 pKa 2.6 - 3.0	Solid 1-10 g Sodium carbonate 63 mg/gram cefamandole, pH 6-8.5	Reconstitute with WFI, saline or dextrose 5% to 100-285 mg/mL.	IM/ IV bolus over 3-5 minutes/ IV infusion over 15-30 minutes	Lilly, Antibacterial

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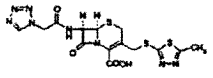
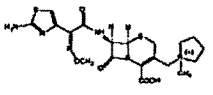
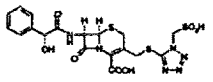
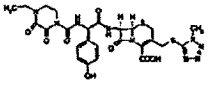
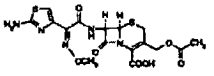
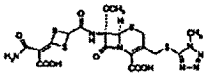
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Cefazolin sodium/ Ancef, Kefzol		1) Lyophilized powder 0.5-10 g pH 4.5 - 6. 2) Frozen solution 10-20 mg/mL, Dextrose ~ 40-48 mg/mL pH 4.5-7.	Reconstitute with WFI, or saline to 225-330 mg/mL for IM, and dilute with WFI. to ~ 100 mg/mL for IV bolus, and dilute with saline, dextrose or lactated Ringer's to 10 mg/mL for IV infusion	IM/ IV bolus over 3-5 minutes/ IV infusion	Smith-Kline Beecham and, Lilly, Antibiotic
Cefepime HCl/ Maxipime		Solid mixture 0.5-2 g, L-Arginine 725 mg/g cefepime pH 4.0-6.0	Reconstitute with saline, dextrose 5% or lactated Ringer's to 280 mg/mL for IM, 100-160 mg/mL for IV bolus, 20-40 mg/mL for IV infusion.	IM/ IV bolus over 3-5 minutes/ IV infusion over 30 minutes	BMS, Antibiotic
Cefonicid sodium/ Monocid		Lyophilized powder 0.5-1 g, pH 3.5 - 6.5	Reconstitute with WFI to 225-325 mg/mL for IM and IV bolus, and dilute with saline, dextrose 5% or lactated Ringer's to 10 mg/mL for IV infusion.	IM/ IV bolus over 3-5 minutes/ IV infusion	Smith-Kline Beecham, Antibiotic
Cefopera-zone sodium/ Cefobid		1) Crystalline powder 0.5-1 g, pH 4.5 - 6. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 36-46 mg/mL pH 4.5-7.	Reconstitute with saline or dextrose 5% to 280 mg/mL for IV bolus. Dilute with lidocaine 2% to ~ 200 mg/mL for IM. Dilute with saline, dextrose 5% or lactated Ringer's to 2-25 mg/mL for IV infusion.	Deep IM/ IV bolus over 3-5 minutes/ IV infusion over 15-30 minutes	Pfizer, Antibiotic
Cefotaxime sodium/ Claforan		1) Powder 0.5-2 g, pH 4.5 - 6. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 14-34 mg/mL, Sodium citrate pH 5-7.5	Reconstitute with WFI to 230-330 mg/mL for IM, 50-180 mg/mL for IV bolus, and dilute with saline or dextrose to 10 mg/mL for IV infusion.	Deep IM/ IV bolus over 3-5 minutes/ IV infusion over 15-30 minutes	Hoechst Marion Roussel, Antibiotic
Cefotetan disodium/ Cefotan		1) Powder 1-10 g pH 4.5-6.5. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 22-38 mg/mL, Sodium bicarbonate pH 4-6.5	For IM, reconstitute with WFI, saline, 0.5% or 1% lidocaine to 400-500 mg/mL. For IV, reconstitute with WFI to 95-180 mg/mL, and dilute with saline or dextrose 5% to 10 mg/mL for IV infusion.	Deep IM/ IV bolus over 3-5 minutes/ IV infusion over 20-60 minutes	Zeneca, Antibiotic

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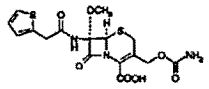
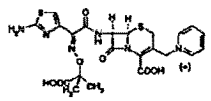
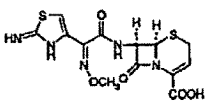
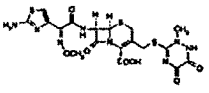
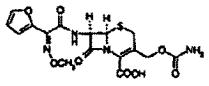
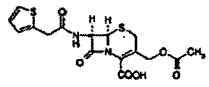
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Cefoxitin sodium/ Mefoxin		1) Powder 1-10 g pH 4.2-7.0. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 22-40 mg/mL, Sodium bicarbonate pH 6.5	Reconstitute with WFI to 100-200 mg/mL for IV bolus. For IV infusion reconstitute with saline or dextrose 5% to 100 mg/mL, then dilute to 10 mg/mL	IV bolus over 3-5 minutes/ IV infusion over ~ 30 minutes	Merck, Antibiotic
Ceftazidime/ (Ceptaz, Fortaz, Tazidime, Tazicef)		1) Powder w/wo Sodium carbonate at 118 mg/g ceftazidime, w/wo L-Arginine at 349 mg/gram ceftazidime pH 5-7. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 50 mg/mL, Sodium bicarbonate pH 4-6.5	For IM, reconstitute with WFI, saline, 0.5% or 1% lidocaine to 250 mg/mL. For IV, reconstitute with WFI to 90-170 mg/mL, and dilute with saline or dextrose 5%. to 10-40 mg/mL for IV infusion.	Deep IM/ IV bolus over 3-5 minutes/ IV infusion over ~ 30-60 minutes	Glaxo Wellcome, Lilly and, SmithKline Beecham, Antibiotic
Ceftizoxime sodium/ Cefizox		Crystalline powder 0.5-2 g pH = 6-8	Reconstitute with WFI to 270 mg/mL for IM, 95 mg/mL for IV bolus, and dilute with IV fluids to 10-40 mg/mL for IV infusion.	Deep IM/ IV over 3-5 minutes/ IV Infusion	Fujisawa, Antibiotic
Ceftriaxone sodium/ Rocephin		1) Crystalline powder 0.25-10 g, pH = 6-8. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 24-38 mg/mL, pH 6.7	For IM, reconstitute with WFI, saline, dextrose 5% or lidocaine 1% to 250 mg/mL. For IV infusion, reconstitute with WFI to 100 mg/mL, then dilute with saline or dextrose 5% to 10-40 mg/mL.	Deep IM/ IV Infusion over 30 minutes	Roche, Antibiotic
Cefuroxime, sodium/ Zinacef		1) Crystalline powder 0.75-7.5 g, pH = 6-8.5. 2) Frozen solution 15-30 mg/mL, Dextrose ~ 28 mg/mL, Sodium citrate 60-120 mg/mL pH 5-7.5	Reconstitute with WFI to 220 mg/mL for IM, and 90 mg/mL for IV bolus. For IV infusion, reconstitute with saline or dextrose 5% to 7.5-15 mg/mL.	Deep IM/ IV over 3-5 minutes/ IV Infusion over 15-60 minutes	Glaxo Wellcome, Antibiotic
Cephalothin sodium/ Keflin Neutral (Not in 1999 PDR)		1) Powder 1-20 g, Sodium carbonate 30 mg/gram cephalothin pH = 6-8.5 2) Frozen solution 20-40 mg/mL, Dextrose ~ 50 mg/mL, Sodium bicarbonate pH = 6-8.5	Reconstitute with saline or dextrose 5% to 250 mg/mL for IM, 100 mg/mL for IV, and 20-40 mg/mL for IV infusion.	Deep IM/ IV over 3-5 minutes/ IV infusion	Lilly, Antibiotic

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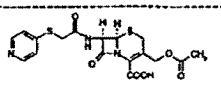
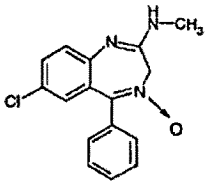
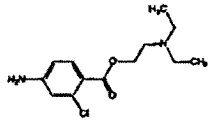
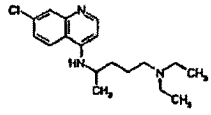
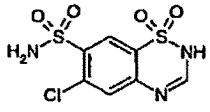
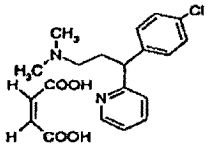
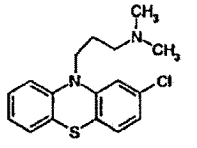
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Cephapirin sodium/ Cefadyl (Not in 1999 PDR)		Powder 0.5-20 g, pH = 6-8.	Reconstitute with saline or dextrose 5% to 500 mg/mL for IM, 50-200 mg/mL for IV, and 100 mg/mL for IV infusion.	Deep IM/ IV over 3-5 minutes/ IV infusion	Apothecon, Antibiotic
Chlordiaz-epoxide HCL/ Librium		Powder 100 mg, Supplied diluent: PG 20% TWEEN 80 at 4%, Benzyl alcohol 1.5%, Maleic acid 1.6% pH = 3	Reconstitute with supplied diluent to 50 mg/mL for IM. Reconstitute with saline or WFI to 20 mg/mL for IV bolus.	IM/ Slow IV bolus over 1 minute	ICN, Tranquilizer
Chloro-procaine HCl/ Nesacaine		Solution 10-30 mg/mL Sodium chloride 3.3-6.7 mg/mL, w/wo EDTA 0.1 mg/mL, w/wo Methylparaben 1 mg/mL, pH 2.7-4.0	None	Single injection or continuously through an indwelling catheter.	Astra, Local anesthetic
Chloroquine HCl/ Aralen		Solution, 50 mg/mL pH 5.5-6.5	None	IM	Sanofi Winthrop, Antimalaria and antiamebic
Chloro-thiazide sodium/ Diuril		Lyophilized powder 500 mg, Mannitol 250 mg, Thimerasol 0.4 mg, pH 9.2-10	Reconstitute with 18 mL WFI to 28 mg/mL.	IV/ IV Infusion	Merck, Diuretic and hypertensive
Chlorphenir-amine maleate/ Chlor-trimeton (Not in 1999 PDR as injectable)		Solution, 10-100 mg/mL pH 4-5.2	None	IV (not the 100 mg/mL)/ SC/ IM	Schering, Antihistamine
Chlorproma-zine HCl/ Thorazine		Solution 25 mg/mL, Sodium chloride 6 mg/mL, Sodium bisulfite 1 mg/mL, Sodium sulfite 1 mg/mL, w/wo benzyl alcohol 2%, Ascorbic acid 2 mg/mL, pH 3-5	None for IM. Dilute with saline to 1 mg/mL for IV.	Deep IM in buttock/ IV bolus at 0.5-1 mg/minute	Smith-Kline Beecham, Antipsychotic, antiemetic (nausea), tranquilizer

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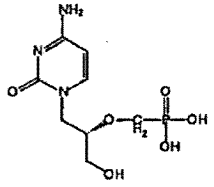
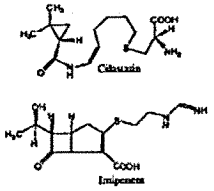
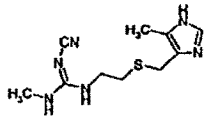
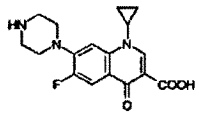
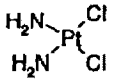
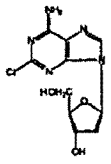
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Cidofovir/ Vistide		Solution 75 mg/mL, pH 7.4	Dilute into 100 mL saline to ~ 3-5 mg/mL.	IV infusion at 5 mg/kg over 1 hour. Required predose of 2 grams probenecid orally (reduces renal clearance by blocking active renal tubular secretion).	Gilead, Antiviral treatment of cytomegalovirus in AIDS patients
Cilastatin (inhibitor of renal dipeptidase, dehydro-peptidase I) and Imipenam/ Primaxin		Powder 500-750 mg each, Sodium carbonate 10-20 mg (IV), pH 6.5-7.5	IM: Reconstitute with lidocaine 1% to 250 mg/mL suspension. IV: Reconstitute with 100 mL saline or dextrose then diluted with 100 mL saline or dextrose to 2.5-4 mg/mL solution	IM/ IV infusion	Merck, Antibiotic treatment of serious infections
Cimetidine HCl/ Tagamet		1) Solution 150 mg/mL Phenol 5 mg/mL pH 4-6. 2) Infusion solution 6 mg/mL Sodium chloride 9 mg/mL.	None for IM. Dilute with saline, dextrose 5% or lactated Ringer's to 15 mg/mL for IV bolus and 6 mg/mL for IV infusion.	IM/ Slow IV bolus at least 5 minutes/ IV Infusion over 15-20 minutes	Smith-Kline Beecham, Antiulcerative (histamine H2-receptor antagonist
Ciprofloxacin/ Cipro		1) Solution 10 mg/mL, Lactic acid, pH 3.3-3.9. 2) Infusion solution 2 mg/mL, Dextrose 5%, Lactic acid, pH 3.5-4.6.	Dilute with saline, dextrose 5% or lactated Ringer's to 1-2 mg/mL.	IV infusion over 60 minutes, 200-400 mg every 12 hours	Bayer, Antibacterial
Cisplatin/ Platinol		1) Lyophilized powder, after reconstitution contains 1 mg/mL, Mannitol 10 mg/mL, Sodium chloride 9 mg/mL, pH = 3.5-5.5. 2) Solution 1 mg/mL Sodium chloride 9 mg/mL.	Reconstitute with WFI to 1 mg/mL	IV infusion	Bristol-Meyers Oncology, Antineoplastic
Cladribine/ Leustatin		Solution 1 mg/mL, Sodium chloride 9 mg/mL, Sodium phophates, pH 5.5-8.0	Dilute with 500 mL saline to 0.09 mg/kg/day (not recommended to use dextrose 5% due to increased drug degradation)	IV infusion over 24 hours after	Ortho, Antineoplastic

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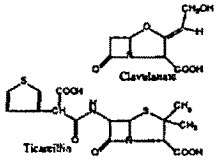
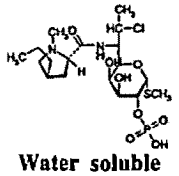
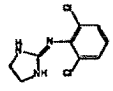
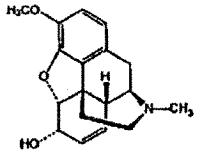
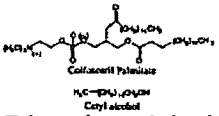
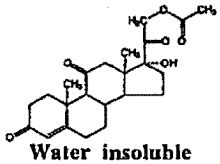
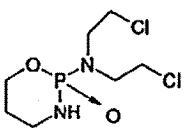
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Clavulanate potassium and ticarcillin disodium/ Timentin		1) Powder Clavulanate 0.1g, Ticarcillin 3 g. 2) Frozen solution Clavulanate 1 mg/mL, Ticarcillin 30 mg/mL	Reconstitute with WFI or saline to 8 mg/mL clavulanate and 200 mg/mL ticarcillin, further dilute with saline or lactated Ringer's to 10-100 mg/mL	IV infusion over 30 minutes	SmithKline Beecham, Antibiotic
Clindamycin Phosphate/ Cleocin phosphate	 **Water soluble phosphate ester prodrug**	1) Solution 150 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9.4 mg/mL pH = 5-6. 2) Ready to use solution 0.5-18 mg/mL Dextrose 5%, EDTA 0.04 mg/mL.	Dilute concentrated solution with saline or lactated Ringer's to ≤ 18 mg/mL.	IV infusion at 30 mg/hour	Pharmacia & Upjohn, Antibiotic
Clonidine/ Duraclon		Solution 0.1 mg/mL, Sodium chloride 9 mg/mL pH 5-7	None	IV infusion	Roxane, Analgesic
Codeine phosphate (Not in 1999 PDR as an injectable)		Solution, 15-60 mg/mL, w/wo Chlorobutanol 5 mg/mL, EDTA 1 mg/mL, Sodium metabisulfite 1-2 mg/mL, Acetate buffer pH 3-6.	None	SC/ IM/ IV occasionally	Elkins-Sinn and Wyeth, Analgesic, anticough
Colfosceril palmitrate (DPPC), Cetyl alcohol and Tyloxapol/ Exosurf neonatal	 Tyloxapol: oxyethylated tertiary octylphenol formaldehyde polymer	Lyophilized powder DPPC 108 mg Cetyl alcohol 12 mg Tyloxapol 8 mg, Sodium chloride 47 mg pH 5-7 (A synthetic lung surfactant)	Reconstitute with 8 mL WFI.	Intratracheal Suspension	Glaxo Wellcome, Prevention and treatment of Respiratory Disease Syndrome in low birth weight infants
Cortisone Acetate/ Cortone	 **Water insoluble ester prodrug**	**Suspension** 50 mg/mL, **Sodium carboxy-methylcellulose** 5 mg/mL, TWEEN 80 at 4 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL	None	IM only	Merck, Endocrine disorders, rheumatoid arthritis, allergies
Cyanocobal-amin (Vitamin B12)	MW = 1355, porphoryn like with Co (+) at the center, synthesized by bacteria	Solution 0.03-1 mg/mL Sodium chloride Benzyl alcohol, pH 4.5-7	None	SC/ IM	Elkins-Sinn, Nutrient
Cyclophos-phamide/ Cytoxan		Lyophilized powder 100-2000 mg Mannitol 75 mg/100 mg cyclophosphamide pH 3-9	Reconstitute with WFI to 20 mg/mL. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus/ IV infusion/ IP/ intrapleural	Bristol-Myers Squibb, Antineoplastic

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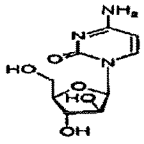
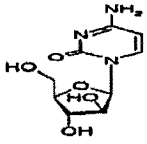
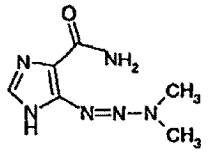
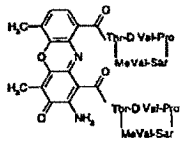
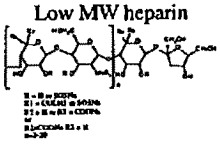
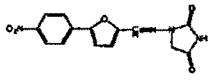
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Cyclosporin/ Sandimmune	Cyclic peptide (11 amino acids), MW ~ 1200	Solution, 50 mg/mL **Cremophor EL 65%, Ethanol 35%,** blanketed with nitrogen	Dilute with saline or dextrose 5% to 1-2.5 mg/mL (1 mL into 20-100 mL).	IV infusion over 2-6 hours	Novartis, Immuno-suppresent
Cytarabine (Ara-C)/ Cytosar-U		Lyophilized powder 500-2000 mg pH 5	Reconstitute with saline or WFI with benzyl alcohol 0.9% to 20-100 mg/mL.	Intrathecal/ SC/ IV bolus/ IV Infusion/	Pharmacia & Upjohn, Antineoplastic, Antiviral
Cytarabine (Ara-C)/ DepoCyte		**Suspension Multivesicular Lipid Particle** 5 mg/mL Cholesterol 4 mg/mL Dioleoylphosphatidylcholine (DOPC) 5.7 mg/mL, Dipalmitoylphosphatidylglycerol (DPPG) 1 mg/mL Sodium chloride 9 mg/mL pH 5.5-8.5	None	Intrathecal	Chiron (Developed by DepoTech) Antineoplastic, Antiviral
Dacarbazine/ DTIC-Dome		Solid 100-200 mg Mannitol and Citric acid, pH 3-4	Reconstitute with WFI to 10 mg/mL. For IV infusion may be further diluted with saline or dextrose 5% to 0.4 mg/mL	IV over 1 minute/ IV Infusion over 15-30 minutes	Bayer, Antineoplastic
Dactino-mycin/ Cosmegen		Lyophilized powder 0.5 mg, Mannitol 20 mg, pH 5.5-7	Reconstitute with 1.1 mL WFI. For IV infusion further dilute with saline or dextrose 5%.	IV bolus/ IV Infusion/	Merck, Antibiotic
Dalteparin/ Fragmin	Low MW heparin 	Solution (prefilled syringe and multi-use vial) 64-160 mg/mL Sodium chloride, w/wo Benzyl alcohol 0.15% pH 5.0-7.5	None	SC	Pharmacia & Upjohn, Antithrombotic
Danaparoid/ Orgaran	84% heparin sulfate, 12% dermatan sulfate, 4% chondroitin sulfate (isolated from porcine intestinal mucosa)	Solution (prefilled syringe or ampule) 1250 anti-Xa units/mL, Sodium chloride, Sodium sulfite 0.15% pH 7	None	SC	Organon, Antithrombotic
Dantrolene sodium/ Dantrium		Lyophilized powder 20 mg, Mannitol 3000 mg, pH 9.5	Reconstitute with 60 mL WFI to 0.3 mg/mL. For IV infusion further dilute with IV fluids.	IV bolus/ IV infusion over 1 hour.	Procter & Gamble Pharm., (Muscle relaxant) Treatment of hypermetabolism and hyperthermia

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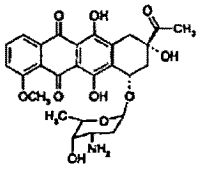
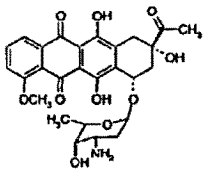
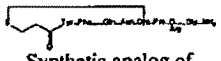
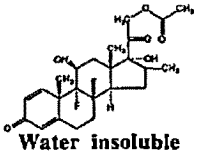
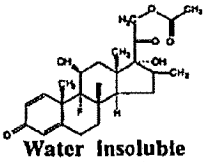
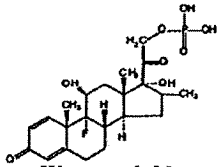
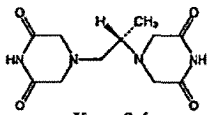
InnoPharma Exhibit 1046.0424

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Daunorubicin HCl/ Cerubidine		Lyophilized powder 21.4 mg, Mannitol 100 mg pH 4.5-6.2	Reconstitute with 4 mL WFI to 5 mg/mL, then further dilute with 10-15 mL saline and then inject into rapidly flowing IV infusion of saline or dextrose 5%.	IV infusion	Bedford, Antibiotic
Daunorubicin Citrate/ DaunoXome		Solution liposome 2 mg/mL, Distearoylphosphatidylcholine: Cholesterol in 2:1 molar ratio, lipid to drug ratio of 18.7:1 diameter of 45 nm	Dilute 1:1 with dextrose 5% to 1 mg/mL.	IV infusion over 60 minutes	NeXstar (now Gilead), Antibiotic
Desmopressin acetate/ DDAVP	 Synthetic analog of natural hormone 8-arginine vasopressin (ADH)	Solution 4 ug/mL, Sodium chloride 9 mg/mL, w/wo Chlorobutanol pH 4	None for SC or IV bolus. For IV infusion dilute with saline to (0.3 ug/kg) in 50 mL.	SC/ IV bolus/ IV infusion over 15-30 minutes	Rhone-Poulenc, Rorer, Hemophilia (maintain homeostasis)
Dexamethasone Acetate/ Decadron-LA	 **Water insoluble acetate ester prodrug**	**Suspension** 8 mg/mL Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, TWEEN 80 at 0.75 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Gentle swirl contents to resuspend settled particles.	IM/ Intralesional/ Intra-articular/ Soft tissue	Merck, Anti-inflammatory
Dexamethasone Acetate/ Dalalone D.P.	 **Water insoluble acetate ester prodrug**	**Suspension** 16 mg/mL **Sodium carboxymethylcellulose** 5 mg/mL, TWEEN 80 at 0.75 mg/mL, Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Gentle swirl contents to resuspend settled particles.	IM/ Intra-articular/ Soft tissue (Not intralesional)	Forest, Anti-inflammatory
Dexamethasone Phosphate sodium/ Decadron	 **Water soluble phosphate ester prodrug**	**Solution** 4 and 24 mg/mL w/wo Lidocaine 10 mg/mL, Creatinine 8 mg/mL, Sodium citrate 10 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5 under nitrogen	For IV infusion dilute with saline or dextrose 5%.	IV bolus/ IV infusion/ IM/ Intralesional/ Intra-articular/ Soft tissue	Merck, Anti-inflammatory
Dexrazoxan/ Zinecard	 pKa = 2.1	Powder 250-500 mg, Provided diluent: 25 and 50 mL of Sodium lactate 0.167 Molar, pH 3.5-5.5	Reconstitute with provided diluent to 10 mg/mL. For IV infusion dilute with saline or dextrose 5% to 1.3-5.0 mg/mL.	IV bolus/ IV infusion	Pharmacia & Upjohn, Cardioprotective agent used in conjunction with doxorubicin

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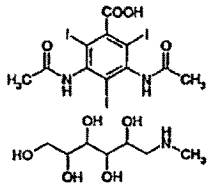
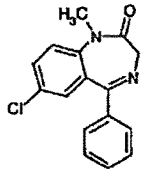
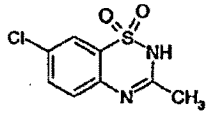
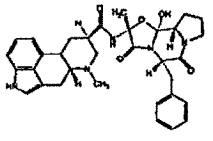
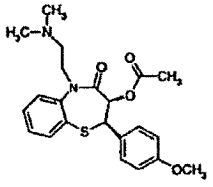
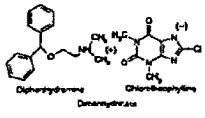
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Diatrizoate meglumine (Not in 1999 PDR)		Solution 300-600 mg/mL Sodium citrate, EDTA pH 6-7	None	IV/ IM/ Intra-arterial/ Intra-articular or selected area for visualization	Nycomed and Bracco, Radiopaque medium for "visualizing" *in vivo*
Diazepam/ Valium		Solution 5 mg/mL **Propylene glycol 40%, Ethyl alcohol 10%,** Benzyl alcohol 1.5%, Sodium benzoate 5%, Benzoic acid pH 6-7	None	IM/ IV through running IV tube at 1 minute per 5 mg diazepam	Roche, Management of anxiety disorders, Skeletal muscle relaxant
Diazoxide/ Hyperstat		Solution 15 mg/mL **pH 11.6**	None	IV bolus/ "IV Minibolus" (1-3 mg/kg every 5-15 minutes up to 150 mg)	Schering, Antihypertensive (prompt reduction of blood pressure)
Digoxin/ Lanoxin	Secondary glycoside extracted from the leaves of *Digitalis lanata*, (insoluble in water)	Solution 0.25 mg/mL **Propylene glycol 40%, Ethyl alcohol 10%,** Sodium phosphate and 0.08%, Citric acid. pH of 6.8 to 7.2	None or can be diluted 4-fold with WFI, saline or dextrose 5%, but must be used immediately due to precipitation	IV over 1-5 minutes/ rarely IM due to pain with IM injection.	Glaxo Wellcome, Cardiotonic
Dihydro-ergotamine mesylate/ D.H.E 45		Solution 1 mg/mL, **Glycerin 15%, Ethyl alcohol 6.1%,** pH 3.6	None	IV bolus/ IM/ SC	Novartis, Migraine headaches
Diltiazem/ Cardizem		1) Solution 5 mg/mL, **Sorbitol 71 mg/mL** Citric acid 0.75 mg/mL, Sodium citrate 0.65 mg/mL, pH 3.7-4.1. 2) Lyophilized powder in a dual chamber syringe **Syringe A:** Diltiazem 25 mg, Mannitol 37.5 mg, **Syringe B:** 5 mL WFI with Sodium chloride 0.6% and Benzyl alcohol 0.5% pH 4.0-7.0. 3) Lyophilized powder, 100 mg, Mannitol 75 mg	Reconstitute the contents within the Lyo-ject syringe. For IV infusion dilution a solution with saline to 0.5-1.2 mg/mL, or reconstitute the 100 mg lyophilized powder with saline to 1 mg/mL.	IV bolus over 2 minutes/ IV Infusion.	Hoechst Marion Roussel, Antianginal; Antihypertensive; Arrhythmia; Atrial Fibrillation; Calcium Channel Blocker
Dimenhy-drinate (Not in 1999 PDR as an injectable)		Solution 50 mg/mL **Propylene glycol 50%,** Benzyl alcohol 5%, pH 6-7	None for IM. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 5 mg/mL	IM/ IV	Steris, Antiemetic

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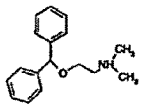
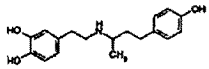
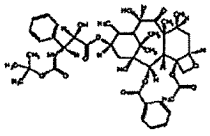
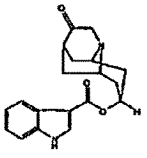
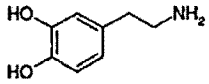
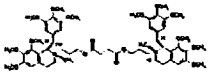
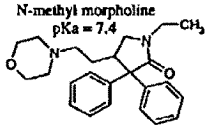
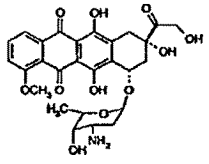
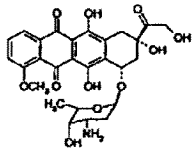
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Diphenhydramine HCl/ Benadryl		Solution 50 mg/mL Benzethonium chloride 0.1% pH 5-6	None for IM or IV bolus. For IV infusion may be diluted with saline, dextrose 5% or lactated Ringer's	Deep IM/ Slow IV bolus/ IV Infusion/ (Not SC)	Parke-Davis, Antihistamine, also motion sickness
Dobutamine HCl		Solution 12.5 mg/mL, Sodium bisulfite 0.24 mg/mL, pH 2.5-5.5	Dilute with saline, dextrose 5%, lactated Ringer's to 0.5-5.0 mg/mL.	IV infusion	Lilly, Cardiotonic (inotropic agent)
Docetaxel/ Taxotere		Solution 40 mg/mL in **TWEEN 80** Provided **diluent of Ethyl alcohol 13%** in water	Dilute with provided diluent (13% ethyl alcohol) to 10 mg/mL.	IV infusion over 1 hour	Rhone-Poulenc Rorer, Antineoplastic
Dolasetron mesylate/ Anzemet		Solution 20 mg/mL Mannitol 38 mg/mL, Acetate buffer pH 3.2-3.8	None for IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 0.25 mg/mL.	IV bolus at 100 mg per 30 seconds/ IV infusion at 0.35-1.8 mg/kg over 15 minutes	Hoechst Marion Roussel, Antinaseant, Antiemetic
Dopamine		Solution 40-160 mg/mL, Sodium metabisulfite 0.9%, Sodium citrate buffer, pH 3.3	Dilute with saline, dextrose 5% or lactated Ringer's to ~ 0.4-3.0 mg/mL	IV infusion	Astra, Cardiotonic and antihypotensive
Doxacurium chloride/ Noromax		Solution 1 mg/mL Benzyl alcohol 0.9% pH 3.9-5	None or dilute with saline or dextrose 5% to as low as 0.1 mg/mL.	IV bolus	Glaxo Wellcome, Skeletal muscle relaxant
Doxapram HCl/ Dopram		Solution 20 mg/mL Benzyl alcohol 0.9% pH 3.5-5	None for IV bolus. For IV infusion dilute with saline or dextrose 5% to 1 mg/mL	IV bolus/ IV infusion	Robbins, Respiratory stimulant
Doxorubicin HCl/ Adriamycin PFS and RDF; Rubex		1) Lyophilized powder 10-150 mg, Lactose 5 mg/mg doxorubicin, Methylparaben 0.1 mg/mg doxorubicin pH 3.8-6.5. 2) Solution 2 mg/mL Sodium chloride 9 mg/mL pH 3.0	Reconstitute with saline to 2 mg/mL	IV in not less than 3-5 minutes through a Y-site or a 3-way stopcock of a free-flowing infusion of saline or dextrose 5%.	Pharmacia & Upjohn and Astra and BMS (powder only), Antineoplastic
Doxorubicin HCl/ Doxil **(Pegylated stealth liposome formulation)**		**Liposomal dispersion** 2 mg/mL, N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium (MPEG-DSPE) 3.2 mg/mL, Hydrogenated soy phosphatidylcholine (HSPC) 9.6 mg/mL, Cholesterol 3.2 mg/mL, Ammonium sulfate 2 mg/mL, Histidine	Dilute the dose into 250 mL of dextrose 5%.	IV infusion over 30 minutes	Sequus, Antineoplastic, AIDS-related Kaposi's sarcoma

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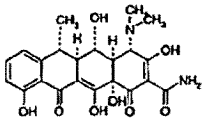
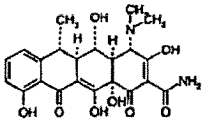
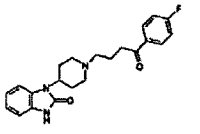
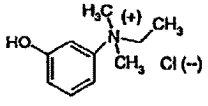
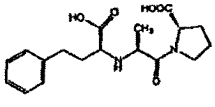
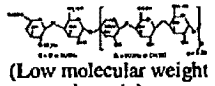
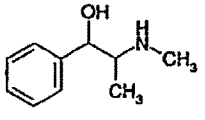
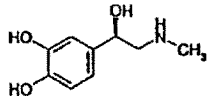
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Doxycycline hyclate (HCl hemihydrate)/ Atridox		Powder **Two syringe mixing system.** **Syringe A:** Poly(DL-lactide) ~ 33 mg/mL dissolved in 5 mL of N-methyl-2-pyrrolidone (NMP), **Syringe B:** Doxycycline hyclate 42.5 mg	Couple syringe A to syringe B and inject liquid contents into the powder, then mix 100 time in the syringe.	Subgingival (solution that solidifies upon contact with the crevicular fluid providing 7-day controlled release	Block, Antibiotic
Doxycycline hyclate (HCl hemihydrate)/ Vibramycin		Powder, 100-200 mg, Ascorbic acid 480-960 mg pH 1.8-3.3	Reconstitute with WFI to 10 mg/mL, then further dilute with saline, dextrose 5% or lactated Ringer's to 0.1-1.0 mg/mL	IV infusion over 1-4 hours	Pfizer, Antibiotic
Droperidol citrate/ Fentanyl Droperidol		Solution 2.5 mg/mL, Fentanyl citrate 0.05 mg/mL, Lactic acid pH 3-4	None for IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 0.01-0.05 mg/mL.	IM/ IV bolus/ IV infusion	Astra, Tranquilizer, Antipsychotic
Edrophonium chloride/ Tensilon		Solution 10 mg/mL, Sodium sulfite 0.2%, w/wo Phenol 0.45%, Citric acid pH 5.4	None	IV bolus/ IM/ SC	ICN, Choleringeric (inhibition of acetyl-cholinesterase)
Enalaprilat/ Vasotec		Solution 1.25 mg/mL Sodium chloride (isotonic) Benzyl alcohol 0.9% pH 6.5-7.5	None or dilution of 0.6-1.2 mg with 50 mL saline, dextrose 5% or lactated Ringer's.	IV infusion over 5 minutes	Merck, Antihypertensive (ACE Inhibitor)
Enoxaparin sodium/ Lovenox	 (Low molecular weight heparin)	Solution (Prefilled syringes available) 100 mg/mL pH 5.5-7.5	None	SC	Rhone-Poulenc Rorer, Antithrombolytic
Ephedrine sulfate (Not in 1999 PDR as an injectable)		Solution 25-50 mg/mL pH 4.5-7	None	Slow IV/ IM/ SC	Abbott, Sympathomimetic (nasal decongestant), mydriatic, allergy in emergency
Epinephrine HCl/ Epipen Epinephrine autoinjector (Adrenalin)		Solution 0.5-1.0 mg/mL Sodium chloride 1.8 mg/mL Sodium metabisulfite 0.5%, pH 2.2-5	None	IM	Dista, Emergency treatment of allergies

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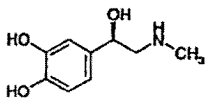
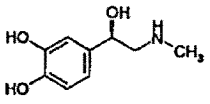
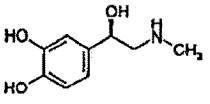
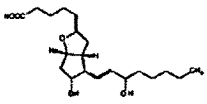
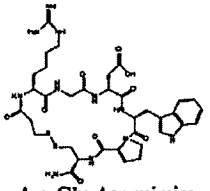
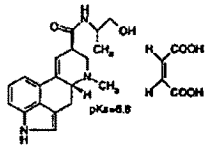
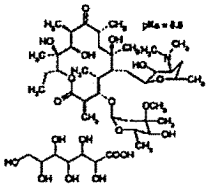
InnoPharma Exhibit 1046.0428

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Epinephrine HCl/ Susphrine		**Suspension** 5 mg/mL **Glycerin 325 mg/mL. Thioglycolic acid 6.6 mg/mL,** Phenol 5 mg/mL, Ascorbic acid 10 mg/mL,	Shake contents of vial to disperse particles to uniformity.	SC	Fores, Asthma
Epinephrine HCl and Bupivacaine HCl/ Sensorcaine		Solution 0.005 mg/mL Bupivacaine 2.5-7.5 mg/mL, Sodium metabisulfife 0.5%, Citric acid pH 3.3-5.5	None	Local infiltration	Astra, Local anesthesia (Bupivacaine)
Epinephrine HCl and Lidocaine HCl/ Xylocaine		Solution 0.005 mg/mL Lidocaine 10-15 mg/mL, Sodium chloride Sodium metabisulfife 0.5%, w/wo Methylparaben 1 mg/mL Citric acid pH 5-7	Dilute 20-200-fold with saline	IV infusion	Astra, Anesthesia (Lidocaine)
Epoprostenol sodium/ Flolan		Lyophilized powder 0.5-1.5 mg Mannitol 50 mg, Sodium chloride 2.9 mg Glycine 3.8 mg, **pH 10.2-10.8.** Provided diluent: Water with Glycine 1.9 mg/mL, Sodium chloride 1.5 mg/mL.	Reconstitute with provided diluent to 0.003-0.015 mg/mL.	IV infusion	Glaxo Wellcome, Antihypertensive
Eptifibatide/ Integrillin	 Arg-Gly-Asp mimic: [binds to (GP) IIb/IIIa ($\alpha_{IIb}\beta_3$)]	Solution 0.75-2 mg/mL Citric acid 5.25 mg/mL pH 5.25	None for IV bolus. For IV infusion dilute with saline or dextrose 5% to 0.75 mg/mL.	IV bolus/ IV infusion	Cor and Key, Treatment of acute coronary syndrome: In patients undergoing PCI (Inhibits platelet aggregation)
Ergonovine maleate/ Ergotrate maleate (Not in 1999 PDR)		Solution 0.2 mg/mL, Phenol 0.25%, Ethyl lactate 0.1%, Lactic acid 0.1%, pH 2.7-3.4	Dilute with 5 mL saline.	IV/ IM over 1 minute	Lilly, Oxytocic
Erythro-mycin gluceptate/ Ilotycin gluceptate (Not in 1999 PDR)		Powder 1000 mg pH 7.7	Reconstitute with WFI to 50 mg/mL, then further dilute with saline, dextrose 5% or lactated Ringer's to 1.0 mg/mL	IV infusion	Dista, Antibiotic

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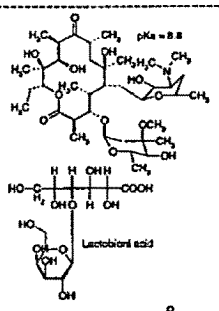
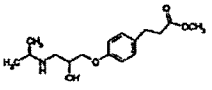
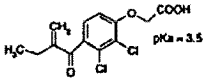
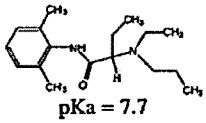
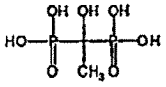
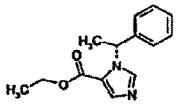
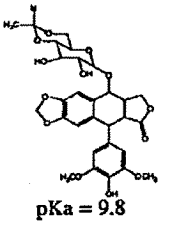
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Erythro-mycin lactobionate		Powder 500-1000 mg pH 7.7	Reconstitute with WFI to 50 mg/mL, then further dilute with saline, dextrose 5% or lactated Ringer's to 1.0 mg/mL	IV infusion	Lederle, Antibiotic
Esmolol HCl/ Brevibloc		Solution 250 mg/mL **Propylene glycol 25%,** **Ethyl alcohol 25%,** Sodium acetate pH 3.3-5.5	Dilute with saline, dextrose 5% or lactated Ringer's to 10 mg/mL.	IV infusion	Ohmeda (Baxter), Antiarrhythmic
Ethacrynate sodium/ Sodium edecrin		Lyophilized powder 50 mg, Mannitol 62.5 mg pH = 6.3-7	Reconstitute with 50 mL saline or dextrose 5% to 1 mg/mL	Slow IV bolus/ IV infusion	Merck, Diuretic
Etidocaine HCl/ Duranest	 pKa = 7.7	Solution 10-15 mg/mL Epinephrine 0.005 mg/mL, Sodium chloride 6-7 mg/mL, w/wo Sodium metabisulfite 0.5 mg/mL, w/wo Citric acid, pH 3.0-5.0	None	Local infiltration	Astra, Local anesthetic
Etidronate disodium/ Didronel		Solution 50 mg/mL	Dilute with saline to 0.6-1.2 mg/mL	IV infusion over 2 hours	MGI, Treatment of hypercalcemia
Etomidate/ Amidate (Not in 1999 PDR)		Solution 2 mg/mL **Propylene glycol 35%**	None	IV bolus over 30-60 seconds	Abbott, Hypnotic
Etoposide/ Etoposide injection and VePesid	 pKa = 9.8	**Non-aqueous Solution** 20 mg/mL **PEG 300 60%,** **Ethyl alcohol 30%,** **TWEEN 80 at 8.0%,** Benzyl alcohol 3.0 %, Citric acid 2 mg/mL pH = 3-4	Dilute with saline or dextrose 5% to 0.2-0.4 mg/mL.	IV infusion over 30-60 minutes	Astra and Bristol-Myers-Squibb, Antineoplastic

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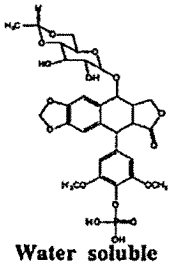
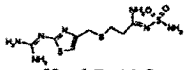
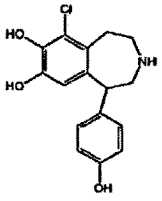
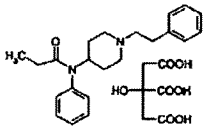
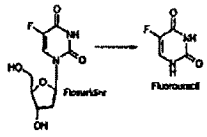
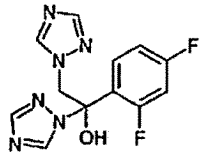
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Etoposide Phosphate/ Etopophos	 **Water soluble phosphate ester prodrug**	Lyophilized powder 100-1000 mg, Dextran 40 at 300-3000 mg Sodium citrate 32-327 mg/mL,	Reconstitute with WFI, saline or dextrose 5% to 10-20 mg/mL which is further diluted with saline or dextrose 5% to 0.2-0.4 mg/mL.	IV infusion over 30-60 minutes	Bristol-Myers-Squibb, Antineoplastic
Famotidine/ Pepcid	 pKa 6.7, 11.2	Solution 10 mg/mL L-aspartic acid 4 mg/mL, Mannitol 20 mg/mL, Benzyl alcohol 0.9%, pH 5-6	For IV bolus dilute with saline, dextrose 5% or lactated Ringer's to 2-4 mg/mL, and for IV infusion dilute to 0.2 mg/mL.	IV bolus over > 2 minutes/ IV infusion over 15-30 minutes	Merck, Antiulcerative (inhibition of gastric secretion)
Fenoldopam mesylate/ Corlopam		Solution 10 mg/mL, **Propylene glycol 50%**, Sodium metabisulfite 1 mg/mL, Citric acid 3.4 mg/mL, Sodium citrate 0.61 mg/mL	Dilute with saline or dextrose 5% to 0.04 mg/mL.	IV infusion	Neurex, Antihypertensive
Fentanyl citrate Sublimaze (See Droperidol)		Solution 0.050 mg/mL pH 4-7.5	None for IM and IV bolus. For IV infusion dilute with saline or dextrose 5% to 0.0025-0.020 mg/mL	IM/ IV bolus over 1-2 minutes/ IV infusion	Asra, Baxter and Elkins- Sinn, Analgesic
Floxuridine/ FUDR		Powder 500 mg pH 4-5	Reconstitute with 5 mL WFI to 100 mg/mL then further diluted with saline or dextrose 5% to 0.1-0.6 mg/kg/day.	Intra-arterial infusion	Roche, Antineoplastic
Fluconazole/ Diflucan (selective inhibitor of fungal cytochrome P-450 sterol C-14 alpha-demethylation)		Solution 2 mg/mL Sodium chloride 9 mg/mL, or Dextrose 56 mg/mL, pH 4-8	None	IV infusion at ≤ 200 mg/hour	Pfizer, Antifungal

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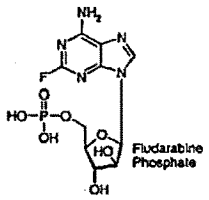
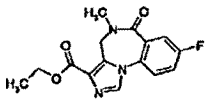
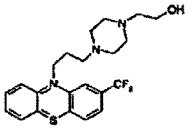
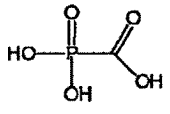
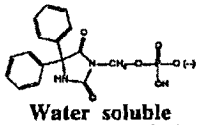
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Fludarabine Phosphate	 **Water soluble phosphate ester prodrug**	Lyophilized powder 50 mg, Mannitol 50 mg pH 7-8	Reconstitute with 2 mL WFI to 25 mg/mL then further diluted with 100-125 mL saline or dextrose 5% to ~ 0.5 mg/mL.	IV infusion over 30 minutes	Berlex, Antineoplastic
Flumazenil/ Romazicon		Solution 0.1 mg/mL, Sodium chloride 9 mg/mL, Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL, EDTA 0.01%, Acetic acid 0.01%, pH 4	None or dilute with saline, dextrose 5% or lactated Ringer's.	IV bolus over 15 seconds through a freely running IV infusion line	Roche, Treatment of benzodiazepine overdose (benzo-diazepine antagonist)
Fluorouracil (Not in 1999 PDR as an injectable)		Solution 50 mg/mL pH 9.2	None for IV bolus. For IV infusion dilute with dextrose 5% to 1-10 mg/mL.	IV bolus/ IV infusion	Roche, Antineoplastic
Fluphenazine HCl/ Prolixin (Not in 1999 PDR as an injectable)		Solution, 2.5 mg/mL Sodium chloride (isotonic), Methylparaben 0.1%, Propylparaben 0.01% pH 5	None	IM	Apothecon Antipsychotic
Fomiversen sodium/ Vitravene	**ANTI-Sense oligonucleotide** 5'-GCG TTT GCT CTT CTT CTT GCG-3'	Solution 6.6 mg/mL Sodium chloride, Sodium carbonate, Sodium bicarbonate pH 8.7	None	Intravitreal (0.5 mL/eye)	Ciba Vision, Antiviral
Foscarnet sodium/ Foscavir		Solution 24 mg/mL pH 7.4	None for central line infusion, but infusion in peripheral line must be diluted with saline or dextrose 5% to 12 mg/mL.	IV infusion	Astra, Antiviral
Fosphenytoin/ Cerebyx	 **Water soluble hydroxy-methyl phosphate ester prodrug**	Solution 75 mg/mL (50 mg/mL phenytoin equivalents, PE) Tromethamine, pH = 8.6-9.0	None for IM. For IV infusion dilute with saline or dextrose 5% to 1.5- 25 mg PE/mL.	IM/ IV infusion at ≤ 150 PE/mlnute	Parke-Davis, Anticonvulsant

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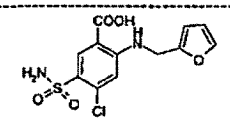
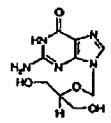
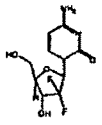
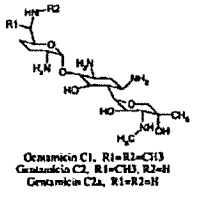
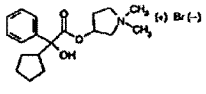
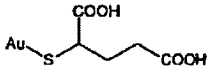
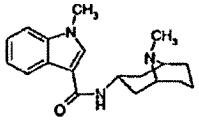
InnoPharma Exhibit 1046.0432

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Furosemide (Frusemide)/ Formerly Lasix		Solution 10 mg/mL Sodium chloride (isotonic) pH 8-9	None for IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus over 1-2 minutes/ IV infusion at ≤ 4 mg/minute	Astra and Baxter and Elkins-Sinn, Antihypertensive; Diuretic
Ganciclovir sodium (DHPG)/ Cytovene		Lyophilized powder 500 mg pH 11 (Solubility at pH 7 = 6 mg/mL, pKa 2.2, 9.4, active drug is triphosphate)	Reconstitute with 10 mL WFI to 50 mg/mL then further dilute with 100 mL saline, dextrose 5% or lactated Ringer's to ~ 5 mg/mL.	IV infusion at 5 mg/kg over 1 hour	Syntex (Roche), Treatment of CMV retinitis in immune-compromised patients
Gemcitabine HCl/ Gemzar		Lyophilized powder 200-1000 mg, pH 2.7-3.3	Reconstitute with saline to 40 mg/mL which may be further diluted with saline to 0.1 mg/mL.	IV infusion over 30 minutes	Lilly , Antineoplastic
Gentamicin sulfate/ Garamycin		Solution 10-40 mg/mL Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL, Sodium bisulfite 3.2 mg/mL, EDTA 0.1 mg/mL pH 3-5.5	None for IM. For IV infusion dilute with 50-200 mL saline or dextrose 5%.	IM/ IV Infusion over 0.5-2 hours	Schering, Antibiotic
Glucagon	His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr	Lyophilized powder 1 mg Lactose 49 mg. Provided diluent: Water with Glycerin 1.2% pH < 3	Reconstitute with provided diluent to 1 mg/mL. If the dose is > 2 mg, then reconstitute with WFI.	IV at ≤ 1 mg/min	Lilly, Treatment of hypoglycemia
Glyco-pyrrolate/ Robinul		Solution 0.2 mg/mL Benzyl alcohol 0.9% pH 2-3	None	IM/ IV bolus	Robbins, Anticholinergic
Gold thiomaleate sodium / Aurolate, Myochrysine		Solution 50 mg/mL Benzyl alcohol 0.5% pH 5.8-6.5	None	IM (Intragluteally)	Merck & Co., Antirheumatic
Granisetron HCl/ Kytril		Solution 1 mg/mL Sodium chloride 9 mg/mL w/wo Benzyl alcohol 10 mg/mL w/wo Citric acid 9 mg/mL, pH 4.7-7	None for IV bolus. For IV infusion dilute with 20-50 mL saline or dextrose 5% (10-40 ug/kg).	IV bolus over 30 seconds/ IV infusion over 5 minutes	Smith-Kline Beecham, Antinauseant, Antiemetic

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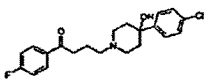
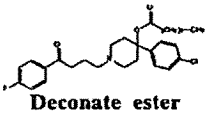
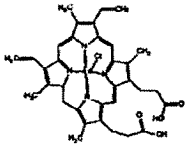
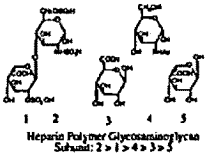
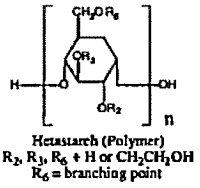
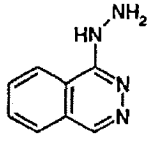
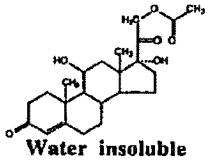
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Haloperidol lactate/ Haldol		Solution 5 mg/mL, Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL, Lactic acid pH 3-4	None	IM/ Seldom via IV bolus or IV infusion	Ortho-McNeil, Psychotic disorders, Tourette's Disorder
Haloperidol Decanoate/ Haldol decanoate	 **Deconate ester prodrug for prolonged effect**	**Non-aqueous solution** 50-100 mg/mL **in Sesame Oil** Benzyl alcohol 1.2%	None	IM	Ortho-McNeil, psychotic disorders, Tourette's Disorder
Hemin/ Panhematin (a.k.a Hematin)		Lyophilized powder 313 mg, **Sorbitol 300 mg** Sodium carbonate 215 mg,	Reconstitute with 43 mL WFI to 7 mg/mL.	IV infusion using a 0.45 um filter	Abbott, Treatment of acute intermittent porphyria related to menstration
Heparin sodium	 Heparin Polymer Glycosaminoglycan Subunit: 2 > 1 > 4 > 3 > 5	Solution 10-20,000 units/mL, Benzyl alcohol ≤ 10 mg/mL w/wo Sodium chloride 1 mg/mL pH 5-7.5	None or dilute with saline or lactated Ringer's to 10-100 units/mL.	IV infusion	Wyeth-Ayerst and Lilly, Anticoagulant
Hetastarch/ Hespan	 Hetastarch (Polymer) R_2, R_3, R_6 = H or CH_2CH_2OH R_6 = branching point	Solution 60 mg/mL, Sodium chloride 9 mg/mL pH 3.5-7.0	None	IV infusion	DuPont, Plasma volume expansion
Hydralazine HCl/ Apresoline (Not in 1999 PDR as an injectable)		Solution 20 mg/mL **Propylene glycol 10%,** Parabens 1 mg/mL pH 3-4	None	IM/ IV	SoloPak and CibaGeneva, Antihypertensive, Vasodilating Agent
Hydro-cortisone Acetate/ Hydrocortone Acetate (Slow onset of action, but long duration)	 **Water insoluble acetate ester prodrug**	Suspension 50 mg/mL **Sodium carboxy-methylcellulose 5 mg/mL,** TWEEN 80 at 4 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL	None	IM/ Intralesional/ Intra-articular	Merck, Replacement therapy in adrenocortical deficiency, Anti-inflammatory

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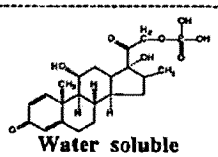
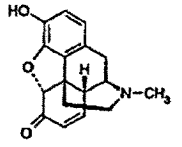
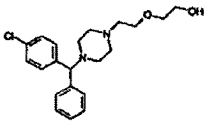
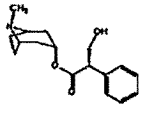
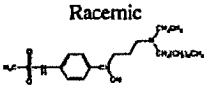
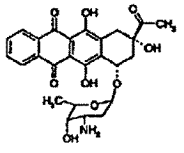
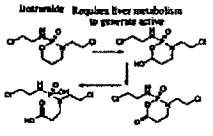
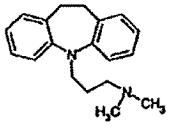
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Hydro-cortisone Phosphate sodium / Hydrocortone Phosphate	 **Water soluble phosphate ester prodrug**	Solution 50 mg/mL Creatinine 8 mg/mL, Sodium bisulfite 3.2 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL, Sodium citrate 10 mg/mL pH 7.5-8.5	None or dilute with saline or dextrose 5%.	SC/ IM/ IV bolus/ IV infusion	Merck, Replacement therapy in adrenocortical deficiency, Anti-inflammatory
Hydromor-phone/ Dilaudid HCl		1) Solution 10 mg/mL Sodium citrate 2 mg/mL, Citric acid 2 mg/mL pH 4-5.5. 2) Lyophilized powder 250 mg	Dilute solution with saline to 2 mg/mL. Reconstitute powder with 25 mL WFI to 10 mg/mL and dilution with saline to 2 mg/mL.	SC/ IM/ IV (over 2-3 minutes)	Knoll, Analgesic
Hydroxyzine HCl/ Vistaril		Solution 25-50 mg/mL, Benzyl alcohol 0.9%, pH 3.5-6	None	IM	Pfizer, Tranquilizer
Hyoscyamine sulfate/ Levsin		Solution 0.5 mg/mL	None	SC/ IM/ IV bolus	Schwarz, Peptic ulcers
Ibutilide fumarate/ Corvert	Racemic 	Solution 0.1 mg/mL Sodium chloride 8.9 mg/mL pH 4.6	None or dilute with 50 mL saline or dextrose 5% to 0.017 mg/mL.	IV infusion	Pharmacia & Upjohn, Antiarrhythmic
Idarubicin HCl/ Idamycin		Solution 1 mg/mL **Glycerin 25 mg/mL**, pH 3.5	None	IV infusion over 10-15 minutes in running line of saline or dextrose 5%	Pharmacia & Upjohn, Antineoplastic
Ifosfamide/ Ifex		Powder 1000-3000 mg pH 6	Reconstitute with WFI to 50 mg/mL then further dilute with saline, dextrose 5% or lactated Ringer's to 0.6-20 mg/mL.	IV infusion over at least 30 minutes with Mesna	Bristol-Myers-Squibb, Antineoplastic
Imipenem (See Cilastatin)					
Imipramine HCl/ Tofranil (Not in 1999 PDR as an injectable)		Solution 12.5 mg/mL Sodium bisulfite 0.5 mg/mL, Sodium sulfite 0.5 mg/mL, Ascorbic acid 1 mg/mL pH 4-5	None	IM	Geigy, The original tricyclic antidepressant

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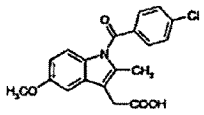
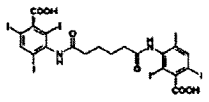
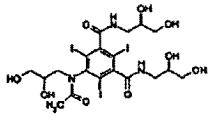
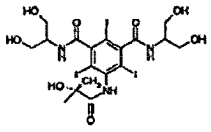
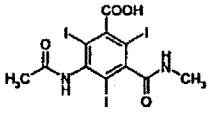
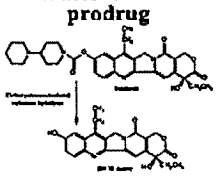
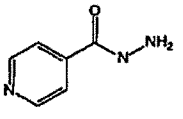
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Indomethacin sodium/ Indocin I.V.		Lyophilized powder, 1 mg pH 6-7.5	Reconstitute with saline to 0.5-1 mg/mL.	IV bolus	Merck, Nonsteroidal antiinflammatory
Iodipamide meglumine/ Cholografin Meglumine (Not in 1999 PDR)		Solution 520 mg/mL, Sodium citrate 3 mg/mL, EDTA 0.04% pH 6.5-7.7	Warm to body temperature.	IV infusion over 10-45 minutes	Squibb, Diagnostic aid (Radiopaque medium)
Iohexol/ Omnipaque (Not in 1999 PDR)		Solution 140-350 mg/mL, EDTA TRIS 1.2 mg/mL pH 6.8-7.7	Warm to body temperature.	IV/ Intra-arterial/ Intrathecal/	Nycomed, Diagnostic aid (Radiopaque medium)
Iopamidol/ Isovue (Not in 1999 PDR)		Solution 200-370 mg/mL EDTA, TRIS 1 mg/mL pH 6.5-7.5	Warm to body temperature.	IV/ Intra-arterial/ Intrathecal	Braco, Diagnostic aid (Radiopaque medium)
Iothalamate meglumine (or sodium)/ Conray (Not in 1999 PDR)		Solution 170-600 mg/mL	Warm to body temperature.	IV/ Intra-arterial	Mallinckrodt, Diagnostic aid (Radiopaque medium)
Irinotecan HCl/ Camptosar	**Water soluble prodrug** 	Solution 20 mg/mL, **Sorbitol 45 mg/mL**, Lactic acid 0.9 mg/mL pH 3.0-3.8	Dilute with dextrose 5% or saline to 0.12-1.1 mg/mL.	IV infusion over 90 minutes	Pharmacia & Upjohn, Metastastic carcinoma
Isoniazid/ Nydrazid		Solution 10 mg/mL, Chlorobutanol 0.25%, pH 6.0-7.0	None	IM	Apothecon, Tuberculosis
Isoproterenol HCl/ Isuprel HCl		Solution 0.2 mg/mL Sodium chloride 7 mg/mL, Sodium metabisulfite 1 mg/mL, Lactic acid 0.12 mg/mL, Sodium lactate 1.8 mg/mL pH 3.5-5.5	None for SC or IM. For IV bolus dilute with saline or dextrose 5% to 0.02 mg/mL, for IV infusion dilute to 0.0004-0.004 mg/mL.	SC/ IM IV bolus/ IV infusion/ [Intracardiac (extreme emergency)]	Sanofi Winthrop (Elkins-Sinn), Smooth muscle relaxant

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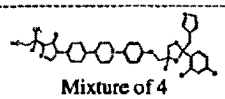
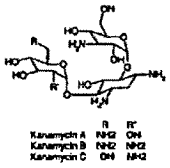
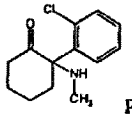
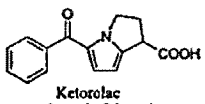
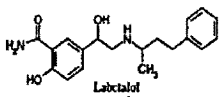
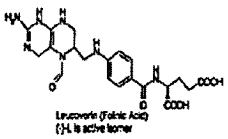
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Itraconazole/ Sporanox	 Mixture of 4 diastereoisomers (two enantiomeric pairs)	Solution 10 mg/mL **Hydroxypropyl-β-cyclodextrin 40 %,** Propylene glycol 2.5%, pH 4.5	Dilute with saline to 5 mg/mL.	IV infusion	Janssen, Antifungal
Kanamycin sulfate/ Kantrex (Not in 1999 PDR)		Solution 37-333 mg/mL Sodium bisulfite 0.5%, Sodium citrate 2%, pH 4.5	None for IM. For IV infusion dilute with dextrose 5% or saline to 2.5-5 mg/mL.	IM/ IV infusion over 30-60 minutes/ Intraperitoneal instillation.	Apothecon, Antibiotic
Ketamine HCl/ Ketalar (Not in 1999 PDR)	 pKa = 7.5	Solution 10-100 mg/mL Sodium chloride (isotonic) Benzethonium chloride 0.1%, pH 3.5-5.5	None or dilute the 100 mg/mL with WFI, saline or dextrose 5% to 50 mg/mL	IM/ IV bolus over 60 seconds	Parke-Davis, Anesthetic
Ketorolac tromethamine/ Toradol	 Ketorolac racemic, only S is active pKa = 3.5	Solution (vials or cartridge-needle units) 15-30 mg/mL **Ethyl alcohol 10%,** Sodium chloride 6.7-8.7 mg/mL, w/wo citric acid 0.1%, pH 7-8	None	IM/ IV	Syntex (Roche), Analgesic, Nonsteroidal antiinflammatory
Labetalol HCl/ Normodyne and Trandate	 Labetalol racemic R,R = Dilevalol	Solution (vials and prefilled syringes) 5 mg/mL Dextrose 45 mg/mL, Methylparaben 0.8 mg/mL. Propylparaben 0.1 mg/mL, EDTA 0.1 mg/mL, Citric acid pH 3-4	None for IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 1 mg/mL.	IV bolus over 2 minutes/ IV infusion	Schering and Glaxo Wellcome, Antihypertensive
Leucovorin calcium/ Wellcovorin		Lyophilized powder 50-350 mg Sodium chloride 40-140 mg pH = 8.1	Reconstitute with WFI to 10-20 mg/mL.	IM/ IV bolus/ IV infusion (at < 160 mg/min)	Immunex, Glaxo Wellcome and Elkins Sinn. Antidote for folic acid antagonist; (Reduce toxic effect of high-dose methotrexate therapy in osteosarcoma
Leuprolide/ Lupron and Lupron Depot	5-Oxo-L-prolyl-L-histidyl- L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)	1) Solution for SC: 5 mg/mL Sodium chloride (isotonic) Benzyl alcohol 9 mg/mL **2) Lyophilized microspheres for IM.** (Depot dual-chamber syringe or single-dose vial) **Syringe A or in vial:** Solid 3.75-15 mg leuprolide, Purified gelatin 0.65-2.6 mg, **DL-lactic/glycolic acids copolymer 33-132 mg** D-mannitol 6.6-26 mg. **Syringe B or supplied diluent:** Aqueous solution of **Sodium carboxy-methylcellulose 5 mg,** TWEEN 80 at 1.0 mg, D-mannitol 50 mg, Acetic acid	None for SC solution. For IM reconstitute the **microspheres** with 1.5 mL of provided diluent to a **suspension** of 3-25 mg/mL.	IM/ SC	TAP, LH-RH agonist, Prostate cancer; Endometriosis; In children with central precocious puberty, Inhibition of the growth of certain hormone dependent tumors

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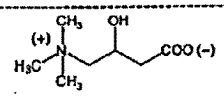
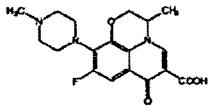
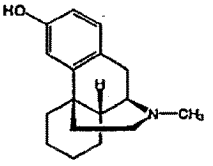
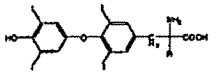
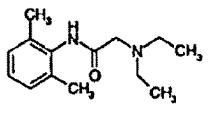
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Levocarnitine/ Carnitor		Solution 200 mg/mL pH 6.0-6.5	None	IV over 2-3 minutes (50 mg/kg)	Sigma-Tau, Treatment in patients lacking endogenous levocarnitine
Levofloxacin/ Levaquin		1) Solution 25 mg/mL, Sodium chloride (isotonic) pH 3.8-5.8 2) Ready-to-use solution 5 mg/mL, Dextrose 5% pH 3.8-5.8	Dilute with saline, dextrose 5% or lactated Ringer's to 5 mg/mL.	IV infusion over ≥ 60 minutes.	Ortho-McNeil, Antibacterial
Levorphanol tartrate/ Levo-Dromoran		Solution 2 mg/mL, Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL or, Phenol 4.5 mg/mL pH 4.3	None or dilute with 5 mL saline.	SC/ IM/ IV bolus/ IV infusion	ICN, Analgesic
Levo-thyroxine sodium/ Synthrod		Lyophilized powder 0.2-0.5 mg Mannitol 10 mg, Sodium phosphate tribasic 0.7-1.7 mg pH 7.5	Reconstitute with 5 mL saline.	IM/ IV at 0.1 mg over < 1 minute	Knoll, Hormone replacement; Hypothyroidism
Lidocaine HCl/ Xylocaine	 Lidocaine pKa = 7.9	1) Solution (vials and prefilled syringes) 5-40 mg/mL, Sodium chloride 6-7 mg/mL, Methylparaben 1 mg/mL pH 5-7 2) Solution 5-20 mg/mL Sodium chloride, Epinephrine 0.005 mg/mL, Sodium metabisulfite 0.5 mg/mL, Methylparaben 1 mg/mL Citric acid pH 3.3-5.5. 3) Solution 15 mg/mL Dextrose 7.5%	None for IM but for IV bolus only < 20 mg/mL, and for IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 1-4 mg/mL.	IM/ IV bolus/ IV infusion/ Local infiltration	Astra, Analgesic; Antidysrhythmic (class IB)

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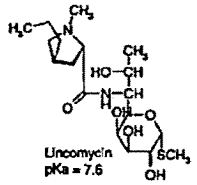
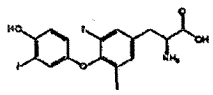
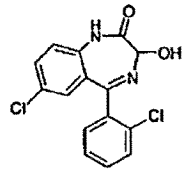
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Lincomycin HCl/ Lincocin HCl (Not in 1999 PDR)	 Lincomycin pKa = 7.6	Solution 300 mg/mL Benzyl alcohol 9.5 mg/mL pH 3-5.5	None or for IV infusion dilute with saline or dextrose 5% to ≤ 10 mg/mL.	IM/ IV infusion at < 10 mg/mL/ Sub-conjunctival	Upjohn, Antibacterial
Liothyronine sodium/ Triostat		Solution 0.01 mg/mL pH 10.5	None	IV bolus	Jones, Thyroid hormone
Lorazepam/ Ativan	 Lorazepam Sol. water = 0.08 mg/mL pKa = 11.5, 13	Solution 2-4 mg/mL **PEG 400 at 0.18 mL/mL, in Propylene glycol** Benzyl alcohol 2%	None for IM. For IV dilute with equal volume of saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus at ≤ 2 mg/min	Wyeth-Ayerst, Anxiolytic; sedation; status epilepticus

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ATTACHMENT F - COMPILATION

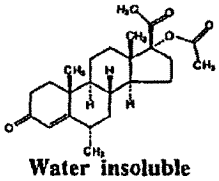
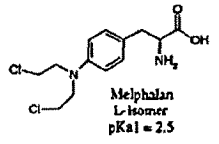
TAB 14

Parenteral Formulations of Small Molecules Therapeutics Marketed in the United States (1999) Part III

ROBERT G. STRICKLEY

Axys Pharmaceuticals, Inc., South San Francisco, California

[Editor's Note: This Review Article on Injectable Products is being published in three parts. The introduction and summary appeared in the November/December 1999 issue of the *Journal*. Part II appeared in the January/February 2000 issue. This is Part III.]

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Medroxyprogesterone Acetate/ Depo-Provera	 **Water insoluble acetate ester prodrug**	**Suspension** 150-400 mg/mL, **PEG 3350: 20-29 mg/mL,** TWEEN 80 at 2.4 mg/mL, Sodium chloride: 8.7 mg/mL, Methylparaben: 1.4 mg/mL, Propylparaben: 0.15 mg/mL	None	IM once every 3 months	Pharmacia & Upjohn, Contraceptive
Melphalan HCl/ Alkeran	 Melphalan L-isomer pKa1 = 2.5	Lyophilized powder 50 mg, Povidone 20 mg. Provided 10 mL diluent of Water 35%, **Propylene glycol 60%, Ethyl alcohol 5%,** Sodium citrate 0.2 g with pH 6.5-7.0	Reconstitute vigorously with provided diluent to 5.0 mg/mL, then further dilute with saline to ≤ 0.45 mg/mL.	IV infusion over 15-20 minutes	Glaxo-Wellcome, Antineoplastic, Alkylating agent.

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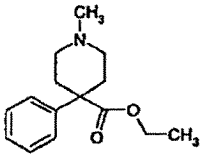
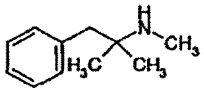
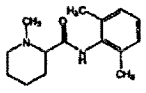
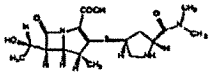
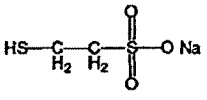
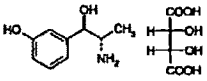
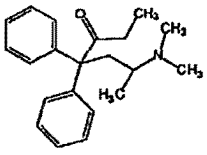
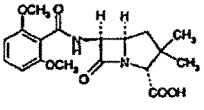
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Meperidine HCl/ Mepergan (a.k.a. Demerol)		Solution 25 mg/mL Promethazine 25 mg/mL, EDTA 0.1 mg/mL, Calcium chloride 0.04 mg/mL, Sodium formaldehyde sulfoxylate 0.75 mg/mL, Sodium metabisulfite 0.25 mg/mL, Sodium acetate, pH 3.5-6	None for SC or IM. For IV infusion dilute with at least 5 mL saline to 10 mg/mL.	SC/ IM/ IV infusion at 25 mg/min	Wyeth-Ayerst, Analgesic, Sedative, Anesthetic
Mephentermine sulfate/ Wyamine sulfate (Not in 1999 PDR)		Solution 15-30 mg/mL Parabens 2 mg/mL, Acetate buffer pH 4-6.5	None for IM or IV bolus. For IV infusion dilute with saline or dextrose 5% to 1 mg/mL.	IM/ IV bolus/ IV infusion	Wyeth-Ayerst, Antihypnotic
Mepivacaine HCl/ Polocaine		Solution 10-20 mg/mL	None	Local	Astra, Anesthetic
Meropenam/ Merrem		Powder 500-1000 mg, Sodium carbonate pH 7.3-8.3	For IV bolus reconstitute with WFI to 50 mg/mL. For IV infusion reconstitute with saline or dextrose 5% to 5 mg/mL.	IV bolus over 3-5 minutes / IV infusion over 15-30 minutes	Zeneca, Antibiotic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Mesna/ Mesnex		Solution 100 mg/mL, w/wo Benzyl alcohol 10 mg/mL, EDTA 0.25 mg/mL, pH 6.5-8.5	Dilute with saline, dextrose 5% or lactated Ringer's to 20 mg/mL.	IV bolus over ≤ 1 minute	Bristol-Myers Squibb, Detoxifying agent (antineoplastic adjunct in conjunction with Ifosfamide administration)
Metaraminol bitartrate/ Aramine		Solution 10 mg/mL Sodium chloride 4.4 mg/mL, Methylparaben 0.15%, Propylparaben 0.02%, Sodium bisulfite 0.2%, pH 3.2-4.5	None for SC, IM or IV bolus. For IV infusion dilute with 500 mL saline or dextrose 5% to 0.03 - 0.2 mg/mL.	SC/ IM/ IV bolus/ IV infusion	Merck, Adrenergic (increases blood pressure in treatment of hypotension)
Methadone HCL/ Dolophine HCL		Solution 10 mg/mL Sodium chloride 9 mg/mL pH = 3-6.5	None	SC/ IM	Roxane, Analgesic, Sedation, Detoxification for heroin addiction
Methicillin sodium/ Staphcillin (Not in 1999 PDR)		Powder 1000-6000 mg, Sodium citrate 50 mg/gram methicillin, pH 6-8.5	Reconstitute with WFI to 500 mg/mL. No dilution for IM. For IV dilute with saline to 20 mg/mL, and for IV infusion to 2-20 mg/mL.	IM/ IV bolus/ IV infusion over 20-30 minutes	Apothecon, Antimicrobial

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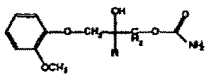
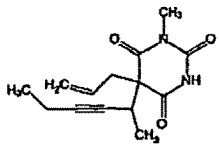
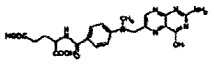
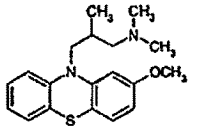
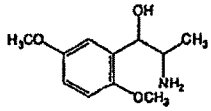
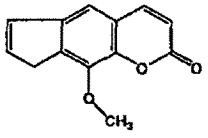
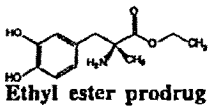
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Metho-carbamil/ Robaxin		Solution 100 mg/mL, **PEG 300 at 50%,** pH = 4-5	None for IM or IV bolus. For IV infusion dilute with ≤ 250 mL saline or dextrose 5%.	IM/ IV bolus at ≤ 30 mg/min/ IV infusion over 10-15 minutes	A.H. Robbins, Skeletal muscle relaxant in the treatment of painful musculoskeletal condition
Methohexital sodium		Powder 500-5000 mg, Sodium carbonate 30-300 mg, **pH 9-11**	Reconstitute with WFI to 166 mg/mL then further dilute with saline or dextrose 5% to 10 mg/mL.	IV bolus/ IV infusion	Jones Medical Industries, Ultra short acting anesthetic
Methotrexate sodium		1) Solution 25 mg/mL Sodium chloride 2.6-4.9 mg/mL, w/wo Benzyl alcohol 9 mg/mL, pH ~ 8.5. 2) Lyophilized powder 20-1000 mg, **pH 9-11**	Reconstitute the powder with saline or dextrose 5% to 1-50 mg/mL	IM/ IV/ Infusion/ Intra-arterial/ Intrathecal	Immunex, Antineoplastic, Immuno-suppressant, Antirheumetic
Metho-trimeprazine/ Levoprine (Not in 1999 PDR)		Solution 20 mg/mL Benzyl alcohol 0.9%, EDTA 0.065% (w/v), Sodium metabisulfite 0.3%, pH 4.5	None	IM	Immunex, Analgesic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Methoxamine HCl/ Vasoxyl		Solution 20 mg/mL Sodium chloride (isotonic) Citric acid 3 mg/mL, Sodium citrate 3 mg/mL, Potassium metabisulfite 1 mg/mL, pH 3-5	None for IM or IV bolus. For IV infusion dilute with dextrose 5% to 0.15 mg/mL.	IM/ IV bolus slowly (emergency)/ IV infusion	Glaxo Wellcome, Antihypotensive (increases blood pressure)
Methoxsalen/ Uvadex		Solution 0.02 mg/mL Sodium chloride 8 mg/mL, **Propylene glycol 5%, Ethyl alcohol 5%** Sodium acetate 1.7 mg/mL, Acetic acid 1.5 mg/mL pH not reported	Injected into photoactivation bag, then add 240 mL buffy coat, 300 mL plasma, and 200 mL saline, then reinfused.	IV infusion	Therakos, Photoactive substance used in extracorporeal treatment of leukocyte enriched buffy coat.
Methyldopate HCl/ Aldomet Ester HCl	 **Ethyl ester prodrug**	Solution 50 mg/mL **Monothioglycerol 2 mg/mL,** Sodium bisulfite 3.2 mg/mL, EDTA 0.5 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL, Citric acid 5 mg/mL, pH 3-4.2	Dilute with dextrose 5% to 10 mg/mL.	IV infusion over 30-60 minutes	Merck, Antihypertensive

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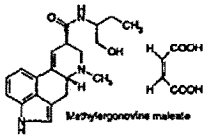
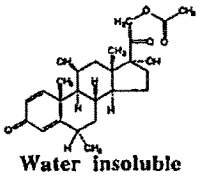
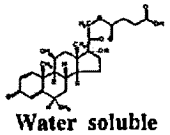
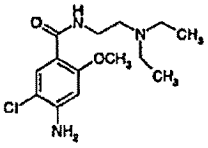
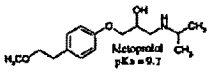
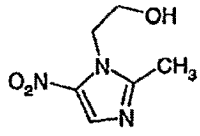
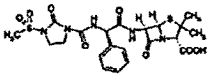
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Methyl-ergonovine maleate/ Methergine (Not in 1999 PDR)		Solution 0.2 mg/mL Sodium chloride 3 mg/mL, Tartaric acid 0.25 mg/mL, pH 2.7-3.5	None	IM/ IV in life threatening situation	Sandoz, Oxytocic, used to control postpartum hemorrhage
Methyl-prednisolone Acetate/ Depo-Medrol	 **Water insoluble acetate ester prodrug**	**Suspension** 20-80 mg/mL **PEG 3350 3%,** TWEEN 80 at 2 mg/mL, Sodium chloride (isotonic), Benzyl alcohol 9 mg/mL, Sodium phosphates 2 mg/mL, pH 3.5-7.0	None	IM/ Intrasynovial/ Soft tissue or Intralesional	Pharmacia & Upjohn, Anti-inflammatory glucocorticoid
Methyl-prednisolone Succinate sodium / Solu-Medrol	 **Water soluble succinate ester prodrug**	Lyophilized powder 40-2000 mg w/wo Lactose 25 mg/mL, Benzyl alcohol 9 mg/mL Sodium phosphates 18 mg/mL pH 7-8	Reconstitute with WFI to 40-65 mg/mL. For IV infusion further dilute with saline or dextrose 5%.	IM/ IV bolus/ IV infusion	Pharmacia & Upjohn, Anti-inflammatory glucocorticoid

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Metoclo-pramide HCL/ Reglan		Solution 5 mg/mL Sodium chloride 8.5 mg/mL, pH 4.5.6.5	None for IM or IV bolus. For IV infusion dilute with 50 mL saline, dextrose 5% or lactated Ringer's to ~ 0.2 mg/mL.	IM/ IV bolus/ IV infusion	A.H. Robbins, Antiemetic, Anticholinergic
Metoprolol tartrate/ Lopressor		Solution 1 mg/mL Sodium chloride 9 mg/mL, pH 7.5	None	IV bolus over 2 minutes	Novartis, Antihypertensive, Antianginal, Antiarrhythmic
Metronidazole/ Flagyl		**1)** Solution 5 mg/mL, Sodium chloride 7.9 mg/mL, Sodium phosphate 0.5 mg/mL, Citric acid 0.22 mg/mL, pH 5-7, **2)** Lyophilized powder 500 mg (HCl salt) Mannitol 415 mg **pH 0.5-2.0**	Reconstitute with 4.4 mL WFI or saline to 100 mg/mL then further dilute with saline, dextrose 5% or lactated Ringer's to ≤ 8 mg/mL then **neutralize with Sodium carbonate to pH 6-7**	IV bolus/ IV infusion	SCS, Antibacterial
Mezlocillin sodium Mezlin		Crystalline powder 1-20 grams pH 4.5-8	Reconstitute with WFI, saline, dextrose 5% or lidocaine 0.5% (IM only) to 100-300 mg/mL, and for IV infusion further dilute with saline or dextrose 5%	IM/ IV bolus/ IV infusion	Bayer, Antibiotic

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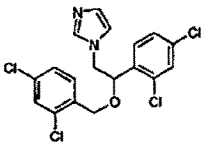
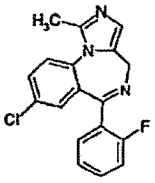
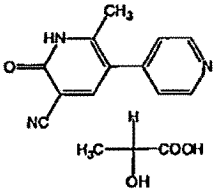
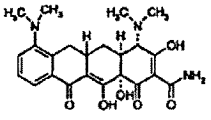
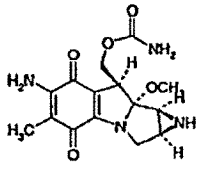
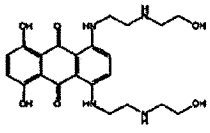
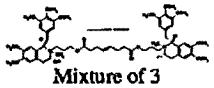
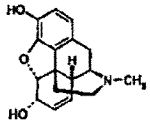
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Miconazole Monistat i.v. (Not in 1999 PDR as injectable, only as a cream)		Solution 10 mg/mL Cremophor 11.5%, Lactic acid 1 mg/mL, Methylparaben 0.5 mg/mL, Propylparaben 0.05 mg/mL, pH 3.7-5.7	Dilute with saline or dextrose 5% to 1 mg/mL	IV infusion over 30-60 minutes/ Intrathecal/ Bladder instillation	Janssen, Antifungal
Midazolam HCL/ Versed		Solution 1-5 mg/mL Sodium chloride 8 mg/mL, Benzyl alcohol 10 mg/mL, EDTA 0.01%, pH 3	None or dilute with saline or dextrose 5%	IM/ Slow IV bolus of 1 mg/mL	Roche, Anesthetic
Milrinone lactate/ Primacor		Solution 0.2-1.0 mg/mL Dextrose 47 mg/mL, Lactic acid 0.3-1.3 mg/mL pH 3-4	None or dilute with saline or dextrose 5% to 0.2 mg/mL.	IV infusion	Sanofi Winthrop, Cardiotonic, Inotropic/ Vasodilator
Minocycline HCL/ Minocin		Lyophilized powder 100 mg pH 2-3	Reconstitute with WFI to 20 mg/mL then diluted with 500-1000 mL saline or dextrose 5% to 0.1-0.2 mg/mL.	IV infusion	Lederle, Antibacterial

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Mitomycin/ Mutamycin		Lyophilized powder 5-40 mg Lactose 10-80 mg pH 6-8	Reconstitute with WFI to 0.5 mg/mL, may be further diluted with saline, dextrose 5% or lactated Ringer's to 0.02-0.04 mg/mL.	IV infusion	Bristol-Myers Squibb, Antineoplastic
Mitoxantrone HCL/ Novantrone		Solution 2 mg/mL, Sodium chloride 8 mg/mL, Acetate buffer 0.5 mg/mL, pH 3-4.5	Dilute with ≥ 50 mL saline or dextrose 5%.	IV infusion	Immunex, Antineoplastic
Mivacurium chloride/ Mivacron	 Mixture of 3 diastereoisomers	1) Solution 2 mg/mL Benzyl alcohol 0.9%, pH 3.5-5. 2) Solution 0.5 mg/mL Dextrose 5% pH 3.5-5	None	IV bolus (2 mg/mL)/ IV infusion (0.5 mg/mL)	Glaxo Wellcome, Short-acting muscle relaxant
Morphine sulfate/ Astramorph and Duramorph		Solution 0.5-25 mg/mL, Sodium chloride 9 mg/mL pH 2.5-6	For IV bolus dilute with 5 mL saline. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 0.1-1 mg/mL.	SC/ IM/ Slow IV bolus/ IV infusion/ Intrathecal/ Epidural	Astra, and Elkins-Sinn, Analgesic

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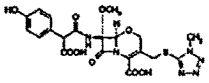
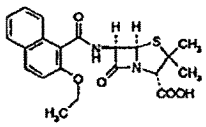
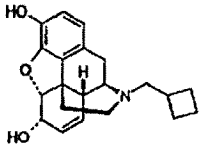
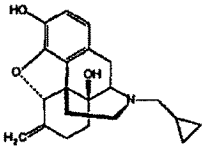
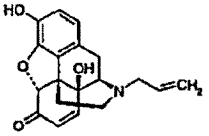
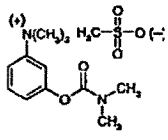
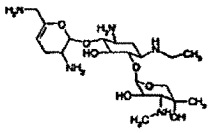
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Moxalactam disodium/ Moxam (Not in 1999 PDR)		Powder 1000-2000 mg Mannitol 150 mg/g moxalactam pH 5.5-6.5	For IM reconstitute with WFI, saline or lidocaine 0.5% to 333 mg/mL. For IV bolus reconstitute with WFI, saline dextrose 5% to 100 mg/mL, and for infusion further dilute with saline or dextrose 5%.	IM/ IV bolus/ IV infusion	Lilly, Antibacterial
Nafcillin sodium/ Unipen (Not in 1999 PDR)		Powder 1000-2000 mg Sodium citrate 35-70 mg pH 6-8.5	Reconstitute with WFI or saline to 250 mg/mL then for IV infusion further dilute with saline or dextrose 5% to 2-40 mg/mL.	IM/ IV bolus/ IV infusion	Wyeth-Ayerst and Apothecon, Antibacterial
Nalbuphine HCL/ Nubain		Solution 10-20 mg/mL w/wo Sodium chloride 2 mg/mL, Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL, Citrates 20 mg/mL, pH 3.5	None	SC/ IM/ IV bolus at 10 mg over 3-5 minutes	Endo, Analgesic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Nalmefene HCl/ Revex		Solution 0.1-1.0 mg/mL Sodium chloride 9 mg/mL, pH 3.9	None or for IV bolus may be diluted 1:1 with saline.	SC/ IM/ IV bolus	Baxter, Narcotic antidote
Naloxone HCl/ Narcan		Solution 0.02-1 mg/mL Sodium chloride 8.3-8.6 mg/mL, (w/wo Methylparaben 0.18 mg/mL, Propylparaben 0.02 mg/mL) pH 3-4	None or for IV infusion dilute with saline or dextrose 5% to 0.004 mg/mL.	SC/ IM/ IV bolus/ IV infusion	Endo, Baxter, Elkins Sinn, Narcotic antagonist
Neostigmine methylsulfate/ Prostigmin		Solution 0.25-1 mg/mL w/wo Parabens 2 mg/mL, w/wo Phenol 4.5 mg/mL, Acetate pH 5.9	None	SC/ IM/ IV bolus	ICN, Cholinergic (acetylcholine esterase inhibitor)
Netilmicin sulfate/ Netromycin		Solution 100 mg/mL Benzyl alcohol 10 mg/mL, Sodium metabisulfite 2.4 mg/mL, Sodium sulfite 0.8 mg/mL, EDTA 0.1 mg/mL, pH 3.5-6	None for IM. For IV infusion dilute with 50-200 mL saline, dextrose 5% or lactated Ringer's to 2-3 mg/mL.	IM/ IV infusion	Schering, Antibacterial

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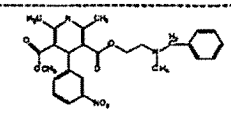
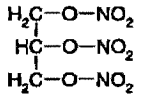
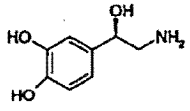
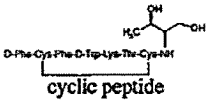
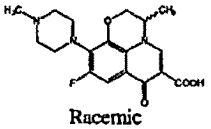
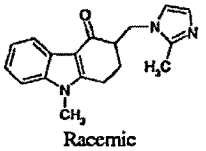
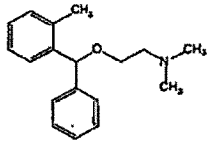
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Nicardipine/ Cardene		Solution 2.5 mg/mL **Sorbitol 48 mg/mL,** Citrates pH 3.5	Dilute with saline or dextrose 5% to 0.1 mg/mL.	IV infusion	Wyeth-Ayerst, Hypertension (Calcium influx inhibitor)
Nitroglycerin/ Nitro-Bid		Solution 5 mg/mL **Propylene glycol 4.5%, Ethyl alcohol 70%** pH 3-6	Dilute with saline or dextrose 5% to 25-40 ug/mL.	IV infusion	Hoechst Marion Roussel, Angina, Vasodilator
Norepinephrine bitartrate (Noradrenaline acid tartrate)/ Levophed (Not in 1999 PDR)		Solution 1 mg/mL Sodium chloride 7.5 mg/mL, Sodium metabisulfite 2 mg/mL, pH 3-4.5	Dilute with 250-1000 mL saline or dextrose 5% to 0.004 mg/mL	IV infusion	Sanofi Winthrop, Adrenergic (vasopressor) Antihypotensive
Octreotide acetate/ Sandostatin	 cyclic peptide	Solution 0.05-1.0 mg/mL Mannitol 45 mg/mL, w/wo Phenol 5 mg/mL, Lactic acid 3.4 mg/mL, Sodium bicarbonate, pH 4.2	None for SC, IM or IV bolus. For IV infusion dilute with 50-200 mL saline or dextrose 5%.	SC/ IM/ IV bolus over 3 minutes/ IV infusion over 15-30 minutes	Novartis, Antidiarrhea, GI hormone, Treatment of acromegaly

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Ofloxacin Floxin I.V.	 Racemic (S-isomer is Levofloxacin) pKa's ~ 4, 9	1) Solution 40 mg/mL, pH 3.5-5.5. 2) Ready-to-use solution 4 mg/mL, Dextrose 5% pH 3.8-5.8	Dilute with saline, dextrose 5% or lactated Ringer's to 4 mg/mL.	IV infusion over 60 minutes	Ortho-McNeil, Antibacterial
Ondansetron HCL/ Zofran	 Racemic	1) Solution 2 mg/mL, Sodium chloride 8.3-9.0 mg/mL, (w/wo Methylparaben 1.2 mg/mL, Propylparaben 0.15 mg/mL), Citric acid buffer pH 3.3-4. 2) Ready-to-use solution 0.64 mg/mL, Dextrose 5%, Citric acid buffer pH 3.0-4.0	For IV bolus inject 32 mg over 3 doses, and for IV infusion dilution with saline or dextrose 5% to 0.64 mg/mL.	IV bolus over 2-5 minutes/ IV infusion over 15 minutes	Glaxo Wellcome, Antiemetic (preventing nausea and vomiting induced chemotherapy)
Orphenadrine citrate/ Norflex		Solution 30 mg/mL Sodium chloride 2.9 mg/mL, Sodium bisulfite, pH < 7	None	IM/ IV bolus over 5 minutes	3M, Skeletal muscle relaxant

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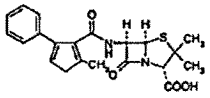
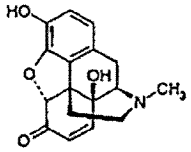
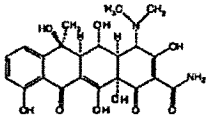
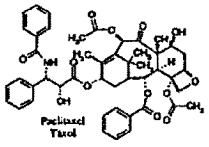
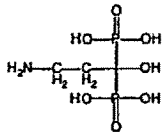
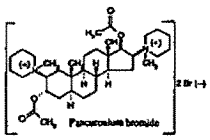
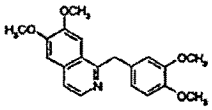
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Oxacillin sodium/ Prostaphilin (Not in 1999 PDR)		Powder 250-4000 mg Sodium phosphates 20 mg/1000 mg oxacillin, pH 6-8.5	Reconstitute with WFI or saline to 175 mg/mL for IM, to 100 mg/mL for IV bolus, and to 0.5-50 mg/mL for IV infusion.	IM/ IV bolus over 10 minutes/ IV infusion over 6 hours	Apothecon, Antibacterial
Oxymorphone HCL/ Numorphan	 pKa's = 8.2, 9.4	Solution 1-1.5 mg/mL, Sodium chloride 8 mg/mL, (w/wo Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL) pH 2.7-4.5	None for SC or IM. For IV dilute with 5 mL saline.	SC/ IM/ IV	ENDO, Analgesic
Oxytetracycline/ Terramycin		Solution 50-125 mg/mL, Lidocaine 20 mg/mL, **Propylene glycol 67-75%,** w/wo **Monothioglycerol 10 mg/mL,** Magnesium chloride 25-60 mg/mL, Sodium formaldehyde sulfoxylate 3-5 mg/mL, Ethanolamine 17-42 mg/mL, w/wo Citric acid 10 mg/mL, w/wo Propyl gallate 0.2 mg/mL	None	IM	Pfizer, Antibiotic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Paclitaxel/ Taxol		Solution 6 mg/mL **Cremophor EL 51%, Ethyl alcohol 49% (v/v)**	Dilute with saline, dextrose 5% or lactated Ringer's to 0.3-1.2 mg/mL.	IV infusion	Bristol-Myers Squibb, Antineoplastic
Pamidronate disodium/ Aredia		Lyophilized powder, 30-90 mg Mannitol 375-470 mg, pH 6.5	Reconstitute with 10 mL WFI to 3-9 mg/mL then further dilute with 1000 mL saline or dextrose 5%.	IV infusion over 4-24 hours	Novartis, Inhibition of bone resorption
Pancuronium bromide/ Pavulon		Solution 1-2 mg/mL Benzyl alcohol 1%, Sodium chloride (isotonic), Sodium acetate 2 mg/mL pH 4	None for IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	IV bolus/ IV infusion	Organon, Muscle relaxant
Papaverine HCL (Not in 1999 PDR)		Solution 30 mg/mL Chlorobutanol 0.5%, EDTA 0.005%, pH 3-4	None or dilute 1:1 with WFI.	IM/ IV bolus over 1-2 minutes	Lilly, Vasodilator (cerebral)

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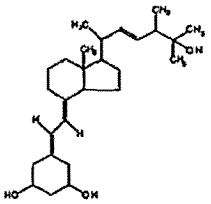
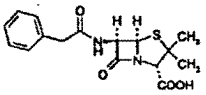
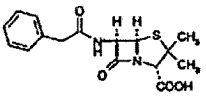
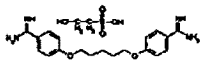
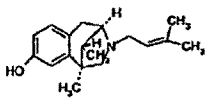
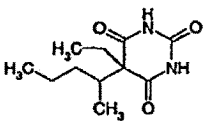
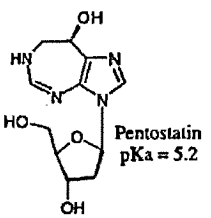
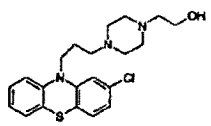
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Paricalcitol/ Zemplar		Solution 0.005 mg/mL **Propylene glycol 30%,** **Ethyl alcohol 20%**	None	IV bolus	Abbott, Treatment of secondary hyperpara-thyroidism associated with chronic failure.
Penicillin G benzathine and Penicillin G procaine / Bicillin		**Suspension** 150,000-600,000 units each/mL Lecithin 0.5% Povidone 0.1%, **Sodium carboxy-methylcellulose 0.55%,** Methylparaben 0.1%, Propylparaben 0.01%, Sodium citrate pH 6-8.5	Shake vial before withdrawing the desired dose.	IM	Wyeth-Ayerst, Antibacterial
Penicillin G potassium/ Pfizerpen		Powder 1,000,000-20,000,000 units Sodium citrate, pH 6-8.5	Reconstitute with WFI, saline or dextrose 5% to 30,000-1,000,000 units/mL.	IM/ IV infusion/ Intrapleural/ Intralesional/ Intrathecal	Pfizer, Antibacterial
Pentamidine isethionate/ Pentam 300 (Not in 1999 PDR)	 Pentamidine isethionate (hydroxy ethane sulfonic acid)	Powder 300 mg pH 4-5.5	Reconstitute with WFI or dextrose 5% to 60-100 mg/mL.	IM/ IV infusion	Fujisawa, Antiprotozoal

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Pentazocine lactate/ Talwin (Not in 1999 PDR as an injectable)		Solution 30 mg/mL Sodium chloride 1.5-2.8 mg/mL, Acetone sodium bisulfite 1-2 mg/mL, Methylparaben 1 mg/mL pH 4-5	None for SC or IM. For IV bolus dilute with saline to 5 mg/mL.	SC/ IM/ IV bolus	Sanofi Winthrop, Analgesic
Pentobarbital sodium/ Nembutal		Solution 50 mg/mL **Propylene glycol 40%,** **Ethyl alcohol 10%** **pH 9.5**	None or dilute with saline, dextrose 5% or lactated Ringer's.	IM/ Slow IV bolus (≤ 50 mg/min)	Abbott, Anticonvulsant, Sedative, Hypnotic, Anesthetic
Pentostatin/ Nipent	 Pentostatin pKa = 5.2	Lyophilized powder 10 mg Mannitol 50 mg pH 7.0-8.5	Reconstitute with 5 mL WFI to 2 mg/mL (IV bolus), which for IV infusion is further diluted with saline or dextrose 5% to 0.18-0.33 mg/mL.	Slow IV bolus/ IV infusion	Supergen, Antineoplastic (transition state inhibitor of adenosine deaminase)
Perphenazine/ Trilafon		Solution 5 mg/mL Sodium bisulfite, Citric acid, pH 4-5.5	None for IM. For IV dilute with saline to 0.5 mg/mL.	IM/ rarely IV or IV infusion at 1 mg/1-2 minutes	Schering, Antipsychotic, Antinausea

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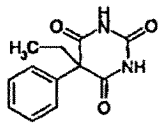
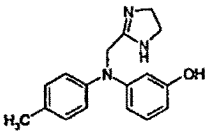
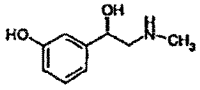
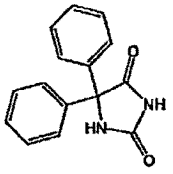
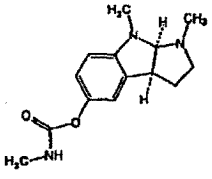
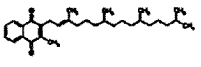
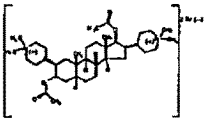
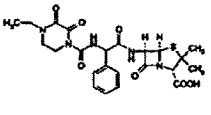
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Phenobarbital sodium/	 Phenobarbital pKa 1= 7.3, pKa2 = 11.8	Solution 30-130 mg/mL, **Propylene glycol 68%, Ethyl alcohol 10% pH 9.2-10.2**	None	IM/ Slow IV	Elkins-Sinn, Wyeth-Ayerst, Antipsychotic,
Phentolamine mesylate/ Regitine		Lyophilized powder 5 mg Mannitol 25 mg pH 4.5-6.5	Reconstitute with 1 mL WFI to 5 mg/mL which may be further diluted with saline to 0.1-1.0 mg/mL.	IM/ IV bolus/ IV infusion	Novartis, Antihypertensive
Phenyl-ephrine HCL/		Solution 10 mg/mL Sodium chloride 3.5 mg/mL, Citrate buffer 5 mg/mL, Sodium metabisulfite 2 mg/mL pH 3-6.5	None for SC or IM. For IV bolus dilute with saline to 1 mg/mL, and for IV infusion to 0.02-0.04 mg/mL.	SC/ IM/ IV bolus/ IV infusion	Baxter, Elkins-Sinn, Mydriatic, Decongestant
Phenytoin sodium/ (a.k.a. Dilantin)		Solution 50 mg/mL **Propylene glycol 40%, Ethyl alcohol 10% pH 10-12.3**	None	IM/ IV bolus at 50 mg/minute	Elkins-Sinn, Anticonvulsant

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Physo-stigmine salicylate		Solution 1 mg/mL Benzyl alcohol 2%, Sodium bisulfite 0.1%, pH 3.5-5.0	None	IM/ IV bolus at ≤ 1 mg/minute	Forrest, Cholinergic (Antidote for cholinesterase inhibitor)
Phytonadione (a.k.a Vitamin K1)/ Aqua-MEPHYTON		**Aqueous dispersion** 2-10 mg/mL **Polyoxyethylated fatty acid 70 mg/mL,** Dextrose 37 mg/mL, Benzyl alcohol 0.9%, pH 3.5-7	None for SC, IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's	SC/ IM/ IV bolus at ≤ 1 mg/minute/ IV infusion	Merck, Vitamin K deficiency
Pipe-curonium bromide/ Arduan		Lyophilized powder 10 mg pH 6	Reconstitute with 10 mL saline, dextrose 5% or lactated Ringer's to 1 mg/mL.	IV bolus	Organnon, Long acting neuromuscular blocking agent
Piperacillin sodium/ Piperacil		Lyophilized powder 2-40 grams pH 5.5-7.5	Reconstitute with WFI or saline to 400 mg/mL (IM) or 200 mg/mL (IV bolus), then further dilute with 50-100 mL saline, dextrose 5% or lactated Ringer's (IV infusion)	IM/ IV bolus over 3-5 minutes/ IV infusion over 30 minutes	Lederle, Antibacterial

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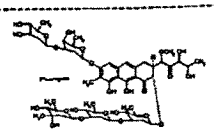
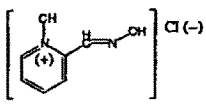
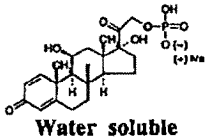
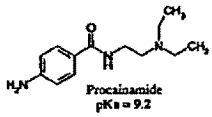
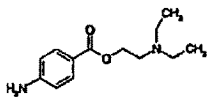
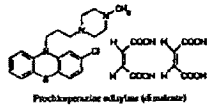
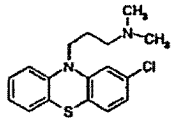
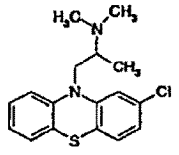
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Plicamycin (Mithramycin) /Mithracin		Lyophilized powder 2.5 mg Mannitol 100 mg, Sodium phosphates pH 7	Reconstitute with 5 mL WFI to 0.5 mg/mL then further dilute with 1000 mL dextrose 5% or saline	IV infusion over 4-6 hours	Bayer, Antineoplastic
Pralidoxime chloride/ Protopam		Lyophilized powder 1000 mg pH 3.5-4.5	Reconstitute with 20 mL WFI to 50 mg/mL for IV bolus, and for IV infusion further dilute with 100 mL saline.	IV bolus over 2 minutes/ IV infusion over 15-30 minutes	Wyeth-Ayerst, Antidote for overdose or poisoning due to anticholinesterase
Prednisolone Phosphate sodium/ Hydeltrasol (Not in 1999 PDR as injectable)	 **Water soluble phosphate ester prodrug**	Solution 20 mg/mL **Niacinamide 25 mg/mL,** Phenol 5 mg/mL EDTA 0.5 mg/mL, Sodium bisulfite 1 mg/mL, pH 7-8	None or for IV infusion dilute with 50-1000 mL saline or dextrose 5%.	IM/ IV bolus/ IV infusion/ Soft tissue/ Intra-articular/ Intra-lesional	Merck, Anti-inflammatory, Adrenocortical steroid, Asthma, Glucocorticoid
Procainamide HCl	 Procainamide pKa = 9.2	Solution 100-500 mg/mL Benzyl alcohol 0.9%, Sodium bisulfite < 0.09%, pH 4-6	None for IM. For IV bolus dilute with dextrose 5% to 10-20 mg/mL, and for IV infusion dilute to 2-20 mg/mL.	IM/ IV bolus/ IV infusion (25-50 mg/minute)	Elkins-Sinn, Antiarrhythmic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Procaine HCL/ Novocaine (Not in 1999 PDR)		Solution 10-100 mg/mL, Sodium chloride (isotonic), Acetone sodium bisulfite < 4 mg/mL, pH 3-5.5	None or dilute with dextrose 5%.	Infiltration/ Peripheral or sympathetic nerve block/ Subarachoid block	Sanofi Winthrop, Local anesthetic
Pro-chlorperzine edisylate/ Compazine		Solution 5 mg/mL Sodium saccharin 0.9 mg/mL, Benzyl alcohol 0.75%, Sodium biphosphate 5 mg/mL, Sodium tartrate 12 mg/mL, pH 4-6	None for IM. For IV bolus dilute with saline to 1 mg/mL, and for IV infusion dilute to 0.01-0.02 mg/mL.	IM/ IV bolus/ IV infusion/	SmithKline Beecham, Antiemetic, Antipsychotic
Promazine HCL/ Sparine (Not in 1999 PDR)		Solution 50 mg/mL Sodium formaldehyde sulfoxylate < 1 mg/mL, Sodium citrate pH 4-5.5	None for IM. For IV bolus dilute with saline to 2.5-25 mg/mL.	IM/ IV bolus	Wyeth-Ayerst, Antipsychotic, Tranquilizer
Promethazine HCL/ (Phenergan) (See also Meperdine/ Mepergan		Solution 25 mg/mL Meperidine 25 mg/mL, EDTA 0.1 mg/mL, Calcium chloride 0.04 mg/mL, Sodium formaldehyde sulfoxylate 0.75 mg/mL, Sodium metabisulfite 0.25 mg/mL, Sodium acetate, pH 3.5-6	None for SC or IM. For IV infusion dilute with at least 5 mL saline to 10 mg/mL.	SC/ IM/ IV infusion at 25 mg/min	Wyeth-Ayerst, Analgesic (narcotic), Sedative, Anesthetic

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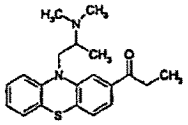
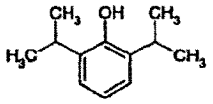
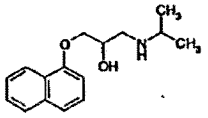
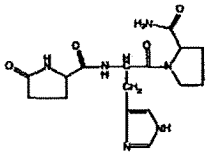
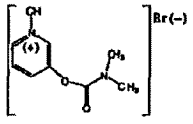
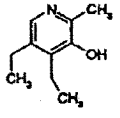
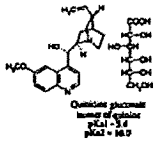
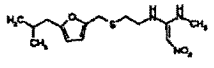
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Propiomazine HCL/ Largon (Not in 1999 PDR)		Solution 20 mg/mL Sodium formaldehyde sulfoxylate, Sodium acetate pH 4.7-5.3	None	IM/ IV bolus at 10 mg/min	Wyeth-Ayerst, Tranquilizer, Sedative, Hypnotic
Propofol/ Diprivan	 pKa =11	**Emulsion,** 10 mg/mL, Soybean oil 100 mg/mL, Glycerol 22.5 mg/mL, Egg lecithin 12 mg/mL, EDTA pH 7-8.5 (under nitrogen to prevent oxidation)	None (shake well)	IV bolus/ IV infusion	Zeneca, Anesthetic, Sedative
Propranolol/ Inderal		Solution 1 mg/mL Citric acid pH 2.8-3.5	None for IV bolus, but for IV infusion dilute with dextrose 5% to 0.02-0.1 mg/mL.	IV bolus/ IV infusion	Wyeth-Ayerst, Antiarrhythmic, Antihypertensive emergencies, Antianginal
Protirelin/ Thyrel		Solution 0.5 mg/mL Sodium chloride 9 mg/mL pH 6.5	None	IV bolus	Ferring, Diagnostic assessment of thyroid function

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Pyridostigmine bromide/ Mestinon		Solution 2 mg/mL Methylparaben 0.2%, Propylparaben 0.02%, Sodium citrate pH 5	None	IM/ IV bolus	ICN, Cholinesterase inhibitor
Pyridoxine/ (vitamin B6) (Not in 1999 PDR as an injectable)		Solution 100 mg/mL, Benzyl alcohol 1.5%, **pH 2-3.8**	None	SC/ IM/ IV	Steris
Quinidine gluconate (Not in 1999 PDR as an injectable)		Solution 80 mg/mL EDTA 0.005%, Phenol 0.25%, pH 5.5-7	None for IM. For IV dilute with 50 mL dextrose 5% to 16 mg/mL	IM/ IV infusion	Lilly, Antimalaria, Antiarrhythmic
Ranitidine HCL/ Zantac		1) Solution 25 mg/mL, Phenol 5 mg/mL, Sodium phosphates 3.5 mg/mL pH 6.7-7.3, 2) Solution 1 mg/mL, Sodium chloride 4.5 mg/mL, Citric acid 0.3 mg/mL, Sodium phosphates 1.8 mg/mL pH 6.7-7.3	None for IM (25 mg/mL). For IV bolus dilute with saline to 2.5 mg/mL. For IV infusion use the premixed 1 mg/mL formulation or dilute with dextrose 5% to 0.5 mg/mL.	IM/ IV bolus/ IV infusion	Glaxo Wellcome, Antiulcerative

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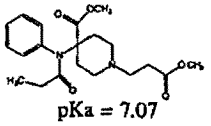
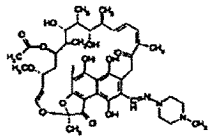
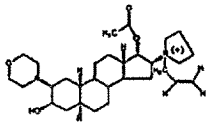
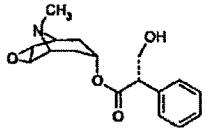
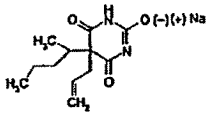
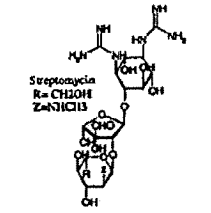
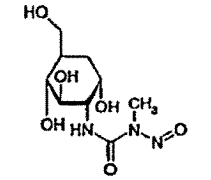
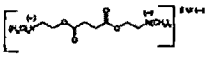
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Remifentanil HCl/ Ultiva	 pKa = 7.07	Lyophilized powder 1-5 mg Glycine 15 mg pH 3	Reconstitute with WFI to 1 mg/mL, then further dilute with saline, dextrose 5% or lactated Ringer's to 0.02-0.25 mg/mL.	IV infusion	Glaxo Wellcome, Analgesic
Rifampin/ Rifadin I.V.	 Rifampin pKa1 = 1.7 (4-phenoxy) pKa2 = 7.9 (3-piperazine)	Powder 600 mg Sodium formaldehyde sulfoxylate 10 mg, pH 7.8-8.8	Reconstitute with WFI to 60 mg/mL, then further dilute with 100-500 mL saline or dextrose 5%.	IV infusion	Hoechst Marion Roussel, Antibacterial
Rocuronium bromide/ Zemuron		Solution 10 mg/mL Sodium acetate 2 mg/mL pH 4	None for IV bolus. For IV infusion dilute with saline or dextrose 5% or lactated Ringer's to 0.5 mg/mL.	IV bolus/ IV infusion	Organnon, Nondepolarizing neuromuscular blocking agent
Scopolamine HBr (Hyoscine HBR)/ (Not in 1999 PDR as injectable)		Solution 0.4-1 mg/mL Methylparaben 1.8 mg/mL Propylparaben 0.2 mg/mL pH 3.5-6.5	None for SC or IM. For IV bolus and infusion dilute with WFI.	SC/ IM/ IV bolus/ IV infusion	Fujisawa, Anticholinergic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Secobarbital sodium (in Tubex cartridge)		Solution 50 mg/mL **Propylene glycol 50%,** Phenol < 2.5 mg/mL **pH 9.5-10.5**	None for IM. For IV dilute with WFI, saline or lactated Ringer's to 5 mg/mL.	IM (< 5 mL)/ Slow IV bolus at < 50 mg/15 seconds	Wyeth-Ayerst, Sedative, Hypnotic, Preanesthetic
Streptomycin sulfate		Solution 400 mg/mL Sodium citrate 12 mg/mL, Phenol 0.25%, Sodium metabisulfite 2 mg/mL pH 4.5-7	None for IM. For IV infusion dilute with 100 mL dextrose 5%.	Deep IM/ IV infusion not recommended, but it may be performed	Pfizer, Antibacterial
Streptozocin/ Zanosar		Lyophilized powder 1000 mg Citric acid 220 mg, pH 3.5-4.5	Reconstitute with 9.5 mL saline or dextrose 5% to 100 mg/mL (IV bolus), then further dilute with 10-200 mL saline or dextrose 5% (IV infusion).	IV bolus/ IV infusion over 0.2-6 hours	Pharmacia & Upjohn, Antineoplastic, (inhibits DNA synthesis)
Succinylcholine chloride/ Anectine		Solution 20 mg/mL Sodium chloride (isotonic) Methylparaben 0.1%, pH 3.5	None for IM or IV bolus. For IV infusion dilute with saline or lactated Ringer's to 1-2 mg/mL.	IM/ IV bolus/ IV infusion	Glaxo Wellcome, Muscle relaxant - ultra short acting

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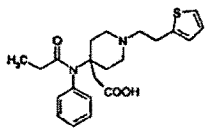
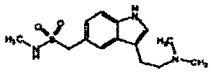
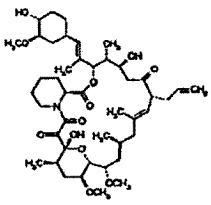
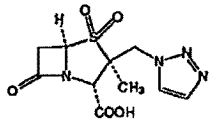
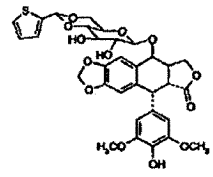
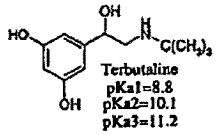
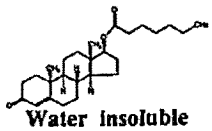
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Sufentanil citrate/ Sufenta		Solution 0.05 mg/mL pH 3.5-6	None	IM/ IV bolus/ IV infusion/ Epidural for labor or delivery	Taylor, Analgesic (narcotic)
Sulbactam (See ampicillin)					
Sulfa-methoxazole (See trimethoprim					
Sumatriptan succinate/ Imitrex		Solution 12 mg/mL Sodium chloride 7 mg/mL pH 4.2-5.3	None	SC	Glaxo Wellcome, Migraine headache
Tacrolimus (FK 506)/ Prograf		**Non-aqueous Solution** 5 mg/mL **Ethyl alcohol 80%, Cremophor EL 20%**	Dilute 250 or 1000-fold into saline or dextrose 5% to 0.004-0.02 mg/mL	IV infusion	Fujisawa, Immuno-suppresent (transplant rejection)

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Tazobactam sodium and Piperacillin sodium/ Zosyn		Lyophilized powder 250 - 500 mg (Tazobactam), 2000-4000 mg (Piperacillin) pH 4.5-5.5	Reconstitute with 20-40 mL WFI, saline or dextrose 5%, then further dilute with saline or dextrose 5% to 50-150 mL.	IV infusion	Lederle, Antibacterial combination
Teniposide (VM-26)/ Vumon		**Non-aqueous Solution** 50 mg/mL **Cremophor EL 500 mg/mL, Ethyl alcohol 42%, Dimethylacetamide 60 mg/mL,** Benzyl alcohol 30 mg/mL pH 5 (Maleic acid)	Dilute with saline or dextrose 5% to 0.1-1 mg/mL	IV infusion over 30-60 minutes	Bristol-Myers Squibb, Antineoplastic (causes breaks in DNA)
Terbutaline sulfate/ Brethine and, Bricanyl	 Terbutaline pKa1=8.8 pKa2=10.1 pKa3=11.2	Solution 1 mg/mL Sodium chloride 8.9 mg/mL pH 3-5	None	SC	Novartis and Hoechst Marion Roussel, Broncodilator
Testosterone Enanthate/ Delatestryl	 **Water insoluble hexanate ester prodrug**	**Non-aqueous solution** 200 mg/mL **Sesame oil,** Chlorobutanol 5 mg/mL	None	IM	BTG

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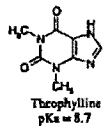
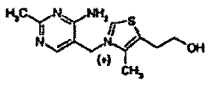
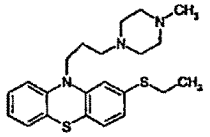
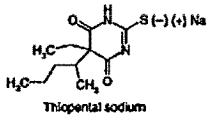
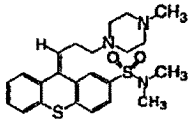
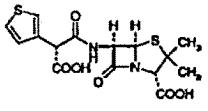
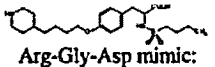
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Theophylline/ Aerolate (Not in 1999 PDR as injectable)	 Theophylline pKa = 8.7	Solution 0.4 - 4 mg/mL, pH 4.3	None	IV infusion	Abbott, Baxter, McGraw, Bronchodilator
Thiamine (Vitamin B1) HCL/		Solution 100 mg/mL Sodium formaldehyde sulfoxylate 1 mg/mL, Chlorobutanol 3.5 mg/mL pH 2.5-4.5	None for IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus/ IV infusion	Elkins-Sinn, Vitamin
Thiethyl-perazine maleate/ Torecan		Solution 5 mg/mL **Sorbitol 20 mg/mL** Sodium metabisulfite 0.25 mg/mL, Ascorbic acid 1 mg/mL, pH 3-4	None	IM	Roxane, Antiemetic (nausea and vomiting
Thiopental sodium/ Pentothal sodium	 Thiopental sodium	Lyophilized powder 250-5000 mg Sodium carbonate 60 mg/1000 mg thiopental **pH 10-11**	Reconstitute. with WFI, saline or dextrose 5% to 2-50 mg/mL	IV infusion	Baxter, Short acting anesthetic
Thiotepa/ Thioplex		Lyophilized powder 15 mg pH 5.5-7.5	Reconstitute with 1.5 mL WFI to 10 mg/mL, then further dilute with saline to ~ 2 mg/mL.	IV bolus/ Intracavitary/ Intravesical	Immunex, Antineoplastic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Thiothixene HCL/ Navane		1) Lyophilized powder 10 mg Mannitol 100 mg pH 2.3-3.7 2) Solution 2 mg/mL, Dextrose 5%, Benzyl alcohol 0.9%, Propyl gallate 0.02% pH 2.5-3.5	Reconstitute the powder with 2.2 mL WFI to 5 mg/mL.	IM	Pfizer, Antipsychotic
Ticarcillin disodium/ Ticar		Lyophilized powder 1-30 grams pH 6-8	For IM reconstitute. with WFI, saline or lidocaine 1% (without epinephrine) to 385 mg/mL. For IV bolus reconstitute with saline, dextrose 5% or lactated Ringer's to 200 mg/mL, then for IV infusion further dilute with saline, dextrose or lactated Ringer's to 30-100 mg/mL.	IM/ IV bolus/ IV infusion	SmithKline Beecham, Antibacterial
Tirofiban HCL/ Aggrastat	 Arg-Gly-Asp mimic: [binds to (GP) IIb/IIIa ($\alpha_{IIb}\beta_3$)]	Solution 0.05-0.25 mg/mL, Sodium chloride 8-9 mg/mL, Citrates 0.6-3 mg/mL; pH 5.5-6.5	Dilute with saline or dextrose 5% to 0.05 mg/mL.	IV infusion	Merck, Antithrombolytic (nonpeptide antagonist of platelet receptor GPIIb/IIIa)

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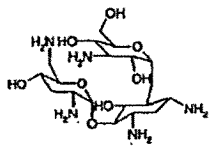
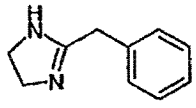
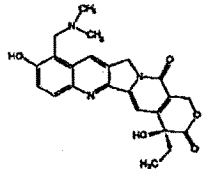
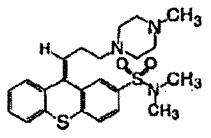
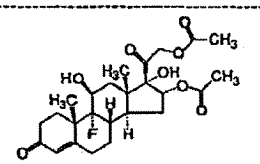
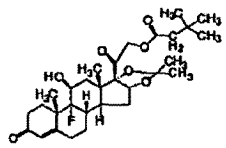
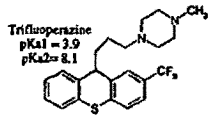
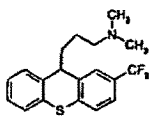
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Tobramycin sulfate/ Nebcin		Solution 10-40 mg/mL Phenol 1.25-5 mg/mL, Sodium bisulfite 1.6-3.2 mg/mL, EDTA 0.1 mg/mL, pH 3-6.5	None for IM. For IV infusion dilute into 50-200 mL	IM/ IV infusion	Lilly and Lederle, Antibacterial
Tolazoline HCL/ Priscoline HCL (Not in 1999 PDR)		Solution 25 mg/mL Tartaric acid 6.5 mg/mL, Sodium citrate 6.5 mg/mL pH 3-4	None for SC, IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	SC/ IM/ IV bolus/ IV infusion/ Intra-arterial	Ciba Geneva, Vasodilator)
Topotecan/ Hycamtin		Lyophilized powder 4 mg Mannitol 48 mg, Tartaric acid 20 mg, pH 2.5-3.5	Reconstitute with 4 mL WFI, then further dilute with saline or dextrose 5%.	IV infusion	SmithKline Beecham, Antineoplastic
Torsemide/ Demadex		Solution 10 mg/mL PEG 400 TRIS pH (no details reported)	Dilute with saline or dextrose 5% to 0.1-1 mg/mL.	IV infusion	Roche, Diuretic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Triamcinolone Diacetate/ Aristocorte		**Suspension** 20-40 mg/mL **PEG 3350 at 3%,** **TWEEN 80 at 0.2%** Sodium chloride 8.5 mg/mL, Benzyl alcohol 9 mg/mL, pH ~ 6	None	IM/ Intra-articular/ Intrasynovial/ Intralesional	Fujisawa, Glucocorticoid
Triamcinolone Hexacetonide/ Aristospan		**Suspension** 5-20 mg/mL **Sorbitol 50%,** TWEEN 80 at 0.2-0.4% Benzyl alcohol 9 mg/mL, pH 4.5- 6.5	None	Intra-articular/ Intralesional	Fujisawa, Glucocorticoid
Trifluoperazine HCL/ Stelazine		Solution 2 mg/mL Sodium saccharin 0.3 mg/mL, Benzyl alcohol 0.75%, Sodium tartrate 4.75 mg/mL, Sodium biphosphate 11.6 mg/mL, pH 4-5	None	IM	SmithKline Beecham, Antipsychotic
Triflupromazine (Not in 1999 PDR)		Solution 10-20 mg/mL, Benzyl alcohol 1.5%, Sodium chloride pH 3.5-5.2	None	IM/ IV bolus	Apotheeon, Antipsychotic, Tranquilizer

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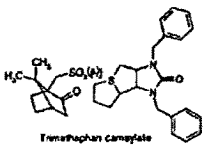
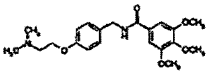
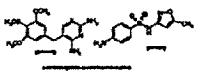
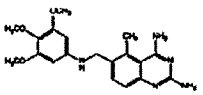
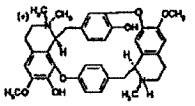
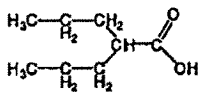
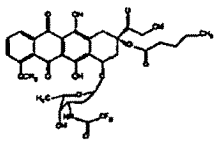
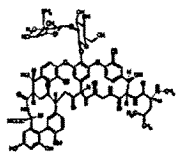
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Trimethaphan camsylate/ Arfonad (Not in 1999 PDR)		Solution 50 mg/mL Sodium acetate pH 5.2	Dilute with dextrose 5% to 1 mg/mL.	IV infusion	Roche, Antihypertensive
Trimetho-benzamide HCL/ Tigan		Solution 100 mg/mL, Methyl and propylparabens 0.1% (or phenol 0.45%), w/wo EDTA 0.1 mg/mL Sodium citrate 0.5 mg/mL, Citric acid 0.2 mg/mL pH 5	None	IM	Roberts, Antiemetic (control of nausea and vomiting)
Trimetho-prim & Sulfa-methoxazole/ Bactrim and Septra		Solution 16 mg/mL trimethoprim, 80 mg/mL sulfamethoxazole, **Propylene glycol 40%,** **Ethyl alcohol 10%,** **Diethanolamine 0.3%,** Benzyl alcohol 1%, Sodium metabisulfite 0.1% **pH 10**	Dilute 20-40 fold into dextrose 5%.	IV infusion	Roche and Monacrh, Antibacterial combination
Trimetrexate glucuronate/ Neutrexin		Lyophilized powder 25-200 mg pH 3.5-4.5	Reconstitute with WFI or dextrose 5% to 12.5 mg/mL then further dilute with dextrose 5% to 0.25-2 mg/mL.	IV infusion	U.S. Biosciences, In combination with leucovorin in treatment of pneumonia

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Tubocurarine chloride (Not in 1999 PDR)		Solution 3 mg/mL Sodium chloride (isotonic), Benzyl alcohol 0.9%, w/wo Chlorobutanol, w/wo Sodium metabisulfite 1 mg/mL, w/wo Sodium bisulfite 0.1%, Citric acid 1 mg/mL pH 2.5-5	None	IM/ IV bolus	Abbott, Lilly, Muscle relaxant
Valproate sodium/ Depacon		Solution 100 mg/mL EDTA 0.4 mg/mL pH 7.6	Dilute with 50 mL saline, dextrose 5% or lactated Ringer's.	IV infusion	Abbott, Antiepileptic
Valrubicin/ Valstar		**Nonaqueous solution** 40 mg/mL **Cremophor EL 50%,** **Ethyl alcohol 50%**	Dilute 20 mL with 55 mL saline to 10.6 mg/mL.	Intravesical instillation in the urinary bladder	Anthra, Antineoplastic
Vancomycin HCL/ Vancocin HCL		Lyophilized powder 500-1000 mg pH 2.5-4.5	Reconstitute with WFI to 50 mg/mL, then further dilute with saline, dextrose 5% or lactated Ringer's to ~ 5 mg/mL.	Intermittent or continuous IV infusion	Lilly, Antibiotic (tricyclic glycopeptide)

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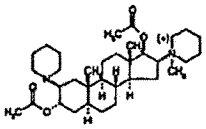
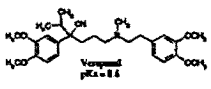
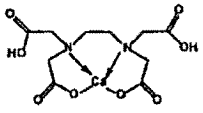
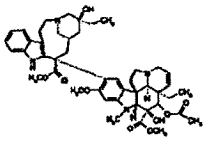
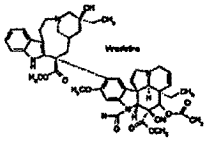
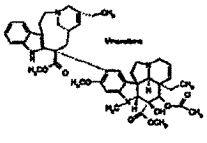
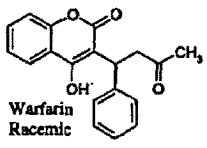
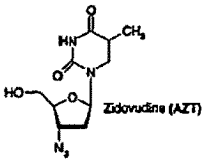
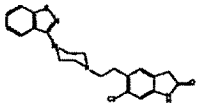
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Vecuronium bromide/ Norcuron		Lyophilized powder 10-20 mg Mannitol 97-194 mg, Citric acid 20-41 mg, Sodium phosphate dibasic 16-32 mg, pH 4	Reconstitute with WFI to 1 mg/mL (IV bolus), then further dilute with saline, dextrose 5% or lactated Ringer's to 0.1 mg/mL (IV infusion)	IV bolus/ IV infusion	Organon, Muscle relaxant
Verapamil HCL/ Isoptin (Not in 1999 PDR as an injectable)		Solution 2.5 mg/mL, Sodium chloride 8.5 mg/mL pH 4-6	None	IV bolus/ IV infusion	Knoll, Antianginal, Antiarrhythmic
Versenate disodium calcium (EDTA)		Solution 200 mg/mL	For IM to minimize pain add lidocaine or procaine 0.5%. For IV infusion dilute with 250-500 mL saline or dextrose 5%.	IM/ IV infusion	3M, Reduction of plasma levels of lead
Vinblastine sulfate/ Velban		Lyophilized powder 10 mg pH 3.5-5.5	Reconstitute with saline to 1 mg/mL.	IV bolus	Lilly, Antineoplastic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Vincristine sulfate/ Oncovin		Solution 1 mg/mL, Mannitol 100 mg/mL, Methylparaben 1.3 mg/mL, Propylparaben 0.2 mg/mL, Acetic acid pH 3.5-5.5	None for IV bolus. For IV infusion dilute with saline or dextrose 5%	IV bolus/ IV infusion	Lilly, Antineoplastic
Vinorelbine tartrate/ Navelbine		Solution 10 mg/mL pH 3.5	Dilute with saline or dextrose 5% to 2-5 mg/mL (IV bolus), or to 0.5-2 mg/mL (IV infusion).	IV bolus/ IV infusion	Glaxo Wellcome, Antineoplastic
Warfarin sodium/ Coumadin		Lyophilized powder 5.5 mg Mannitol 100 mg, Sodium chloride 0.3 mg, Sodium phosphates 14 mg, pH 8.1-8.3	Reconstitute. with WFI to 2 mg/mL.	Slow IV over 2 minutes	Du Pont Pharma, Anticoagulant
Zidovudine/ Retrovir		Solution 10 mg/mL pH 5.5	Dilute with 5% dextrose to < 4 mg/mL.	IV infusion	Glaxo Wellcome, Antiviral
Ziprasidone mesylate/		Solution mg/mL Sulfobutylether-ß-cyclodextrin pH 7 (Details not reported)		IM SC	Pfizer, Antipsychotic (Phase III completed 1999)

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ATTACHMENT F - COMPILATION

TAB 15

Review of Excipients and pH's for Parenteral Products Used in the United States

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New Brunswick, New Jersey

ABSTRACT: Excipients used in U.S. parenteral products were categorized according to their function. The concentrations used in commercial products were also identified. The range of pH value in various products was tabulated with emphasis on products with extreme pH's. The uses of excipients in parenteral dosage form were discussed.

Introduction

The choice of excipients used in parenteral products is not as liberal as in other dosage forms because of two major concerns: safety in parenteral use and feasibility in sterilization. Acceptance of a substance to be used as an excipient in parenteral products often involves lengthy safety testing or production trials. To avoid uncertainty, most formulators tend to employ compounds used in existing parenteral products. This survey is intended to provide an overall view of excipients used in parenteral products available in the United States. For reason of stability or solubility the pH of a product could not always be adjusted to physiological pH (7.4). When problems arise formulators are often inquisitive about the pH of other products. This review, therefore, focuses on products with extreme pH's, and shows tabulation of pH range, acid or base used for adjustment, and product identity.

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Method

The *Physician's Desk Reference* (PDR), 1977–1980 editions (1), were the major source of information. For products not described in the PDR, manufacturers were contacted and the package inserts solicited.

Excipients were categorized according to their presumed function in the formulation. Concentrations were all calculated on % (w/v) base. For dry products, concentrations were calculated according to the commonly diluted volume. For each excipient, ascending concentrations were illustrated by the corresponding products and manufacturer. Examples of only three products were given if there were three or more products containing the same concentration of excipient. One exception is the category of buffer for which only the highest concentration was listed. All of this is shown in Table I.

Many products did not list pH in the PDR. Nevertheless, in these cases information was gathered from other references (2, 3), and Table II illustrates the variety of products employing extreme pH's. For conciseness only one example was given for each particular pH range.

Discussion

This survey brought to light the use of a few excipients uncommon for parenteral use such as phenylmercuric nitrate, dioctyl sodium sulfosuccinate, pectin, etc. Most of these excipients were found in old formulations not covered by the present FDA regulations. On the other hand, some excipients recommended

TABLE I.

I. Antimicr

1) Benz

2) Benz

3) Buty

4) Chlo

5) Met

6) Met

7) Myr

8) Phe

November-Dece

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TABLE I. Excipients for Parenteral Products

I. Antimicrobial Preservatives		
1) Benzyl alcohol	0.5%	Cleocin Phosphate (Upjohn)
	0.75%	Stelazine (SKF)
		Compazine (SKF)
	0.83%	Solu-Medrol (Upjohn)
	0.88%	Cortisone Acetate (Upjohn)
	0.9%	Pronestyl (Squibb)
		Kenolog (Squibb)
		Vistaril (Pfizer)
	1.0%	Solu-Medrol (Upjohn)
	1.2%	Prolixin Decanoate (Squibb)
	1.5%	Valium (Roche)
		Vesprin (Squibb)
	2.0%	Adrenosem (Beecham)
		Aminophyllin (Searle)
	4.0%	Kestrin (Hyrex)
	5.0%	Durabolin (Organon)
	10.0%	Deca-Durabolin (Organon)
2) Benzethonium chloride	0.01%	Ketaject (Bristol)
		Flexoject (Mayrand)
3) Butylparaben	0.015%	Duracillin A.S. (Lilly)
4) Chlorobutanol	0.25%	Nydrazid (Squibb)
		Novocain (Winthrop)
	0.5%	Hexa-Betalin (Lilly)
		Atropine Sulfate (Lilly)
5) Metacresol	0.16%	NPH Iletin (Lilly)
	0.1%	Demerol Hydrochloride (Winthrop)
	0.25%	Protamine, Zinc & Iletin (Lilly)
6) Methylparaben	0.01%	Lidoject-1 (Mayrand)
	0.045%	Celbenin (Beecham)
	0.065%	Apresoline Hydrochloride (Ciba)
	0.1%	Bicillin L-A (Wyeth)
		Prolixin (Squibb)
		Talwin (Winthrop)
	0.13%	Crysticillin (Squibb)
	0.15%	Neo-Betalin 12 (Lilly)
	0.18%	Garamycin (Schering)
		Bactocill (Beecham)
7) Myristylgamma picolinium chloride	0.17%	Depo-Provera (Upjohn)
8) Phenol	0.065%	NPH Iletin (Lilly)
	0.18%	Crysticillin (Squibb)
	0.25%	Ergotrate Maleate (Lilly)
	0.45%	Tensilon (Roche)
		Prostigmin (Roche)
	0.5%	Sus-Phrine (Berlex)
		Tagamet (SKF)

continued

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TABLE I. *Continued*

9) Phenylmercuric nitrate	0.001%	Estraburin (Ayerst)
10) Propylparaben	0.005%	Bactocill (Beecham)
		Ceibenin (Beecham)
	0.01%	Prolixin (Squibb)
		Bicillin L-A (Wyeth)
		Bicillin C-R (Wyeth)
	0.02%	Crysticillin (Squibb)
		Garamycin (Schering)
	0.035%	Apresoline Hydrochloride (Ciba)
11) Thimerosal	0.001%	Wydase (Wyeth)
	0.01%	Test-Estrin (Marlyn)
		MICRhoGAM (Ortho)
	0.02%	Theelin R-P (Parke-Davis)
II. Solubilizers, Wetting Agents or Emulsifiers		
1) Dimethylacetamide	0.01%	Serpasil (Ciba)
2) Dioctyl sodium sulfosuccinate	0.015%	Testoject (Mayrand)
3) Egg yolk phospholipid	1.2%	Intralipid 10% (Cutter)
4) Ethyl alcohol	0.61%	Syntocinon (Sandoz)
	3.0%	Morrhuate Sodium (Lilly)
	6.0%	Kestrin (Hyrex)
	10.0%	Valium (Roche)
		Dilantin (Parke-Davis)
	49.0%	Crystodigin (Lilly)
5) Ethyl lactate	0.1%	Ergotrate Maleate (Lilly)
6) Glycerin	14.6%	Gynergen (Sandoz)
	15.0%	Cedilanid-D (Sandoz)
		DHE 45 (Sandoz)
	25.0%	Sus-Phrine (Berlex)
7) Lecithin	0.5%	Bicillin L-A (Wyeth)
		Wycillin (Wyeth)
	1.5%	Duracillin A.S. (Lilly)
	2.3%	Crysticillin (Squibb)
8) PEG-40 Castor oil[a]	7.0%	AquaMEPHYTON (MSD)
	11.5%	Monistat (Janssen)
9) Polyethylene glycol 300	0.01%	Apresoline Hydrochloride (Ciba)
	5.0%	Serpasil (Ciba)
	30.0%	Sandril (Lilly)
	50.0%	Seconal sodium (Lilly)
		Robaxin (Robins)
10) Polysorbate 20	0.01%	Test-Estrin (Marlyn)
11) Polysorbate 40	0.05%	Bicillin L-A (Wyeth)
12) Polysorbate 80	0.04%	Kenalog (Squibb)
	0.18%	Depo-Provera (Upjohn)
	0.20%	Aristospan (Lederle)
	0.39%	Cortisone Acetate (Upjohn)

continued

TABLE I. Co

13) Povl

14) Prop

15) Sodi
16) Sorb
17) Theo
III. Buffers
1) Ace
2) Adi
3) Ber
4) Cit
5) Ma
6) Pot
7) Sod
8) Sod
9) Lac
10) Sod
11) Sod
12) Sod
13) Sod
14) Sod
15) Tar
IV. Antioxid
1) Ace

2) Asc

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TABLE I. *Continued*

	0.40%	Aristospan (Lederle)
		Duracillin A.S. (Lilly)
	4.0%	Librium (Roche)
13) Povidone	0.2%	Kestrin (Hyrex)
	0.3%	Crysticillin (Squibb)
		Wycillin (Wyeth)
	0.5%	Crysticillin (Squibb)
	0.55%	Bicillin C-R (Wyeth)
	0.6%	Bicillin L-A (Wyeth)
	1.0%	Duracillin A.S. (Lilly)
14) Propylene glycol	0.2%	Estradurin (Ayerst)
	20.0%	Librium (Roche)
	40.0%	Valium (Roche)
		Dilantin (Parke-Davis)
	50.0%	Dramamine (Searle)
		Dramoject (Mayrand)
15) Sodium desoxycholate	0.21%	Fungizone (Squibb)
16) Sorbitan monopalmitate	0.05%	Bicillin L-A (Wyeth)
17) Theophylline	5.0%	Dicurin Procaine (Lilly)
III. Buffers		
1) Acetic acid	0.22%	Neo-betalin 12 Crystalline (Lilly)
2) Adipic acid	1.0%	Serpasil (Ciba)
3) Benzoic acid and sodium benzoate	5.0%	Valium (Roche)
4) Citric acid	0.5%	Aldomet (MSD)
5) Maleic acid	1.6%	Librium (Roche)
6) Potassium phosphate	0.1%	Ouabain (Lilly)
7) Sodium phosphate monobasic	1.7%	Solu-Medrol (Upjohn)
8) Sodium phosphate dibasic	0.71%	Celestone (Schering)
9) Lactic acid	0.1%	Ergotrate Maleate (Lilly)
10) Sodium acetate	0.8%	Soluject (Mayrand)
11) Sodium bicarbonate	0.005%	Amipaque (Winthrop)
12) Sodium carbonate	0.06%	Brevital (Lilly)
13) Sodium citrate	4.0%	Duracillin A.S. (Lilly)
14) Sodium tartrate	1.2%	Compazine (SKF)
15) Tartaric acid	0.65%	Priscoline (Ciba)
IV. Antioxidants		
1) Acetone sodium bisulfite	0.2%	Taiwin (Winthrop)
		Bronkephrine (Breon)
	0.4%	Novocain (Winthrop)
	0.8%	Novocain (Breon)
2) Ascorbic acid	0.05%	Serpasil (Ciba)
	0.1%	Torecan (Boehringer)
	0.2%	Thorazine (SKF)
	1.0%	Sus-phrine (Cooper)
		Sandril (Lilly)
	3.0%	Tetracyn IV (Pfizer)

continued

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TABLE I. *Continued*

3) Monothioglycerol	0.1%	Sandril (Lilly)
		Streptomycin Sulfate (Lilly)
	0.2%	Aldomet (MSD)
	0.5%	Phenergan (Wyeth)
4) Propyl gallate	0.02%	Navane (Roerig)
5) Sodium bisulfite	0.05%	Amigen (Travenol)
	0.08%	A-MethaPred (Abbott)
	0.09%	Pronestyl (Squibb)
	0.1%	Decadron (MSD)
		Tubocurarine (Lilly)
	0.16%	A-MethaPred (Abbott)
	0.2%	Levophed Bitartrate (Breon)
		Neo-Synephrine (Winthrop)
		Pronestyl (Squibb)
	0.32%	Nebcin (Lilly)
		Garamycin (Schering)
		Aldomet (MSD)
	0.45%	Kantrex (Bristol)
	0.66%	Kantrex (Bristol)
		Amikin (Bristol)
	1.0%	Intropin (Arnar-Stone)
6) Sodium metabisulfite	0.025%	Phenoject-50 (Mayrand)
		Torecan (Boehringer)
	0.148%	Reglan (Robins)
7) Sodium formaldehyde sulfoxylate	0.005%	Bejectal (Abbott)
	0.01%	Crysticillin (Squibb)
	0.03%	Crysticillin (Squibb)
8) Sodium sulfide	0.004%	Bejectal (Abbott)
		Bejex (Abbott)
9) Sodium sulfite	0.01%	Serpasil (Ciba)
	0.1%	Thorazine (SKF)
	0.2%	Tensilon (Roche)
10) Thioglycolic acid	0.5%	Sus-Phrine (Berlex)
V. Bulking Substances or Tonicity Modifiers		
1) Glycerine	1.6%	Regular Iletin (Lilly)
		Parathyroid (Lilly)
	2.25%	Intralipid (Cutter)
2) Lactose	0.14%	Wydase (Wyeth)
	1.0%	Adriamycin (Adria)
	2.5%	Solu-Medrol (Upjohn)
		A-MethaPred (Abbott)
	4.0%	Premarin (Ayerst)
	5.0%	Rabies Vaccine (Lilly)
3) Mannitol	0.4%	Aseliacrin (Calbio)
	0.5%	Abbokinase (Abbott)
	1.0%	Profasi HP (Serono)

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VI. Oleagi
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5) S
IX. Chelati
1) Ed

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TABLE I. *Continued*

	2.0%	Profasi HP (Serono)
		Cosmegen (MSD)
	2.5%	A-MethaPred (Abbott)
4) Dextrose	3.75%	AquaMEPHYTON (MSD)
	4.4%	Elavil (MSD)
	5.0%	Heavy Solution Nupercaine (Ciba)
5) Sodium chloride	q.s.	too numerous to list
6) Sodium sulfate	1.1%	Depo-Provera (Upjohn)
7) Sorbitol	2.0%	Torecan (Boehringer)
VI. Oleaginous Vehicles		
1) Benzyl benzoate	20.0%	BAL in Oil (Hynson, W. & D.)
	40.0%	Delalutin (Squibb)
2) Cottonseed oil	q.s.	Menoject-L A (Mayrand)
	87.4%	Depo-Testosterone (Upjohn)
3) Castor oil	q.s.	Delalutin (Squibb)
4) Peanut oil	80.0%	BAL in Oil (Hynson, W. & D.)
	q.s.	Pitressin Tannate in Oil (Parke-Davis)
5) Safflower oil[b]	10%	Liposyn (Abbott)
6) Sesame oil	q.s.	Delatestryl (Squibb)
		Drolban (Lilly)
		Prolixin Decanoate (Squibb)
7) Soybean oil[b]	10%	Intralipid 10% (Cutter)
VII. Lubricants		
1) Simethicone	0.004%	Premarin (Ayerst)
VIII. Suspending Agents		
1) Gelatin	2.0%	Rabies Vaccine (Lilly)
2) Methylcellulose	0.03%	Testoject-50 (Mayrand)
	1.05%	Percorten (Ciba)
3) Pectin	0.2%	Soluject (Mayrand)
4) Polyethylene glycol 4000	2.7%	Depo-Provera (Upjohn)
	2.9%	Depo-Medrol (Upjohn)
	3.0%	Aristocort (Lederle)
5) Sodium carboxymethylcellulose	0.05%	Crystiellin (Squibb)
	0.075%	Crystiellin (Squibb)
	0.2%	Steraject-50 (Mayrand)
		Kestrin (Hyrex)
	0.3%	Percoten (Ciba)
	0.49%	Cortisone Acetate (Upjohn)
	0.55%	Bicillin CR (Wyeth)
	0.60%	Bicillin LA (Wyeth)
	0.75%	Kenalog (Squibb)
5) Sorbitol solution	50.0%	Aristospan (Lederle)
IX. Chelating Agents		
1) Edetate disodium	0.00368%	Renovue-DIP (Squibb)

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TABLE I. *Continued*

	0.005%	Papaverine HCl (Lilly)
		Quinidine Gluconate (Lilly)
	0.01%	Garamycin (Schering)
		Nebcin (Lilly)
		Cholografin Meglumine (Squibb)
	0.04%	Renografin (Squibb)
	0.05%	Cleocin (Upjohn)
		Aldomet (MSD)
		Decaject-L.A. (Mayrand)
2) Edetate calcium disodium	0.04%	Amipaque (Winthrop)
3) Edetate tetrasodium	0.01%	Serpasil (Ciba)
X. Local Anesthetics		
1) Procaine HCl	1.0%	Glukor (Hyrex)
2) Benzyl alcohol	5%	Dramamine (Searle)
XI. Specific Stabilizers		
1) Creatinine	0.5%	Decadron-L.A. (MSD)
		Decaject-L.A. (Mayrand)
	0.8%	Decadron (MSD)
2) Glycine	1.5%	MICRhoGAM (Ortho)
	2.25%	Immu-G (Parke-Davis)
		Gamulin Rh (Parke-Davis)
3) Niacinamide	1.25%	Estraduria (Ayerst)
	2.5%	Soluject (Mayrand)
4) Sodium acetyltryptophanate	0.53%	Normal Serum Albumin (Parke-Davis)
		Plasbumin-5 (Cutter)
5) Sodium caprylate	0.4%	Normal Serum Albumin (Parke-Davis)
		Plasbumin-5 (Cutter)
6) Sodium saccharin	0.03%	Stelazine (SKF)
		Compazine (SKF)

[a] Synonym: Emulphor EL-620. [b] Nutrients in o/w emulsions.

by textbooks for parenteral preparations were not found in use by this survey, e.g., corn oil (4-6), thiourea (5), and potassium chloride (4). It is probable that these excipients may be used in foreign products or in U.S. products that are now no longer marketed. Under the current regulatory climate, the list of excipients is likely to become shorter because of deletion as a result of new toxicological findings. Some excipients, although employed in marketed products, may have difficulty in gaining approval if applications were made today. The following discussion is presented in the same order as shown in the tables.

Benzyl alcohol seemed to be the most commonly used preservative in both aqueous and nonaqueous vehicles. Although 1-2% is the range most often recommended, this survey shows many products employing less than 1% concentration. Higher concentrations, 5 or 10%, were used in one sesame oil preparation (Durabolin).

Although not found in this survey, benzalkonium chloride, chlorocresol, phenylethyl alcohol, phenylmercuric acetate could be considered useful preservatives (6).

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The *p*-hydroxybenzoic esters (parabens) are often used in pairs for synergistic activity or for solubility reasons. The ratio of methylparaben to propylparaben varied, for example, 1.9 (Apresoline), 3.3 (Reno-M-30), 6.5 (Garamycin), 7.5 (Neo-Betaline), and 10 (Prolixin). Because of its greater water solubility, methylparaben is often used in aqueous preparations while butylparaben is used in oily formulations. Propylparaben is popular because it is intermediate to the aforementioned parabens as regards water and oil solubility and because it has the greatest activity for the least toxicity, compared with other parabens (7).

A variety of surfactants were found in the survey. Some reduce surface tension so that a hydrophobic surface on the suspended drug can be wetted rapidly; examples include polysorbate 80 in Aristospan and lecithin in Crystalcillin. Also, surfactants may completely solubilize the active agent, for instance, sodium desoxycholate for amphotericin B (Fungizone), and PEG-40 castor oil for miconazole (Monistat). In selecting surfactants other than those on the list, sorbitan monooleate (4) and Pluronics (6)[1] could be considered.

The purpose of labeling excipients on parenteral products is to inform medical professionals. This practice will be of little value, however, if the excipients cannot be properly identified. *The Merck Index* (8) is usually considered a most comprehensive and handy reference for medical professionals to identify chemicals, yet polysorbate 20 and PEG-40 castor oil are not mentioned. Still, it might be more informative if the label on Aqua MEPHYTON stated "PEG-40 Castor oil," rather than "polyethoxylated fatty acid derivative."

Other than using solvents or surfactants, molecular complexation is another way to solubilize drug substance for parenteral dosage form. One example is Dicurin Procaine which employs theophylline to solubilize merethoxylline. This complex renders the diuretic, merethoxylline, more potent and less irritating at the site of injection[2].

All the buffers used are acids or derived from acids, namely, phosphoric acid, carbonic acid, acetic acid, etc. Alkaline buffers such as tromethamine, glycine, etc., were not found in this survey. For high pH's, sodium hydroxide was used exclusively for pH adjustment. In most cases the active substances such as barbiturates or sulfonamides were themselves contributing buffer capacity. Since various amines had been the cations of organic salts in injectable products (tromethamine in Prostin, ethylenediamine in aminophyllin, and meglumine in Renografin), these amines conceivably could be used to buffer parenteral solutions. If the hydrolysis of an active substance is catalyzed by hydroxide ion, employment of basic amine buffers could minimize hydrolysis at autoclave temperatures (9).

The presence of certain counter-ions, either included in the salt form or added as buffer, could reduce pain on intramuscular injection. The former is exemplified by lysine or arginine in cephalosporin preparations (10) the latter by maleic acid in Librium Hydrochloride (11).

Selection of an antioxidant is the most difficult task for a formulator. Not only is preformulation screening of antioxidant efficacy often misleading (12), but other factors such as interaction with the stopper, effectiveness of nitrogen purge, and stability of the antioxidant itself could complicate the entire picture. Other than the antioxidants listed in Table I, tocopherols, ascorbyl palmitate, and butylated hydroxytoluene (BHT), have been recommended for oleaginous vehicles; and thiourea, cysteine, and glutathione for aqueous vehicles

[1] Pluronics, manufactured by Wyandott Chemicals Corp., are surface-active polymers of polyoxyethylene and polyoxypropylenes. Pluronic F-68 was referred as a surfactant for parenteral use in several U.S. patents. The newly developed artificial blood (not sold in this country) uses Pluronic F-68 to emulsify fluorocarbon.

[2] Information furnished by Parenteral Products Development Department, Eli Lilly and Co.

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(5, 6). Dithiothreitol is particularly effective to protect thiol compounds (13). However, its safety in parenteral dosage forms has not been established. Oxystearin listed in Upjohn's Depo-Testosterone is an antioxidant added to cottonseed oil by the oil vendor.

Frequently, a combination of antioxidants was employed to confer synergistic effect. For example, Thorazine contains ascorbic acid, sodium sulfite, and sodium bisulfite, and Torecan employs ascorbic acid and sodium metabisulfite. Many oxidation reactions are catalyzed by transition metals. By inhibiting metal catalysis, a proper chelating agent often enhances the effectiveness of antioxidant (14).

Other than benzyl benzoate, oleaginous solvents are all fixed oils. Besides those listed, corn oil is also recommended (15), although no products were found employing this vehicle. The USP states certain specifications for fixed oils. The fixed oil must be of vegetable origin so that it may be metabolized, it must be liquid at room temperature, and it must not become rancid quickly. Fixed oils of natural origin such as sesame oil and corn oil often contain significant amounts of peroxide[3]. Formulators should take heed, therefore, to choose an oleaginous vehicle for drugs that are prone to be oxidized. Fractionated coconut oil[4] or other semi-synthetic oils[5] can be considered for they are mostly low in peroxide content[3].

The lack of tissue irritation, good absorption, low peroxide content, and favorable physicochemical properties of glyceryl triacetate recommend it as a potential vehicle for parenteral use (16)[3]. Ethyl oleate has also been recommended (5). Oleaginous formulations have slipped from popularity and replaced by aqueous suspensions (17). Thus, one would find penicillin G procaine, once popular in a refined vegetable oil (using 2% aluminum stearate as suspending agent), is now only available in aqueous suspension. Because of the longer shelf-life of penicillin G procaine in an oily preparation rather than an aqueous one, the oily preparations remain in veterinary use.

Procaine is almost exclusively the only local anesthetic used. Instead of being an excipient, it is also incorporated as a counter-ion in a salt form of the active substance such as Penicillin Procain and Dicurin Procain. In Dramamine, 5% benzyl alcohol is employed in a 50% propylene glycol solution. Since propylene glycol is capable of preserving the formulation, benzyl alcohol may contribute solvency or local anesthetic activity (18).

Chelating agents are added to complex, and thereby inactivate, trace amounts of metals such as copper, iron, and zinc which catalyze a variety of reactions, e.g., oxidation (19), hydrolysis (20), and deiodination (21). Autoclave sterilization, exposure to light, or simply aging, often caused discoloration. In many cases the coloring substances cannot be identified and the mechanism of discoloration is unknown, yet chelating agents effectively preserve the elegancy of the product. The most widely used chelating agents are salts of edetic acid (EDTA). As a precaution to avoid hypocalcemia, the calcium salts of edetate have recently become the chelating agent of choice.

Citric acid, tartaric acid, glycerin, sorbitol, etc., can also be considered as chelating agents. However, formulators should be aware of the fact that these compounds are less effective, or often ineffective, in preventing metal-catalyzed reactions. It is noteworthy that Japanese formulators often resort to amino acids such as glycine, cysteine, or tryptophan because Japan does not allow the use of EDTA

[3] By American Official Analytical Chemist (AOAC) method, the peroxide content, in micro equivalents thiosulfate, for the following oils is: sesame oil, 26.2; corn oil, 29.2; glyceryl triacetate, 0.2; and Miglyol, I.7. E. Ivashkiv, Analytical R&D Report, Squibb Institute for Medical Research.

[4] Representatives of fractionated coconut oil are Miglyol 810 and 812, mixture of caprylic and capric triglycerides, manufactured by Dynamit Nobel Chemicals, Sweden.

[5] Example is Neobee M5, a fractionated triglyceride of coconut oil origin that has been reconstituted to produce an alcohol soluble oil. Neobee is manufactured by Drew Chemical Corp., Boonton, NJ.

TABLE II.

pH Range
1.8–2.8
2.0–3.8
3
3–5.5
3.0–5.5
3.4 ± 0.
3.75 ± 0.
3.85 ± 0.
4.0–5.0
4.0–6.0
4.5–5.2
4.8–5.2
5.0–7.5
5.5–6.5
5.9
6.0–7.0
6.2 ± 0.
6.5–7.7
7–10.
8.5
8.5
8.6–9.0
8.5–10.
9.0
9.2
9.5
9.6–10.
11.6
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TABLE II. Parenteral Product pH's

pH Range	Adjusted with	Product
1.8–2.8	—	Tetracycline HCl (2)
2.0–3.8	HCl/NaOH	Hexa-Betalin (Lilly)
3	Maleic acid/NaOH	Librium (Roche)
3–5.5	—	Lincocin (Upjohn) (3)
3.0–5.5	Sodium citrate/citric acid	Neo-Synephrine (Winthrop)
3.4 ± 0.2	Lactic acid	Haldol (McNeil)
3.75 ± 0.5	Methanesulfonic acid/NaOH	D.H.E. 45 (Sandoz)
3.85 ± 0.15	Tartaric acid	Gynergen (Sandoz)
4.0–5.0	Lactic acid/NaOH	Talwin (Winthrop)
4.0–6.0	HCl/NaOH	Pronestyl (Squibb)
4.5–5.2	HCl/NaOH	Vesprin (Squibb)
4.8–5.2	HCl/NaOH	Prolixin (Squibb)
5.0–7.5	HCl/NaOH	Kenalog (Squibb)
5.5–6.5	HCl/NaOH	Kinevac (Squibb)
5.9	Acetic acid/NaOH	Prostigmin (Roche)
6.0–7.0	HCl/NaOH	Nydrazid (Squibb)
6.2 ± 0.3	Citric acid	Cedilanid-D (Sandoz)
6.5–7.7	Sodium carbonate/HCl	Hypaque (Winthrop)
7–10.5	—	Hexadrol Phosphate (Organon)
8.5	NaOH	Methotrexate (Lederle)
8.5	NaOH	Mexate (Bristol)
8.6–9.0	NaOH	Adrucil (Adria)
8.5–10.5	—	Sulfadiazine Sodium (2)
9.0	NaOH	Fluorouracil (Roche)
9.2	NaOH	Diamox (Lederle)
9.5	NaOH	Dantrium (Norwich-Eaton)
9.6–10.4	—	Amytal Sodium (Lilly) (2)
11.6	NaOH	Hyperstat (Schering)
12	NaOH	Dilantin (Parke-Davis)

in any parenteral products (22).

In the area of radiopharmaceuticals, diethylenetriamine pentaacetic acid (DTPA) has been used in various products as a chelating agent (example: Renotec). Stability constants for metal-DTPA complex are all greater than those of edetate (23). DTPA has been used in Europe to treat heavy metal poisoning; thus, it could be safe to use for chelating purposes (24).

In the category of specific stabilizers, some unique examples were found; the physical stability of steroid solutions prepared with the phosphates of hydrocortisone, cortisone, prednisone, or prednisolone, can be increased by the addition of niacinamide or creatinine, as exemplified by Estradurin or Decadron, respectively (25). It is believed that these nitrogen-containing compounds prevent the formation of precipitates by solubilizing steroid alcohol which would otherwise precipitate as a result of hydrolysis during storage (26). However, the chemical stability of these steroids, as described in another patent, were increased by saccharin (27). Although no steroid product was found to contain saccharin. The use of a soluble saccharin derivative, in very small amounts, however, is efficient in stabilizing phenothiazine derivatives (28). The mechanism of stabilization was attributed to

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the formation of a "probability complex" (29).

In most cases, employment of extreme pH's are necessary for solubility reasons. At high pH's, barbiturates and sulfonamides are typical examples. In order to solubilize weak basic substances, low pH's are required. Stability is another major concern in selecting optimal pH's. Hyperstat is a good example of adjusting pH to the minimum (11.6) on a rate-pH profile (30).

Conceivably, a properly designed formulation is a key to a successful parenteral product. Formulators should always bear in mind that the ideal formulation is the one without excipient at all. If it is necessary to use any excipients to preserve potency, elegancy, safety, etc., one should use extreme caution in selecting proper excipients and use them at optimal concentration. It is hoped that this review will serve as a handy reference for formulators to learn from existing products.

Acknowledgments

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EP0310542

Publication Title:

Antigestagenic and antioestrogenic compounds for the treatment of hormone-dependent tumours.

Abstract:

Abstract of EP0310542

Agents containing at least one antigestagenic and at least one antioestrogenic compound are suitable for the treatment of hormone-dependent tumours. Data supplied from the esp@cenet database - Worldwide

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(54) **Antigestagen- und antiöstrogenwirksame Verbindungen zur Behandlung hormonabhängiger Tumoren.**

(57) Mittel, enthaltend mindestens eine antigestagen- und mindestens eine antiöstrogenwirksame Verbindung, sind zur Behandlung hormonabhängiger Tumoren geeignet.

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Beschreibung

Antigestagen- und antiöstrogenwirksame Verbindungen zur Behandlung hormonabhängiger Tumoren

Die Erfindung betrifft Mittel zur Behandlung hormonabhängiger Tumoren, enthaltend mindestens eine Verbindung mit antigestagener (AG) und mindestens eine Verbindung mit antiöstrogener (AÖ) Wirkung sowie die Verwendung einer Kombination von AG mit AÖ für die angegebene Indikation.

Antiöstrogenwirksame Verbindungen sind zur Behandlung von Krankheiten geeignet, die durch Östrogene bedingt oder von Östrogenen abhängig sind, beispielsweise zur Behandlung von östrogenabhängigen Tumoren, wie Mammakarzinom, Prostatahyperplasie oder Meningeom.

So wird zum Beispiel das Antiöstrogen Tamoxifen zur palliativen Behandlung des nichtoperablen Mammakarzinoms sowie zur adjuvanten Therapie nach Primärbehandlung des Mammakarzinoms angewandt. Mit Tamoxifen wird die Krankheit jedoch nicht geheilt. Für die Sekundärtherapie werden Gestagene oder Aromatasehemmer verwendet. In der Praemenopause führen Ovariektomie, Tamoxifen oder LHRH-Analoga (LHRH = Luteinizing hormon releasing hormons) zu vergleichbaren Ansprechraten (Lit. H.T. Mouridsen and R. Paridaens, Eur. J. Cancer Clin. Oncol., 24, S. 99 - 105, 1988).

In neuerer Zeit wird auch die Verwendung von Antigestagenen im Bereich der Tumortherapie, insbesondere für die Indikation Mammacarcinom diskutiert. Eine erste Phase-II-Studie mit 17β-Hydroxy-11β-(4-dimethylaminophenyl)-17α-(prop-1-inyl)-estra-4,9-dien-3-on an postmenopausalen bzw. ovariektomierten Endokrintherapieresistenten Patientinnen mit metastasierendem Mammacarcinom wird von Maudelonde et al. in Hormonal Manipulation of Cancer, Eds. J.G.M. Klijn, R. Paridaens und J.A. Folkens in Raven Press, S. 55 (1987) berichtet.

Der Erfindung liegt die Aufgabe zugrunde, Arzneimittel für die Behandlung hormonabhängiger Tumoren bereitzustellen, die eine hohe, möglichst höhere Wirksamkeit im Vergleich zu den bekannten Mitteln haben.

Diese Aufgabe wird durch die Erfindung gelöst.

Es wurde gefunden, daß in der Kombination von AG und AÖ die Wirksamkeit der Einzelkomponenten beträchtlich verstärkt wird. Die erfindungsgemäße Kombination beruht auf der Erkenntnis, daß das Wachstum hormonabhängiger Tumoren gleichzeitig von Östrogenen und Gestagenen abhängig ist. So konnten in einem Großteil der Mammacarcinome sowohl Östrogen- als auch Progesteronrezeptoren nachgewiesen werden. Durch die Kombination von AG und AÖ auf Rezeptorebene im Tumor wird nicht nur eine Ovarblockade, sondern auch eine Blockade der aus anderen Geweben entstehenden betreffenden Hormone bewirkt. Eine Kombination von AG und AÖ eignet sich daher zur Therapie sowohl des prä- wie des postmenopausalen Mammacarcinoms.

Das Gewichtsverhältnis beider Komponenten kann dabei in weiten Grenzen variiert werden. So können sowohl gleiche Mengen AG und AÖ als auch ein Überschuß eines der beiden Komponente eingesetzt werden. AG und AÖ werden gemeinsam, getrennt, gleichzeitig und/oder zeitlich abgestuft (sequential), in einem Gewichtsverhältnis von im wesentlichen 1:50 bis 50:1, vorzugsweise 1:30 bis 30:1, und insbesondere 1:15 bis 15:1 verwendet.

Vorzugsweise können AG und AÖ kombiniert in einer Dosiseinheit appliziert werden.

Als Antigestagene kommen alle Verbindungen infrage, die eine starke Affinität zum Gestagenrezeptor (Progesteronrezeptor) besitzen und dabei keine eigene gestagene Aktivität zeigen. Als kompetitive Progesteronantagonisten kommen beispielsweise folgende Steroide infrage:
11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-on (RU-38486),
11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-18-methyl-17α-propinyl-4,9(10)-estradien-3-on und
11β-[(4-N,N-Dimethylamino)-phenyl]-17aβ-hydroxy-17aα-propinyl-D-homo-4,9(10),16-estratrien-3-on (alle EP-A 0 057 115);
ferner
11β-p-Methoxyphenyl-17β-hydroxy-17α-ethinyl-4,9(10)-estradien-3-on (Steroids 37 (1981) 361-382) und
11β-(4-Dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on (EP-A 0129 499)

Die Antigestagene werden gemäß vorliegender Erfindung in Mengen von 10 mg bis 200 mg eingesetzt; im allgemeinen wird man mit 50 bis 100 mg 11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9(10)-gonadien-3-on pro Tag oder einer biologisch äquivalenten Menge eines anderen Antigestagens auskommen.

Als antiöstrogen wirkende Verbindungen kommen Antiöstrogene und Aromatasehemmer infrage. Antiöstrogene und Aromatasehemmer gemäß vorliegender Erfindung können sowohl von Steroiden abgeleitet oder nicht-steroidale Verbindungen sein. Unter antiöstrogen wirkenden Verbindungen gemäß vorliegender Erfindung sollen aber nur solche Verbindungen verstanden werden, die möglichst selektiv wirken, d.h. die im wesentlichen nur die Wirkung von Östrogen hemmen und/oder deren Konzentration senken. Die Antiöstrogene wirken als kompetitive Östrogenantagonisten, indem sie Östrogen vom Rezeptor verdrängen, während Aromatasehemmer die Biosynthese des Östrogens unterdrücken. Verbindungen vom Typ des Aminoglutethimids, 3-alkylierte 3-(4-Aminophenyl)-piperidin-2,6-dione und andere, die außer dem Östrogenspiegel auch auf andere Sexualhormonserumkonzentrationen erniedrigend wirken, sind gemäß vorliegender Erfindung als antiöstrogen wirksame Verbindungen nicht geeignet.

Als Antiöstrogene kommen alle gebräuchlichen Antiöstrogene in Betracht, die vorstehend genannte Bedingung erfüllen. Sie können etwa in gleichen Mengen eingesetzt werden wie die bereits im Handel

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befindlichen Antiöstrogene, das heißt die tägliche Dosis beträgt etwa 5 - 100 mg für Tamoxifen oder biologisch äquivalente Mengen eines anderen Antiöstrogens. Als nicht-steroidale Antiöstrogene seien beispielsweise genannt:
Tamoxifen = (Z)-2-[p-(1,2-Diphenyl-1-butenyl)-phenoxy]-N,N-dimethyläthylamin,
Nafoxidin = 1-2-[4-(6-Methoxy-2-phenyl-3,4-dihydro-1-naphthyl)-phenoxy]-äthyl-pyrrolidin, hydrochlorid,
Mer 25 = 1-[p(2-Diäthylaminoäthoxy)-phenyl]-2-(p-methoxyphenyl)-1-phenyläthanol und
Verbindungen vom 1,1,2-Triphenylbut-1-en-Typ, insbesondere das 1,1-Bis(3'-acetoxyphenyl)-2-phenyl-but-1-en (J. Cancer Res. Clin. Oncol., (1986), 112, S. 119 - 124).

Ferner kommen als steroidale Antiöstrogene infrage:
11α-Methoxy-17α-äthinyl-1,3,5(10)-östratrien-3,17β-diol,
16β-Äthylestradiol und
11-(3,17β-Dihydroxy-1,3,5(10)-estratrien-7α-yl)-undecansäure-(N-butyl-N-methyl)-amid (EP-A 0138 504).

Als Aromatasehemmer sind alle Verbindungen geeignet, die die Bildung von Östrogenen aus ihren Vorstufen hemmen, wie beispielsweise das in der deutschen Offenlegungsschrift 33 22 285 beschriebene
1-Methyl-androsta-1,4-dien-3,17-dion,
das in Journal of Clinical Endocrinology and Metabolism. 49, 672 (1979) beschriebene
Testolacton (17a-Oxa-D-homoandrost-1,4-dien-3,17-dion),
die in "Endocrinology" 1973, Vol. 92, No. 3, Seite 874 beschriebenen
Verbindungen
Androsta-4,6-dien-3,17-dion,
Androsta-4,6-dien-17β-ol-3-on-acetat,
Androsta-1,4,6-trien-3,17-dion
4-Androsten-19-chlor-3,17-dion,
4-Androsten-3,6,17-trion,
die in der deutschen Offenlegungsschrift 31 24 780 beschriebenen
19-alkynylierten Steroide,
die in der deutschen Offenlegungsschrift 31 24 719 beschriebenen
10-(1,2-Propadienyl)-steroide,
die in der europäischen Patentanmeldung, Veröffentlichungsnummer 100 566 beschriebenen
19-Thio-androstanderivate,
das in "Endocrinology" 1977, Vol. 100, No. 6, Seite 1684 und der US-Patentschrift 4,235,893 beschriebene
4-Androsten-4-ol-3,17-dion und dessen Ester,
die in der deutschen Offenlegungsschrift 35 39 244 beschriebenen
1-Methyl-15α-alkyl-androsta-1,4-dien-3,17-dione,
die in der deutschen Offenlegungsschrift 36 44 358 beschriebenen
10β-Alkinyl-4,9(11)-östradien-derivate
und das in der europäischen Patentanmeldung 0250262 beschriebene
1,2β-Methylen-6-methylen-4-androsten-3,17-dion.

Als nicht-steroidaler Aromatasehemmer sei beispielsweise das [4-(5,6,7,8-Tetrahydroimidazo[1,5α]-pyridin-5-yl)benzonitril-monohydrochlorid] erwähnt (Cancer Res., 48, S. 834-838, 1988).

Die Dosierung liegt bei 1 - 1000 mg 1-Methyl-androsta-1,4-dien-3,17-dion pro Tag oder biologisch äquivalenten Dosen von anderen Aromatasehemmern.

Antigestagen- und antiöstrogenwirksame Verbindungen können zum Beispiel lokal, topisch, subcutan, enteral oder parenteral appliziert werden.

Für die enterale Applikation kommen insbesondere Tabletten, Dragees, Kapseln, Pillen, Suspensionen oder Lösungen infrage, die in üblicher Weise mit den in der Galenik üblichen Zusätzen und Trägersubstanzen hergestellt werden können. Für die lokale oder topische Anwendung kommen beispielsweise Vaginalzäpfchen oder transdermale Systeme wie Hautpflaster infrage.

Die bevorzugte subcutane Injektion wird mit einer öligen Lösung der betreffenden Komponente (n) vorgenommen.

Eine AG-Dosiseinheit enthält etwa 10 - 200 mg 11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9(10)gonadien-3-on oder eine biologisch äquivalente Menge eines anderen Antigestagens.

Eine AÖ-Dosiseinheit enthält 1 - 100 mg Tamoxifen oder 10 - 200 mg 1-Methyl-androsta-1,4-dien-3,17-dion oder eine biologisch äquivalente Menge einer anderen antiöstrogen wirksamen Verbindung.

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Beispiel 1

10,0 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
140,5 mg	Laktose
69,5 mg	Maisstärke
2,5 mg	Polyvinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
225,0 mg	Gesamtgewicht der Tablette

Beispiel 2

50,0 mg	1-Methyl-androsta-1,4-dien-3,17-dion
115,0 mg	Laktose
50,0 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette

Beispiel 3

25,0 mg	1-Methyl-androsta-1,4-dien-3,17-dion
25,0 mg	11ß-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17ß-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
115,0 mg	Laktose
50,0 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben angegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

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Beispiel 4

10,0 mg	Tamoxifen
10,0 mg	11ß-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17ß-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
135,0 mg	Laktose
60,0 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben angegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

Die folgenden Beispiele 5 bis 12 beziehen sich auf die Zusammensetzungen öliger Lösungen. Die hergestellten Lösungen werden in Ampullen abgefüllt.

Beispiel 5

100,0 mg	Tamoxifen
343,4 mg	Rizinusöl
608,6 mg	Benzylbenzoat
1052,0 mg	= 1 ml

Beispiel 6

55,0 mg	1-Methyl-androsta-1,4-dien-3,17-dion
55,0 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
343,4 mg	Rizinusöl
608,6 mg	Benzylbenzoat
1062,0 mg	= 1 ml

Die erfindungsgemäßen Wirkstoffe können auch mit jeweils der Hälfte der oben angegebenen Zusätze getrennt in zwei Kammern abgefüllt werden.

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Beispiel 7

10 mg	11-(3,17β-Dihydroxy-1,3,5(10)estratrien-7α-yl)-undecansäure-(N-butyl-N-methyl)-amid
0,9 ml	Rizinusöl
0,1 ml	Benzylbenzoat
1,0 ml	

Beispiel 8

10 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
0,9 ml	Rizinusöl
0,1 ml	Benzylbenzoat
1,0 ml	

Beispiel 9

10 mg	1,1-Bis(3'-acetoxyphenyl)-2-phenyl-but-1-en
0,9 ml	Olivenöl
1,0 ml	

Beispiel 10

10 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1(Z)-enyl)-4,9-estradien-3-on
0,9 ml	Olivenöl
1,0 ml	

Beispiel 11

60 mg	11-(3,17β-Dihydroxy-1,3,5(10)estratien-7α-yl)-undecansäure-(N-butyl-N-methyl)-amid
10 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
0,9 ml	Rizinusöl
0,1 ml	Benzylbenzoat
1,0 ml	

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Beispiel 12

60 mg	1,1-Bis(3'-acetoxyphenyl)-2-phenyl-but-1-en
10 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1(Z)-enyl)-4,9-estradien-3-on
1,0 ml	Olivenöl
1,0 ml	

Ergebnisse

Die Ergebnisse der Untersuchungen am hormonabhängigen, östrogen- und progesteronrezeptor-positiven MXT(+)-Mammacarcinom der Maus (Watson C., Medina D., Clark J.H., Cancer Res. 1977, 37, S. 3344-3348) sind den Tabellen 1 und 2 sowie der Abbildung 1 zu entnehmen.

Als MXT-Tumor wurde die XT-Linie M 3.2. verwendet, die freundlicherweise von Dr. A. E. Bogden, EG + G Bogden Laboratories, Worcester, MA, USA als gefrorene Probe zur Verfügung gestellt wurde. Nach Auftauen wurden Stücke mit einem Volumen von ungefähr 2 mm^3 subcutan in intakte, weibliche 8-10 Wochen alte BDF1-Mäuse (Charles River Wiga, BRD) implantiert.

Nachdem der Tumor einen Durchmesser von ungefähr 1 cm erreicht hatte, wurde er weiter auf BDF1-Mäuse übertragen, wie später beschrieben werden wird. Tumoren wurden von verschiedenen Generationen der Übertragungen genommen, eingefroren und in flüssigen Stickstoff aufbewahrt.

Für die Durchführung eines Versuches wurden Tumorstücke einer gefrorenen Probe in 3-5 Mäuse implantiert. Im nächsten Versuchsabschnitt wird die Hormonabhängigkeit der Tumoren durch Implantation in intakte und ovariektomierte Mäuse getestet (J. Med. Chem., 1985, 28, S. 1880-1885).

Wenn in den ovariektomierten Mäusen nach 6 Wochen eine Inhibierung des Tumorwachstums von mehr als 90 % im Vergleich zu den intakten Kontrolltieren auftritt, so können diese Tumoren für weitere Untersuchungen verwendet werden. Zwei bis drei Tumoren wurden von ein bis zwei als Spender dienenden Tieren entnommen und in MEM 199-Medium (MEM = Minimum Essential Medium) in Stücke von ungefähr 2 mm Durchmesser geschnitten. Diese Stücke werden - wie oben beschrieben - subcutan in BDF1-Mäuse (2 Tumoren / Maus) implantiert.

a) Therapie etablierter Tumoren

20 Tage nach Implantation der Tumoren werden die Mäuse nach Tumoren abgetastet. Nur Mäuse mit zwei ertastbaren Tumoren werden verwendet. Diese Tiere werden willkürlich in Gruppen von 9 bis 10 Tieren eingeteilt. Am nächsten Tag wird mit der 2 oder 3 Wochen dauernden Behandlung begonnen. Die Testsubstanzen werden 6 mal wöchentlich s.c. injiziert. Die Tumorflächen werden durch Messen mit einem Greifzirkel 1- oder 2mal wöchentlich gemessen. Als Tumorfläche gilt das Produkt aus dem längsten und dem dazu senkrechten Durchmesser. Am Ende der Behandlung werden die Tiere gewogen und getötet. Die Tumoren, Ovarien, Uteri und Vaginae wurden entfernt und deren Feuchtgewichte bestimmt (J. Med. Chem., loc. cit.).

b) Prophylaxe-Modell

Nach Implantation der Tumoren wurden die Tiere willkürlich in Gruppen von 9 - 10 Tieren eingeteilt. Am nächsten Tag wird mit der Behandlung begonnen. Die Testsubstanzen werden täglich subcutan als ölige Lösungen (10 %ige Benzylbenzoat-Lösung) injiziert, oder es wird eine Ovariektomie durchgeführt. Nach 6wöchiger Behandlung wird mit den Tieren wie oben weiterverfahren.

aa) Therapie etablierter Tumoren

Antiöstrogenwirksame Verbindungen

Eine 6 mal wöchentlich s.c. applizierte Dosis von 30 mg/kg Körpergewicht 11-(3,17β-Dihydroxy-1,3,5(10)estratrien-7α-yl)- undecansäure-(N-butyl-N-methyl)-amid (=AÖ-A) führte bei der Therapie etablierter Tumoren zu einer Wachstumshemmung von 33 % bezogen auf die Tumorfläche.

Antigestagene

Mit dem Antigestagen 11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on (=AG-B) wurde bei s.c.-Applikation von 6 mal wöchentlich 5 mg/kg Körpergewicht eine Wachstumshemmung von 52 % bezogen auf die Tumorfläche beobachtet.

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AG/AÖ-Kombination

Die Kombination der beiden Verbindungen AÖ-A und AG-B in den oben angegebenen Dosen verursacht eine Hemmung von 72 %, bezogen auf die Tumorfläche. Der Effekt der Kombination ist signifikant besser ($p < 0,05$) als die jeweiligen Monotherapien und ist sogar der Ovariektomie, wenn auch nicht signifikant, überlegen.

Werden zur Beurteilung der Wachstumshemmung der Tumoren nicht die Tumorflächen, sondern die Tumorgewichte herangezogen, gelangt man zu vergleichbaren Ergebnissen, wie sich aus Tabelle 1 ergibt.

bb) Prophylaktische Therapie von Tumoren (Tabelle 2)

Im Prophylaxe-Modell des MXT(+)-Tumors, bei dem die Therapie sofort nach der Implantation des Tumors begonnen und für 6 Wochen fortgesetzt wird, hat das Antiöstrogen 1,1-Bis-(3'-acetoxyphenyl)-2-phenyl-but-1-en (=AÖ-C) keinen signifikanten Antitumoreffekt (Dosis = 8 mg/kg)

Das Antigestagen 11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1(Z)-enyl)-4,9-estradien-3-on (= AG-D) hemmt in diesem Modell das Tumorwachstum, und zwar um 68 %. Die Kombination der beiden vorstehend genannten Komponenten AÖ-C und AG-D führt ebenfalls zu einer deutlichen Verstärkung der Antitumorwirkung im Vergleich zu der antigestagen Komponente allein.

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T A B E L L E 1 MXT(+)-MAMMACARCINOM DER MAUS (THERAPIE ETABLIERTER TUMOREN)

	Tumorfläche (mm^2)	% T/C	Tumorgewicht (mg)	% T/C
Kontrolle	251 ± 134	100	2199 ± 1185	100
Ovariektomie	113 ± 61	45	941 ± 368*	43
AÖ-A, 30 mg/kg	168 ± 41	67	1579 ± 389	72
AG-B, 5 mg/kg	120 ± 62	48	976 ± 513*	44
AÖ-A, 30 mg/kg + AG-B, 5 mg/kg	71 ± 23	28	487 ± 153*	22

* $p<0,05$ (U-Test) gegen Kontrolle

Dosierung: 6 x wöchentlich s.c. in Rizinusöl/Benzylbenzoat

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TABELLE 2

EINFLUß VON AG-D ALLEIN UND IN KOMBINATION MIT AÖ-C MIT MXT M 3.2 MAMMATUMOR-MODELL

Substanz	**Dosis** (a) (mg/kg)	**Tumorgewicht** (b) (% T/C)
1. AG-D	1,0	32*
AG-D + AÖ-C	1,0 + 8,0	8*
2. AG-D	1,0	47*
AG-D + AÖ-C	1,0 + 16,0	21*

(a) Dosis : 3 x wöchentlich s.c. in Olivenöl
(b) Werte nach 6 Wochen Therapie

% T/C Therapiegruppe/Kontrolle x 100

* $p < 0,01$ (U-Test nach Wilcoxon)

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Patentansprüche

1) Mittel, enthaltend mindestens eine Verbindung mit antigestagener (AG) und mindestens eine Verbindung mit antiöstrogener (AÖ) Wirkung zur Behandlung hormonabhängiger Tumoren.

2) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß AG und AÖ in einem Gewichtsverhältnis von 1:50 bis 50:1 stehen.

3) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß AG und AÖ in getrennten Dosiseinheiten vorliegen.

4) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß AG und AÖ in einer gemeinsamen Dosiseinheit vorliegen.

5) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AG-Dosis einheit 10 bis 200 mg 11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9(10)-gonadien-3-on oder eine biologisch äquivalente Menge einer anderen antigestagen wirksamen Verbindung enthält.

6) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AG-Dosiseinheit 10 bis 200 mg 11β-[(4,N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-(3-hydroxy-prop-1(Z)-enyl) -4,9-estradien-3-on enthält.

7) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AÖ-Dosiseinheit 1 - 100 mg Tamoxifen oder eine biologisch äquivalente Menge einer anderen antiöstrogen wirksamen Verbindung enthält.

8) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AÖ-Dosiseinheit 10 - 200 mg 1-Methyl-androsta-1,4-dien-3,17 oder eine biologisch äquivalente Menge einer anderen antiöstrogen wirksamen Verbindung enthält.

9) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AÖ-Dosiseinheit 10 - 200 mg 11-(3,17β-Dihydroxy-1,3,5(10)-estratrien-7α-yl)-undecansäure-(N-butyl-N-methyl)-amid enthält.

10) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AÖ-Dosiseinheit 10 - 200 mg 1,1-Bis(3'-acetoxyphenyl)-2-phenyl-but-1-en-enthält.

11) Verwendung einer Kombination einer antigestagen - mit einer antiöstrogenwirksamen Verbindung für die Behandlung hormonabhängiger Tumoren.

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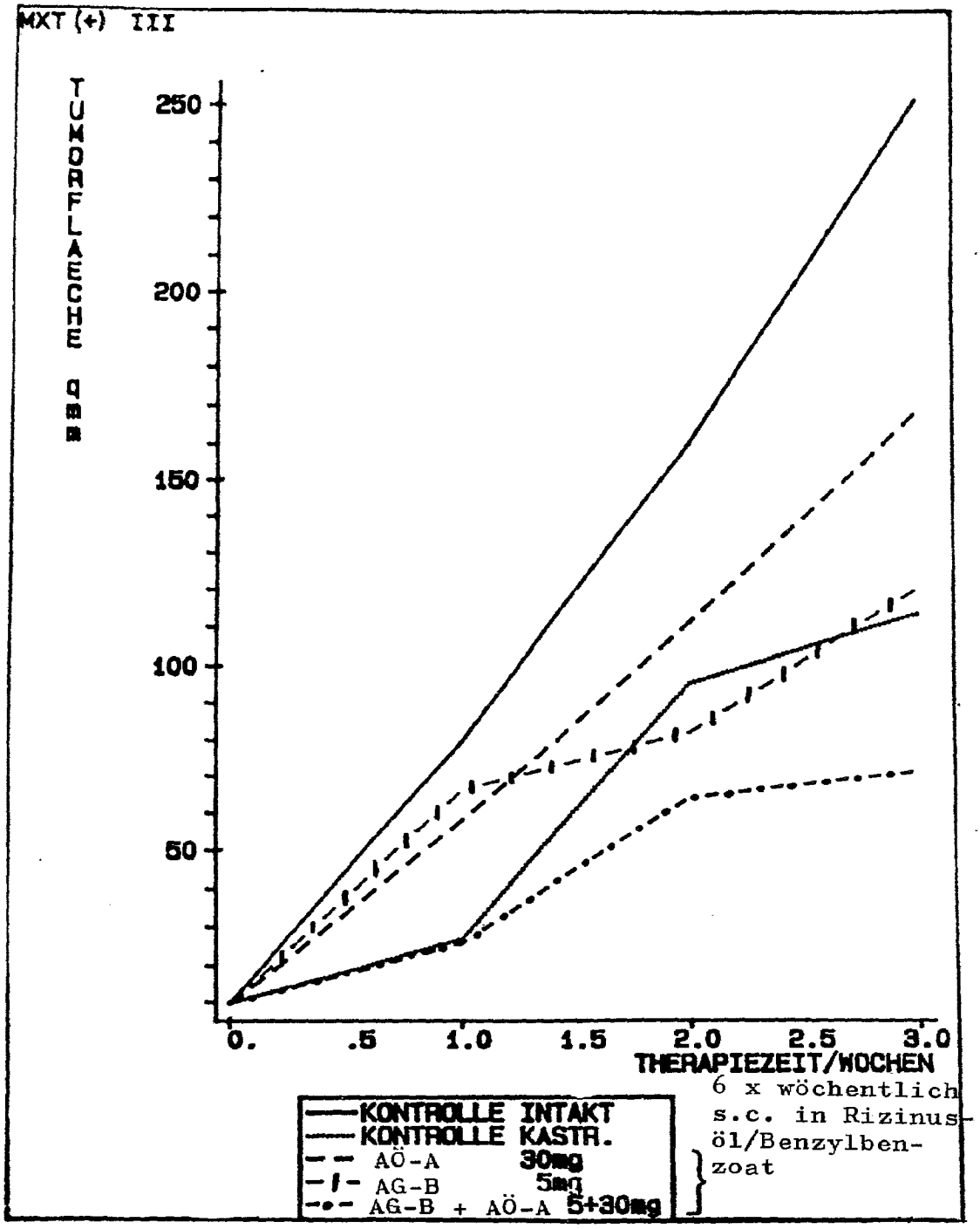

Abb. 1

InnoPharma Exhibit 1046.0483

Europäisches Patentamt

EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung

EP 88 73 0222

EINSCHLÄGIGE DOKUMENTE

Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.4)
D,A	EP-A-0 138 504 (IMPERIAL CHEMICAL INDUSTRIES PLC) * Seite 13, Zeile 12 - Seite 14, Zeile 5; Seite 74, Zeilen 2-8; Ansprüche 6,7 *	1-11	A 61 K 31/565// (A 61 K 31/565 A 61 K 31:135)
D,A	DE-A-3 322 285 (SCHERING AG)	1-11	
D,A	EP-A-0 129 499 (SCHERING AG)	1-11	

RECHERCHIERTE SACHGEBIETE (Int. Cl.4)

A 61 K

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt

Recherchenort	Abschlußdatum der Recherche	Prüfer
DEN HAAG	21-12-1988	BRINKMANN C.

KATEGORIE DER GENANNTEN DOKUMENTE

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
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T : der Erfindung zugrunde liegende Theorien oder Grundsätze
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D : in der Anmeldung angeführtes Dokument
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& : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

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(54) Antigestagenic and antioestrogenic compounds for the treatment of hormone-dependent tumours.

(57) Agents, containing at least one antigestagenic and at least one antioestrogenic compound, are suitable for the treatment of hormone dependent tumours.

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Description

Antigestagenic and anitoestrogenic compounds for the treatment of hormone dependent tumours

The invention concerns agents for the treatment of hormone-dependent tumours, containing at least one compound with antigestagenic (AG) and at least one compound with antioestrogenic (AO) properties, and the use of a combination of AG and AO for the specified indication.

Antioestrogenic compounds are suitable for the treatment of conditions attributable to or dependent upon oestrogens, for example for the treatment of oestrogen-dependent tumours such as carcinoma of the breast, prostatic hyperplasia or meningioma.

Thus, for example, the antioestrogenic, Tamoxifen is applied to the palliative treatment of inoperable carcinoma of the breast and as adjuvant therapy after initial treatment for carcinoma of the breast. The complaint, however, is not cured by Tamoxifen. gestins or aromatase inhibitors are used as secondary therapy. In pre-menopause, ovariectomy, Tamoxifen or LHRH analogues (LHRH = luteinising hormone-releasing hormones) result in comparable response rates. (Lit.: H.T. Mouridsen and R. Paridaens, Eur. J. Cancer Clin. Oncol., 24, pp. 99 – 105, 1988).

More recently, the use of antigestins in the area of tumour therapy has been discussed, in particular in cases of carcinoma of the breast. A first Phase II Study with 17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(prop-1-inyl)-estra-4,9-diene-3-one in post-menopausal or post-ovariectomy patients with metastasising carcinoma of the breast not responsive to endocrine therapy has been reported by Maudelonde et al. in Hormonal Manipulation of Cancer, Eds J.G.M. Klijn, R. Paridaens and J.A. Folkens in Raven Press, p. 55 (1987).

The basic task of the invention is to prepare pharmaceuticals for the treatment of hormone-dependent tumours with a high, if possible higher, effectiveness in comparison with the established agents.

This task has been solved by the invention.

It was found that the effectiveness of the individual components was significantly enhanced in combination of AG and AO. The combination according to the invention is based on the understanding that the growth of hormone-dependent tumours is simultaneously dependent on oestrogen and gestins. Thus, both oestrogen and progesterone receptors were able to be shown in a large proportion of carcinomas of the breast. Through a combination of AG and AO on the receptor level in the tumour, not only an ovarian blockage but also a blockage of the relevant hormones originating in other tissues is brought about. A combination of AG and AO is suitable, therefore, for the treatment of both pre- and postmenopausal carcinoma of the breast.

The weight relationship of both components can, with this, be varied extensively . Thus, not only equal amounts of AG and AO, but a surplus of one of the two components can also be introduced. AG and AO are used together, separately and/or sequentially, primarily in a ratio of 1:50 to 50:1, preferably 1:30 to 30:1, and particularly 1:15 to 15:1.

AG and AO can be administered, preferably, combined into one dosage unit.

Every combination that has a strong affinity to the gestin receptor (progesterone receptor) and thereby does not exhibit any inherent gestagenic activity is considered as antigestagenic. The following steroids, for example, are considered to be competitive progesterone antagonists:
11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-17α-proprinyl-4,9(10)-estradiene-3-one (RU-38486),
11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-18-methyl-17α-proprinyl-4,9(10)-estradiene-3-one and
11β-[(4-N,N-dimethylamino)-phenyl]-17aβ-hydroxy-17aα-proprinyl-D-homo-4,9(10),16-estratriene-3-one (all EP-A 0 057 115);
as well as
11β-p-methoxyphenyl-17β-hydroxy-17α-ethinyl-4,9(10)-estradiene-3-one (Steroids 37 (1981) 361 – 382) and
11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one (EP-A 0129 499)

The antigestins are introduced according to the present invention in amounts of between 10 and 200 mg; in general, management is with from 50 to 100 mg of 11β-[(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9(10)-gonadiene-3-one per day or a biologically equivalent amount of another antigestin.

Antioestrogens and aromatase inhibitors are considered to be antigestagenic compounds. Antioestrogens and aromatase inhibitors according to the present invention may be derived both from steroids or non-steroidal compounds. According to the present invention, however, antioestrogenic compounds should be understood only to include such compounds that act as selectively as possible, i.e. that essentially only inhibit the activity of oestrogen and/or reduce its concentration. The antioestrogens act as competitive oestrogen antagonists by blocking out oestrogen from the receptor, while aromatase inhibitors suppress the biosynthesis of oestrogen. Compounds of the aminoglutethimide, 3-alkylised 3-(4-aminophenyl)-piperidine-2,6-dione and others, type that effect a reduction of other sex hormone serum concentrations in addition to oestrogen levels, are not suitable as antioestrogenics in terms of the present invention.

All current antioestrogens that fulfil the abovementioned conditions are considered as antioestrogenics. They may be employed approximately in the same amounts as the

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already commercially available antioestrogens, that is, in a daily dose of approximately 5 – 100 mg for Tamoxifen or biologically equivalent amounts of another antioestrogen. The following non-steroidal antioestrogens, for example, could be cited:
Tamoxifen = (Z)-2-[p-(1,2-diphenyl-1-butenyl)-phenoxy]-N,N-dimethylethylamine,
Nafoxidin = 1-2-[4-(6-methoxy-2-phenyl-3,4-dihydro-1-naphthyl)-phenoxy]-ethyl-pyrrolidine, hydrochloride,
Mer 25 = 1-[p(2-diethylaminoethoxy)-phenyl]-2-(p-methoxyphenyl)-1-phenylethanol and compounds of 1,1,2-triphenylbut-1-ene type, in particular 1,1-bis(3'-acetoxyphenyl)-2-phenyl-but-1-ene (J. Cancer Res. Clin. Oncol., (1986) 112, pp. 119 – 124).

Moreover, the following are considered to be antioestrogens:
11α-methoxy-17α-ethinyl-1,3,5(10)-estratriene-3,17β-diol,
16β-ethylestradiol and
11-(3,17β-dihydroxy-1,3,5(10)-estratriene-7α-yl)-undecanic acid-(N-butyl-N-methyl)amide (EP-A 0138 504).

All compounds that inhibit the formation of oestrogens from their precursors are suitable as aromatase inhibitors, as, for example, 1-methyl-androsta-1,4-diene-3,17-dione, described in the German Patent Application Publication 33 22 285,
Testolacton (17a-oxa-d-homoandrost-1,4-diene-3,17-dione), described in the Journal of Clinical Endocrinology and Metabolism, 49, 672 (1979),
the compounds, androsta-4,6-diene-3,17-dione,
androsta-4,6-diene-17β-ol-3-one-acetate,
androsta-1,4,6-triene-3,17-dione,
4-androstene-19-chloro-3,17-dione,
4-androstene-3,6,17-trione, described in "Endocrinology" 1973, vol. 92, No. 3, p. 874,
the 19-alkynylised steroids, described in the German Patent Application Publication 31 24 780,
the 10-(1,2-propadienyl)-steroids, described in the German Patent Application Publication 31 24 719,
the 19-thio-derivitives, described in the European Patent Application Publication Number 100 566
the 4-androstene-4-ol-3,17-dione and its ester, described in "Endocrinology" 1977, vol. 100, No. 6, p. 1684 and in US Patent Specification 4,235,893,
the 1-methyl-15α-alkyl-androsta-1,4-diene-3,17-diones, described in the German Patent Application Publication 35 39 244,
the 10β-alkynyl-4,9(11)-estradiene-derivatives, described in the German Patent Application Publication 36 44 358,
and the 1,2β methylene-6-methylene-4-androstene-3,17-dione, described in the European Patent Application 0250262.

As a non-steroidal aromatase inhibitor, [4-(5,6,7,8-tetrahydroimidazo[1,5α]-pyridine-5-yl)benzonitrile-monohydrochloride] can be cited (Cancer Res., 48, pp. 834 – 838, 1988).

The dosage is between 1 and 1,000 mg of 1-methyl-androsta-1,4-diene-3,17-dione per day or the biologically equivalent dose of other aromatase inhibitors.

Antigestagenic and antioestrogenic compounds may, for example, be administered locally, topically, subcutaneously, enterally or parenterally.

For enteral administration, tablets, enteric-coated tablets, capsules, pills, suspensions or solutions are considered, that can usually be manufactured with the customary galenic additives and carrier substances. For local or topical use, for example, pessaries or transdermal systems such as skin patches are considered.

The preferred subcutaneous injection is prepared from an oleaginous solution of the respective components.

One AG dosage unit contains approximately 10 – 200 mg of 11β-[(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9(10)gonadiene-3-one or a biologically equivalent amount of another antigestin.

One AO dosage unit contains approximately 1 – 100 mg of Tamoxifen or 10 – 200 mg of 1-methyl-androsta-1,4-diene-3,17-dione or a biologically equivalent amount of another antioestragenic compound.

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Example 1

10.0 mg	11β-[(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one
140.5 mg	lactose
69.5mg	cornstarch
2.5 mg	polyvinylpyrrolidone 25
2.0 mg	Aerosil
0.5 mg	magnesium stearate
225.0 mg	total weight of the tablet

Example 2

50.0 mg	1-methyl-androsta-1,4-diene-3,17-dione
115.0 mg	lactose
50.0 mg	cornstarch
2.5 mg	poly-N-vinylpyrrolidone 25
2.0 mg	Aerosil
0.5 mg	magnesium stearate
220.0 mg	total weight of the tablet

Example 3

25.0 mg	1-methyl-androsta-1,4-diene-3,17-dione
25.0 mg	11β-[(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one
115.0 mg	lactose
50.0 mg	cornstarch
2.5 mg	poly-N-vinylpyrrolidone 25
2.0 mg	Aerosil
0.5 mg	magnesium stearate
220.0 mg	total weight of the tablet usually produced on a tablet press. If necessary, the active agents according to the invention can also each be divided into halves and pressed into a two-layered tablet.

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Example 4

10.0 mg	Tamoxifen
10.0 mg	11β-[(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one
135.0 mg	lactose
60.0 mg	cornstarch
2.5 mg	poly-N-vinylpyrrolidone 25
2.0 mg	Aerosil
0.5 mg	magnesium stearate
220.0 mg	total weight of the tablet usually produced on a tablet press. If necessary, the active agents according to the invention can also each be divided into halves and pressed into a two-layered tablet.

The following examples 5 to 12 refer to the formulae of oleaginous solutions. The solutions are filled in ampoules.

Example 5

100.0 mg	Tamoxifen
343.4 mg	castor oil
608.6 mg	benzyl benzoate
1052.0 mg	= 1 ml

Example 6

55.0 mg	1-methyl-androsta-1,4-diene-3,17-dione
55.0 mg	11β-[(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one
343.4 mg	castor oil
608.6 mg	benzyl benzoate
1062.0 mg	= 1 ml

The active agents according to the invention can also be divided into two chambers with half of the mixture each.

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Example 7

10.0 mg	11-(3,17β-dihydroxy-1,3,5,(10)estratriene-7α-yl)-undecanic acid-(N-butyl-N-methyl)amide
0.9 ml	castor oil
0.1 ml	benzyl benzoate
1.0 ml	

Example 8

10.0 mg	11β-[(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one
0.9 ml	castor oil
0.1 ml	benzyl benzoate
1.0 ml	

Example 9

10.0 mg	1,1-bis(3'-acetoxyphenyl)-2-phenyl-but-1-ene
0.9 ml	olive oil
1.0 ml	

Example 10

10.0 mg	11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1(Z)-enyl)-4,9-estradiene-3-one
0.9 ml	olive oil
1.0 ml	

Example 11

60.0 mg	11-(3,17β-dihydroxy-1,3,5(10)estratiene-7α-yl)-undecanic acid-(N-butyl-N-methyl)-amide
10.0 mg	11β-[(4-N,N-dimethylamino)-phenyl]- 17α –hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one
0.9 ml	castor oil
0.1 ml	benzyl benzoate
1.0 ml	

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Example 12

60.0 mg	1,1-bis(3'-acetoxyphenyl)-2-phenyl-but-1-ene
10.0 mg	11β-[(4-N,N-dimethylamino)-phenyl]- 17β-hydroxy-17α-(3-hydroxyprop-1(Z)-enyl)-4,9-estradiene-3-one
1.0 ml	olive oil
1.0 ml	

Findings

The results of the investigations of hormone-dependent, oestrogen and progesterone receptor positive MXT (+) breast carcinoma in mice (Watson, C., Medina, D., Clark, J.H., Cancer Res. 1977, 37, pp. 3344 – 3348) can be seen in Table 1 and 2, as well as Figure 1.

XT line M 3.2 was used as the MXT tumour, which was kindly provided by Dr A.E. Bogden, EG + G Bogden Laboratories, Worcester, Mass., USA, as a frozen sample. After thawing, slices with a volume of approximately 2 sq.mm were implanted subcutaneously into healthy, 8 -10 week-old female BDF-1 mice (Charles River Wiga, Germany).

After the tumour had reached a diameter of approximately 1 cm, it was transferred again to BDF mice, as will be described later on. Tumours were taken from various propagation generations, frozen and stored in liquid nitrogen.

For each experiment, slices of tumour from a frozen sample were implanted into 3 - 5 mice. In the next stage, the tumours' hormone-dependency was tested by implantation into healthy and post-ovariectomy mice (J. Med. Chem., 1985, 28, pp. 1880 – 1885).

If the tumour growth in the post-ovariectomy mice demonstrated an inhibition of more than 90% in comparison with the healthy mice after six weeks, then these tumours were further investigated. Two to three tumours were removed from one to two donor animals and divided into specimens of approximately 2 mm in diameter in MEM 199 medium (MEM = Minimum Essential Medium). These specimens were implanted subcutaneously into BDF1 mice (2 tumours per mouse), as described above.

a) Treatment of Established Tumours

20 days after the implantation of the tumours, the mice were scanned for tumours. Only mice with palpable tumours were used. These animals were randomly divided into groups of nine to 10 animals. Treatment, lasting for two or three weeks, was commenced on the following day. The test preparations were injected six times weekly. The tumour areas were measured once or twice per week using callipers. Tumour area was given by the product of the longest diameter and the diameter perpendicular to this. At the end of the treatment, the animals were weighed and killed. The tumours, ovaries, uteri and vaginae were removed and their moist mass determined (J. Med. Chem., loc. cit.).

b) Prophylaxis Model

After implantation of the tumours, the animals were randomly divided into groups of nine to 10 animals. The test preparations were daily injected subcutaneously as oleaginous solutions (10% benzyl benzoate solution) or an ovariectomy was performed. After six weeks of treatment, the animals were proceeded with as above.

aa) Treatment of Established Tumours

Antioestrogenic Compounds

A six times weekly s.c. applied dose of 30 mg/kg body weight of 11-(3,17β-dihydroxy-1,3,5(10)estratrienen-7α-yl)-undecanic acid-(N-butyl-N-methyl)-amide (= AO-A), administered s.c. in the treatment of established tumours led to a 33% suppression of growth in tumour area.

Antigestins

A 52% suppression in growth in tumour area was noted with s.c. administration six times a week of 5 mg/kg body weight of the antigestin, 11β-[(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one (=AG-B).

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AG/AO Combination

The combination of the two compounds, AO-A and AG-B, in the doses specified above, effected a suppression of 72%, in tumour area. The effect of the combination is significantly better ($p < 0.05$) than the respective monotherapies and is actually superior to ovariectomy, if not necessarily significant.

Results are similar if the weight of the tumour, as opposed to the tumour area, is used to measure suppression of tumour growth. These results appear in Table 1.

bb) Prophylactic Treatment of Tumours (Table 2)

In the prophylactic model of the MXT(+) tumour, with which the therapy was commenced immediately after implantation of the tumour and continued for six weeks, the antioestrogen, 1,1-bis-(3'-acetoxyphenyl)-2-phenyl-but-1-ene (= AO-C), had no significant anti-tumour effect (dose = 8mg/kg).

The antigestin, 11β-[(4-N,N-dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1(Z)-enyl)4,9-estradiene-3-one (= AG-D), inhibited the tumour growth in this model, namely by 68%. The combination of the two above-mentioned components, AO-C and AG-D, likewise led to an appreciable intensification of anti-tumour activity in comparison with the antigestagenic constituent alone.

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TABLE 1

MXT(+) CARCINOMA OF THE BREAST IN MICE
(TREATMENT OF ESTABLISHED TUMOURS)

	Tumour Area sq.mm.	%T/C	Tumour Weight mg	%T/C
Control	251 ± 134	100	2199 ± 1185	100
Ovariectomy	113 ± 61	45	941 ± 368*	43
AO_A, 30 mg/kg	168 ± 41	67	1579 ± 389	72
AG-B, 5 mg/kg	120 ± 62	48	976 ± 513*	44
AO-A, 30/mg/kg + AG-B, 5 mg/kg	71 ± 23	28	487 ± 153*	22

* $p < 0.05$ (U U Test) versus Control
Dosage: 6 x per week s.c. in castor oil/benzyl benzoate

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TABLE 2

EFFECT OF AG-D ALONE AND IN COMBINATION WITH AO-C IN MXT M 3.2 CA. BREAST MODEL

	Substance	Dose (a) (mg/kg)	Tumour Weight (b) (%T/C)
1.	AG-D	1.0	32*
	AG-D + AO-C	1.0 + 8.0	8*
2.	AG-D	1.0	47*
	AG-D + AO-C	1.0 + 16.0	21*

(a) Dose: 3 x per week, s.c., in olive oil
(b) Values after six weeks of treatment

% T/C Therapeutic group/Control x 100

* $p < 0.01$ (U Test)

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Patent Claims

1) A drug, containing at least one antigestagenic (AG) compound and at least one antioestrogenic (AO) compound for the treatment of hormone-dependent tumours.
2) A drug according to Claim 1, characterised by AG and AO having a weight ratio of 1:50 to 50:1.
3) A drug according to Claim 1, characterised by AG and AO being available in discrete dosage units
4) A drug according to Claim 1, characterised by AG and AO being available in a combined dosage unit.
5) A drug according to Claim 1, characterised by an AG dosage unit containing 10 to 200 mg of 11β-[(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9(10)-gonadiene-3-one or a biologically equivalent amount of another antigestagenic compound.
6) A drug according to Claim 1, characterised by an AG dosage unit containing 10 to 200 mg of 11β-[(4-N,N-dimethylamino)-phenyl]- 17β-hydroxy-17α-(3-hydroxy-prop-1(Z)-enyl)-4,9-estradiene-3-one.
7) A drug according to Claim 1, characterised by an AO dosage unit containing 1 to 100 mg of Tamoxifen or a biologically equivalent amount of another antioestrogenic compound.
8) A drug according to Claim 1, characterised by an AO dosage unit containing10 to 200 mg of 1-methyl-androsta-1,4-diene-3,17 or a biologically equivalent amount of another antioestrogenic compound.
9) A drug according to Claim 1, characterised by an AO dosage unit containing10 to 200 mg of 11-(3,17β-dihydroxy-1,3,5(10)-estratriene-7α-yl)-undecanic acid-(N-butyl-N-methyl)-amide.
10) A drug according to Claim 1, characterised by an AO dosage unit containing10 to 200 mg of 1,1-bis(3'-acetoxyphenyl)-2-phenyl-but-1-ene.
11) The use of a combination of an antigestagenic compound with an antioestrogenic compound for the treatment of hormone-dependent tumours.

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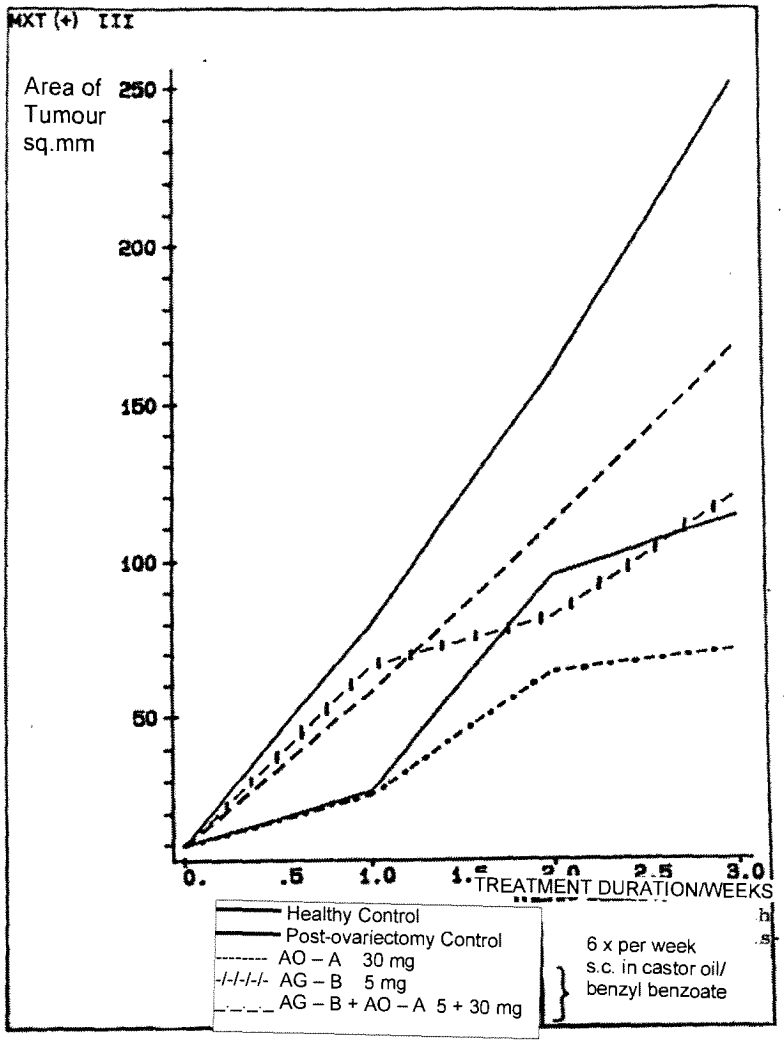

fig. 1

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 73 0222

RELEVANT DOCUMENTS

Category	Identification of Document with Identification, if possible, of Applicable Parts	Claim Concerned	Classification of Application
D,A	EP-A-0 138 504 (IMPERIAL CHEMICAL INDUSTRIES PLC) * page 13. line 12 – page 14, line 5; page 74, lines 2 – 8; claim 6,7 * ---	1 – 11	A 61 K 31/565// (A 61 K 31/565 A 61 K 31:135)
D,A	DE-A-3 322 285 (SCHERING AG) ---	1 – 11	
D,A	EP-A-0 129 499 (SCHERING AG) -----	1 – 11	

SUBJECT AREA RESEARCHED (Int. Cl. 4)

A 61 K

This Search Report is issued for all Patent Claims

Place of Search	Completion Date of Search	Examiner
The Hague	21 December 1998	C. Brinkmann

CATEGORY OF THE NAMED DOCUMENTS

X: of particular interest, considered alone
Y: of particular interest, considered in combination with another publication in the same category
A: technical background
O: unwritten disclosure
P: Intermediate Literature

T: Theories or Principles underlying the Invention
E: Previous Patent Document that was, however, only published on or after the Date of Application
D: Document cited in the Application
L: Document cited on Other Grounds
.....
&: Member of the same Group of Patents, Parallel Document

EPO FORM 1503 03.82 (P0403)

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PATENT
Attorney Docket No. **056291-5004-01**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **John EVANS *et al.***	) Confirmation No.: **2093**
Application No.: **10/872,784**	) Group Art Unit: **1617**
Filed: **October 26, 2007**	) Examiner: **Hui, San-ming R**
FOR: **FORMULATION**	) Date: **August 21, 2008**

FOURTH INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(c)

Pursuant to 37 C.F.R. 1.56 and 1.97(c), Applicants bring to the attention of the Examiner the documents listed on the attached PTO 1449 form. This Information Disclosure Statement is being filed after the events recited in § 1.97(b) but, to the undersigned's knowledge, before the mailing date of either a Final Office Action or a Notice of Allowance. The Commissioner is hereby authorized to charge **$180.00**, as specified by §1.17(p), to Deposit Account No. 50-0310 for this Information Disclosure Statement under the provisions of 37 C.F.R. §1.97(c).

With the exception of the U.S. patents, copies of the listed documents are attached. Applicants respectfully request that the Examiner initial and return the Form PTO-1449, indicating that the information has been considered and made of record herein.

Also submitted with this Information Disclosure Statement as Attachments I to III are the following documents: Attachment I: A copy of EP 1250138B1, which is the European Patent that granted on the European counterpart of the subject Application; Attachment II: A copy of documents from the EPO file relating to the European Opposition pending against EP 1250138B1; and Attachment III: A copy the Supplementary European Search Report received by Applicant in European Application 05016921.8, which is a divisional of the application from which EP 1250138B1 granted. These documents are discussed in the Amendment and Response being filed herewith, specifically in Section (8) of the Remarks beginning at page 29.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." Applicants reserve the right to take appropriate action to establish the

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patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: August 21, 2008 By: _____

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INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) PTO Form 1449 August 21, 2008	Attorney Docket No. **056291-5004-01**	Application No. **10/872,784**
	Applicants: **John EVANS *et al.***	
	Filing Date: **June 22, 2004**	Group Art Unit: **1617**

U.S. PATENT DOCUMENTS

Initial		Document No.	Date	Name	Class	Sub-Class	Filing Date
	1.	US 3,164,520	January 5, 1965	Huber			
	2.	US 4,212,863	July 15, 1980	Cornelius			
	3.	US 4,388,307	June 14, 1983	Cavanak			

FOREIGN PATENT DOCUMENTS

		Document No.	Date	Country	Class	Sub-Class	Translation
	4.	EP 0310542A1	April 5, 1989	EPO			Yes

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

	5.	P.K. Gupta and G.A. Brazeau (eds). *Injectable Drug Development:Techniques to Reduce Pain and Irritation.* Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999)
	6.	P.V. Lopatin, V. P. Safonov, T. P. Litvinova and L. M. Yakimenko. Use of nonaqueous solvents to prepare injection solutions. *Pharm. Chem. J.* ***6***:724-733 (1972)
	7.	S. Nema, R.J. Washkuhn, and R.J. Brendel. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* **51**:166-71 (1997)
	8.	*Physicians' Desk Reference (27th edition).* 1277-1278, 1350-1354, 1391-1392 Medical Economics Company, Oradell, NJ (1973)
	9.	M. F. Powell, T. Nguyen, and L. Baloian. Compendium of excipients for parenteral formulations. *PDA J. Pharm. Sci. Technol.* **52**:238–311 [pages 238-255 provided] (1998)
	10.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) -Part I. *PDA J. Pharm. Sci. Technol.* **53**:324–349 (1999)
	11.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part II *PDA J. Pharm. Sci. Technol.* **54**:69–96 (2000)
	12.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part III. *PDA J. Pharm. Sci. Technol.* **54**:152–169 (2000)
	13.	Y.C. J. Wang and R. R. Kowal. Review of excipients and pH's for parenteral products used in the United States. *J. Parenteral Drug Assoc.* **34**:452–462 (1980).

Examiner	Date Considered

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

InnoPharma Exhibit 1046.0500

Fourth IDS

Attachment I

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 250 138 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
19.10.2005 Bulletin 2005/42

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WO 2001/051056 (19.07.2001 Gazette 2001/29)

(54) **FULVESTRANT FORMULATION**

FULVESTRANT FORMULIERUNG

PREPARATION DE FULVESTRANT

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05016921.8

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(56) References cited:
EP-A- 0 346 014 **WO-A-96/19997**
WO-A-97/21440

- **JOHN C. WATERTON; ET AL.: "A Case of Adenomyosis in a Pigtailed Monkey Diagnosed by Magnetic Resonance Imaging and treated with the Novel Pure Antiestrogen, ICI 182,780" LABORATORY ANIMAL SCIENCE, vol. 43, no. 3, 1993, pages 247-251, XP000998289**

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 250 138 B1

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Description

[0001] The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

[0002] Oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means, and, in postmenopausal women, by the use of aromatase inhibitors.

[0003] An alternative approach to oestrogen withdrawal is to antagonise oestrogens with antioestrogens. These are drugs that bind to and compete for oestrogen receptors (ER) present in the nuclei of oestrogen-responsive tissue. Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of oestrogen-mediated activity (Furr and Jordan 1984, May and Westley 1987).

[0004] The potential for nonsteroidal antioestrogens to display agonistic properties prompted the search for novel compounds that would bind ER with high affinity without activating any of the normal transcriptional hormone responses and consequent manifestations of oestrogens. Such molecules would be "pure" antioestrogens, clearly distinguished from tamoxifen-like ligands and capable of eliciting complete ablation of the trophic effects of oestrogens. Such compounds are referred to as Estrogen Receptor-Downregulators (E.R.D.). The rationale for the design and testing of novel, pure antioestrogens has been described in: Bowler et al 1989, Wakeling 1990a, 1990b, 1990c. Wakeling and Bowler 1987, 1988.

[0005] Steroidal analogues of oestradiol, with an alkylsulphinyl side chain in the 7α position, provided the first examples of compounds devoid of oestrogenic activity (Bowler et al 1989). One of these, 7α-[9-(4,4,5,5,5-pentafluoropentyl sulphinyl)nonyl]oestra-1,3,5-(10)triene-3,17β-diol was selected for intensive study on the basis of its pure oestrogen antagonist activity and significantly increased antioestrogenic potency over other available antioestrogens. *In vitro* findings and early clinical experience with 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol have promoted interest in the development of the drug as a therapeutic agent for oestrogen-dependent indications such as breast cancer and certain benign gynaecological conditions.

[0006] 7α-[9-(4,4,5,5,5-Pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol, or ICI 182,780, has been allocated the international non-proprietary name fulvestrant, which is used hereinafter. When referring to fulvestrant we include pharmaceutically-acceptable salts thereof and any possible solvates of either thereof.

[0007] Fulvestrant binds to ER with an affinity similar to that of oestradiol and completely blocks the growth stimulatory action of oestradiol on human breast cancer cells *in vitro*; it is more potent and more effective than tamoxifen in this respect. Fulvestrant blocks completely the uterotrophic action of oestradiol in rats, mice and monkeys, and also blocks the uterotrophic activity of tamoxifen.

[0008] Because fulvestrant has none of the oestrogen-like stimulatory activity that is characteristic of clinically available antioestrogens such as tamoxifen or toremifene, it may offer improved therapeutic activity characterised by more rapid, complete, or longer-lasting tumour regression; a lower incidence or rate of development of resistance to treatment; and a reduction of tumour invasiveness.

[0009] In intact adult rats, fulvestrant achieves maximum regression of the uterus at a dose which does not adversely affect bone density or lead to increased gonadotrophin secretion. If also true in humans, these findings could be of extreme importance clinically. Reduced bone density limits the duration of oestrogen-ablative treatment for endometriosis. Fulvestrant does not block hypothalamic ER. Oestrogen ablation also causes or exacerbates hot flushes and other menopausal symptoms; fulvestrant will not cause such effects because it does not cross the blood-brain barrier.

[0010] European Patent Application No. 0 138 504 discloses that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration.

[0011] Fulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult. Fulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$ (this is an estimate from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute).

[0012] Currently there are a number of sustained release injectable steroidal formulations which have been com-

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mercialised. Commonly these formulations use oil as a solvent and wherein additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

[0013] In the formulations within Table 1 a number of different oils are used to solubilise the compound and additional excipients such as benzyl benzoate, benzyl alcohol and ethanol have been used. Volumes of oil needed to solubilise the steroid active ingredient are low. Extended release is achievable for periods from 1 to 8 weeks.

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Table 1 - OIL BASED LONG-ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMP'.	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	DOSING
SUSTANON 100	Testosterone proprionate Testosterone phenylproprionate Testosterone isocaproate Testosterone decanoate	30mg 60mg 60mg 100mg	Androgen	Organon	ABPI Data Sheet Comp.1999	Arachis		0.1ml		1ml	3 weeks
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250mgml^{-1}	Progestogen	Schering HC	ABPI Data Sheet Comp.1999	Castor	up to 46%			1 or 2ml	1 week
TOCOGESTAN	Hydroxy progesterone enantate Progesterone α-Tocopherol	200mg 50mg 250mg	Progestogen	Theramax	Dict. Vidal 1999	Ethyl oleate	*40%			2ml	< 1week
TROPHOBOLENE	Estrapronicate Nandrolone undecanoate Hydroxyprogesterone heptanoate	1.3mg 50mg 80mg	Mixed	Theramax	Dict. Vidal 1997	Olive	45%			1ml	15 to 30 days
NORISTERAT	Norethisterone oenanthoate	200mg	Contraceptive	Schering HC	ABPI Data Sheet Comp.1999	Castor	YES			1ml	8 weeks
BENZO-GYNOESTRYL	Estradiol hexahydrobenzoate	5mg	Estradiol	Roussel	Dict. Vidal 1998	Arachis				1ml	1 week
PROGESTERONE -RETARD	Hydroxy progesterone caproate	250mgml^{-1}	Progestogen	Pharlon	Dict. Vidal 1999	Castor	YES			1 or 2ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate Hydroxyprogesterone caproate	5mgml^{-1} 250mgml^{-1}	Mixed	Schering HC	Dict. Vidal 1995	Castor	YES			1 or 2ml	1 - 2 weeks

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PARABOLAN	Trenbolone	76mg	Androgen	Negma	Dict. Vidal 1997	Arachis		75mg	45mg	1.5ml	2 weeks
DELESTROGEN	Estradiol valerate	$20mgml^{-1}$ $40mgml^{-1}$	Estradiol	BMS	J.Pharm. Sci (1964) 53(8) 891	Castor	78% 58%	20% 40%	2% 2%		
DELALUTIN	17-Hydroxy progesterone	$250mgml^{-1}$	Progestrogen	DMS	J.Pharm. Sci.(1964) 53(8) 891	Castor	YES	YES	up to 2%		

BzBz = benzylbenzoate BzOH = benzylalcohol EtOH = ethanol Dict. Vidal = Dictionnaire Vidal
% are w/v and * approximate as measured directly from a single sample

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[0014] In US 5,183,814 Example 3 an oil based injection formulation of fulvestrant is described which comprises 50mg of fulvestrant, 400mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. Manufacture at a commercial scale of a formulation as described in US 5,183,814 will be complicated by the high alcohol concentration. Therefore, there is a need to lower the alcohol concentration in fulvestrant formulations whilst preventing precipitation of fulvestrant from the formulation.

[0015] Table 2 shows the solubility of fulvestrant in a number of different solvents.

Table 2 -

SOLUBILITY OF FULVESTRANT	
SOLVENT	SOLUBILITY ($mgml^{-1}$ at 25°C)
Water	0.001
Arachis oil	0.45
Sesame oil	0.58
Castor oil	20
Miglyol 810	3.06
Miglyol 812	2.72
Ethyl oleate	1.25
Benzyl benzoate	6.15
Isopropyl myristate	0.80
Span 85 (surfactant)	3.79
Ethanol	>200
Benzyl Alcohol	>200

[0016] As can be seen fulvestrant is significantly more soluble in castor oil than any of the other oils tested. The greater solvating ability of castor oil for steroidal compounds is known and is attributed to the high number of hydroxy groups of ricinoleic acid, which is the major constituent of the fatty acids within the triglycerides present in castor oil - see (Riffkin et.al. J. Pharm. Sci., (1964), 53, 891).

[0017] However, even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate. To achieve a therapeutically significant release rate the amount of fulvestrant needed would require the formulation volume to be large, at least 10 ml. This requires the doctor to inject an excessively large volume of formulation to administer a dose significantly high enough for human therapy.

[0018] Currently guidelines recommend that no more than 5mls of liquid is injected intramuscularly in a single injection. Pharmacologically active doses required for a 1 month long acting depot formulation of fulvestrant is around 250mg. Therefore, when dissolved in just castor oil, fulvestrant would need to be administered in at least 10ml of castor oil.

[0019] The addition of organic solvents in which fulvestrant is freely soluble, and which are miscible with castor oil, may be used, such as an alcohol. With the addition of high concentrations of an alcohol concentrations of >50$mgml^{-1}$ of fulvestrant in a castor oil formulation is achievable, thereby giving an injection volumes of <5ml - see Table 3 below. We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 $mgml^{-1}$ - see Table 3 below. The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil.

[0020] Therefore, we present as a feature of the invention a pharmaceutical formulation comprising fulvestrant (preferably fulvestrant is present at 3-10%w/v, 4-9%w/v, 4-8%w/v, 4-7%w/v, 4-6%w/v and most preferably at about 5%w/v) in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

[0021] Another feature of the invention is a pharmaceutical formulation comprising fulvestrant in which the formulation is adapted for intra-muscular injection into a human and which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

[0022] Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection

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comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

[0023] Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant; 35% (preferably 30% and ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

[0024] For the avoidance of any doubt when using the term % weight per volume of formulation for the constituents of the formulation we mean that within a unit volume of the formulation a certain percentage of the constituent by weight will be present, for example a 1% weight per volume formulation will contain within a 100ml volume of formulation 1g of the constituent. By way of further illustration

% of x by weight per volume of formulation	weight of x in 1ml of formulation
30%	300mg
20%	200mg
10%	100mg
5%	50mg
1%	10mg

[0025] Preferred pharmaceutical formulations of the invention are as described above wherein:

1. The total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least 45mgml^{-1}.
2. The total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.
3. The total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5-5.25ml.

[0026] It is appreciated that in the formulation an excess of formulation may be included to allow the attendant physician or care giver to be able to deliver the required dose. Therefore, when a 5ml dose is required it would be appreciated that an excess of up to 0.25ml, preferably up to 0.15ml will also be present in the formulation. Typically the formulation will be presented in a vial or a prefilled syringe, preferably a prefilled syringe, containing a unit dosage of the formulation as described herein, these being further features of the invention.

[0027] Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; at least 3%w/v, at least 5%w/v, at least 7%w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 14% w/v, at least 15% w/v and, preferably, at least 16% w/v. Preferred maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ;28% w/v or less, 22% w/v or less and 20% w/v or less.. Preferred ranges of pharmaceutically-acceptable alcohol present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 3-35%w/v, 4-35%w/v, 5-35%w/v, 5-32%w/v, 7-32%w/v, 10-30%w/v, 12-28%w/v, 15-25%w/v, 17-23%w/v, 18-22%w/v and ideally 19-21%w/v.

[0028] The pharmaceutically-acceptable alcohol may consist of one alcohol or a mixture of two or more alcohols, preferably a mixture of two alcohols. Preferred pharmaceutically-acceptable alcohols for parenteral administration are ethanol, benzyl alcohol or a mixture of both ethanol and benzyl alcohol, preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts. Preferably the formulation alcohol contains 10% w/v ethanol and 10% w/v benzyl alcohol.

[0029] The pharmaceutically-acceptable non-aqueous ester solvent may consist of one or a mixture of two or more pharmaceutically-acceptable non-aqueous ester solvents, preferably just one. A preferred pharmaceutically-acceptable non-aqueous ester solvent for parenteral administration is selected from benzyl benzoate, ethyl oleate, isopropyl myristate,isopropyl palmitate or a mixture of any thereof.

[0030] The ricinoleate vehicle should preferably be present in the formulation in a proportion of at least 30% weight per volume of the formulation, ideally at least 40% or at least 50% weight per volume of formulation.

[0031] It will be understood by the skilled person that the pharmaceutically-acceptable alcohol will be of a quality such that it will meet pharmacopoeial standards (such as are described in the US, British, European and Japanese pharmacopoeias) and as such will contain some water and possibly other organic solvents, tor example ethanol in the US Pharmacopeia contains not less than 94.9% by volume and not more than 96.0% by volume of ethanol when measured at 15.56°C. Dehydrated alcohol in the US Pharmacopeia contains not less than 99.5% ethanol by volume

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when measured at 15.56°C.

[0032] Preferred concentrations of the pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are; at least 5% w/v, at least 8% w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 15% w/v, at least 16% w/v, at least 17% w/v, at least 18% w/v, at least 19% w/v and at least 20% w/v. Preferred maximal concentrations of the pharmaceutically-acceptable non-aqueous ester solvent are; 60% w/v or less, 50%w/v or less, 45% w/v or less, 40% w/v or less, 35% w/v or less, 30% w/v or less and 25% w/v or less. A preferred concentration is 15% w/v. Preferred ranges of pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 5-60%w/v, 7-55%w/v, 8-50%w/v, 10-50%w/v, 10-45%w/v, 10-40%w/v, 10-35%w/v, 10-30%w/v, 10-25%w/v, 12-25%w/v, 12-22%w/v, 12-20%w/v, 12-18%w/v, 13-17%w/v and ideally 14-16%w/v. Preferably the ester solvent is benzyl benzoate, most preferably at about 15%w/v.

[0033] It will be understood by the skilled person that the pharmaceutically-acceptable non-aqueous ester solvent will be of a quality that it will meet pharmacopoeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

[0034] Preferred combinations of pharmaceutically-acceptable alcohol and pharmaceutically-acceptable non-aqueous ester solvent in the formulation are set out below:

Pharmaceutically-acceptable alcohol(%w/v)	**Pharmaceutically-acceptable non-aqueous ester (%w/v)**
10-30	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
17-23	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-	10-35
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-21.	12-18
ethanol and benzyl alcohol, most preferably each at about 10%	benzyl benzoate, most preferably at about 15%

[0035] By the use of the term ricinoleate vehicle we mean an oil which has as a proportion (at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. The ricinoleate vehicle may be a synthetic oil or conveniently is castor oil, ideally of pharmacopoeial standards, as described above.

[0036] We have surprisingly found that the above formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time.

[0037] This finding is indeed surprising for the following reasons.

1. Previously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the injection site as well as a poor release profile. It is believed that the tissue irritation/inflammation was due to the presence of fulvestrant in the form of solid particles. The release profile appeared to be determined by the extent of inflammation/irritation present at the injection site and this was variable and diffcult to control. Also the fulvestrant release rate was not sufficiently high to be clinically significant.
2. Our findings from studies using ^{14}C labelled benzyl alcohol show that it dissipates rapidly from the injection site and is removed from the body within 24 hours of administration.

[0038] It would be expected that ethanol will dissipate at least as quickly, if not more rapidly, from the injection site.

[0039] It is known that benzyl benzoate is metabolised by conjugation to glycine to form hippuric acid by the human liver and excreted into the urine - Martindale: The Extra Pharmacopoeia 32nd edition page 1103, and, therefore, it is unlikely that benzyl benzoate, when used, is present at the injection site during the whole of the extended release period.

[0040] We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and pharmaceutically-acceptable non-aqueous ester solvent, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period

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can still achieved by the formulation of the invention.

[0041] By use of the term "therapeutically significant levels" we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient. Preferably blood plasma levels should be less than 15 $ngml^{-1}$.

[0042] By use of the term "extended release" we mean at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved. In a preferred feature extended release is achieved for 36 days. Preferably extended release of fulvestrant is for at least 2- 5 weeks and more preferably for the following periods (weeks) 2.5-5, 2.5-4, 3-4, 3.5-4 and most preferably for at least about 4 weeks.

[0043] It will be understood that the attendant physician may wish to administer the intramuscular injection as a divided dose, i.e. a 5ml formulation is sequentially administered in two separate injections of 2.5ml, this is a further feature of the invention

[0044] Simply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site.

[0045] Table 3 shows the solubility of fulvestrant in a castor oil vehicle additionally containing alcohols ethanol and benzyl alcohol with or without benzyl benzoate. The results clearly show the positive effect of benzyl benzoate on fulvestrant solubility in castor oil, despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

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Table 3

Table 3 - EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25°C

	% w/v							
Ethanol (96%)	5	5	10	10	10	10	15	15
Benzyl Alcohol	5	5	5	5	10	10	15	15
Benzyl Benzoate		15		15		15		15
Castor Oil	to 100	to100	to 100	to 100	to 100	to 100	to 100	to 100
Fulvestrant Solubility [$mgml^{-1}$]	27	36	46	54	45	65	76	102

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[0046] The following Table 4 shows the solubility of fulvestrant in a range of oil based formulations which contain the same amounts of alcohol and benzyl benzoate but in which the oil is changed. The data also shows solubility of fulvestrant after removal of the alcohols.

Table 4

Solubility comparisons of fulvestrant in oil based formulations with and without alcohols		
	Fulvestrant Solubility mg ml^{-1} @ 25°C	
Formulation [(a)]	Complete vehicle	Vehicle minus alcohols
Castor oil based	81.2	12.6
Miglyol 812-N based	86.8	1.7
Sesame seed/Castor oil (1:1) based	70.1	4.4
Sesame seed oil based	45.7	0.7
Arachis oil based	40.2	< 0.2

[(a)] **Complete Vehicle** Formulations comprised ethanol [96%](10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil. Excess fulvestrant was added to each solvent mixture and solubility determined.

Effect of formulation on precipitation of fulvestrant at the injection site							
	Days						
Formulation [a]	2	3	4	7	10	30	51
Formulation F1 castor oil based	0	0	0	0	0	0	0
Formulation F2 Miglyol 812-N based	++ [b]	+++	+++	+++	+++	++	0
Formulation F3 sesame seed oil/castor oil based	+ [c]	++	++	+++	++	+	+
0, + , ++, +++ = Degree of precipitation (None detected, Mild, Moderate, Severe)							

[a] Formulations comprised fulvestrant (5%), ethanol [96%] (10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil.

[b] Mainly large needle shaped crystals

[c] Small needles and/or sheafs of crystals

[0047] Precipitation of fulvestrant and the release profile was determined with the above formulations in an *in vivo* rabbit study.

[0048] Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits (data normalised to 50mg per 3kg; mean given; number of animals per timepoint = 8, plasma samples assayed for fulvestrant content using lc-ms/ms detection following solvent extraction). As can be seen the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site.

[0049] Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharmaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

[0050] A further feature of the invention is a pharmaceutical formulation adapted for intramuscular injection, as defined above, for use in medical therapy.

[0051] A further feature of the invention is the treatment of a benign or malignant diseases of the breast or reproductive tract, preferably treating breast cancer, by administration to a human in need of such treatment by intramuscular injection an extended release ricinoleate vehicle based pharmaceutical formulation comprising at least 45mgml^{-1} of fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation.

[0052] Preferably 5ml of the intramuscular injection is administered.

[0053] A further feature of the invention is use of fulvestrant in the preparation of a pharmaceutical formulation as describe hereinabove, for the treatment of a benign or malignant disease of the breast or reproductive tract, preferably

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treating breast cancer.

[0054] Additional excipients commonly used in the formulation field including, for example, an antioxidant preservative, a colorant or a surfactant may be used. A preferred optional excipient is a surfactant.

[0055] As described above fulvestrant is useful in the treatment of oestrogen-dependent indications such as breast cancer and gynaecological conditions, such as endometriosis.

[0056] In addition to fulvestrant another similar type of molecule is currently under clinical investigation. SH-646 (11β-fluoro-7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol) is also putatively a compound with the same mode of action as fulvestrant and has a very similar chemical structure. It is believed that the compound will also share with fulvestrant similar physical properties and therefore the current invention will also have application with this compound.

[0057] A further feature of the invention is a pharmaceutical formulation adapted for intra-muscular injection comprising 11β-fluoro-7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol; 35% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of 11β-fluoro-7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol.

[0058] Further features of the invention are those as described above but in which SH-646 is substituted for fulvestrant.

Formulation Example

[0059] Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid with Nitrogen. The solution is sterilised by filtration using one or two filters of 0.2μm porosity. The sterile filtrate is kept under a nitrogen overlay as it is filled under aseptic conditions into washed and depyrogenised, sterile primary containers, for example vials or pre-filled syringes. An overage is included in the primary pack to facilitate removal of the dose volume. The primary packs are overlaid with sterile nitrogen, before aseptically sealing.

See also process flow diagram below

[0060] Quantities of each component of the formulation is chosen according to the required formulation specification, examples are described above. For example quantities are added of each component to prepare a formulation which contains

10% weight per volume of benzyl alcohol
10% weight per volume of ethanol
15% weight per volume of benzyl benzoate
250mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil

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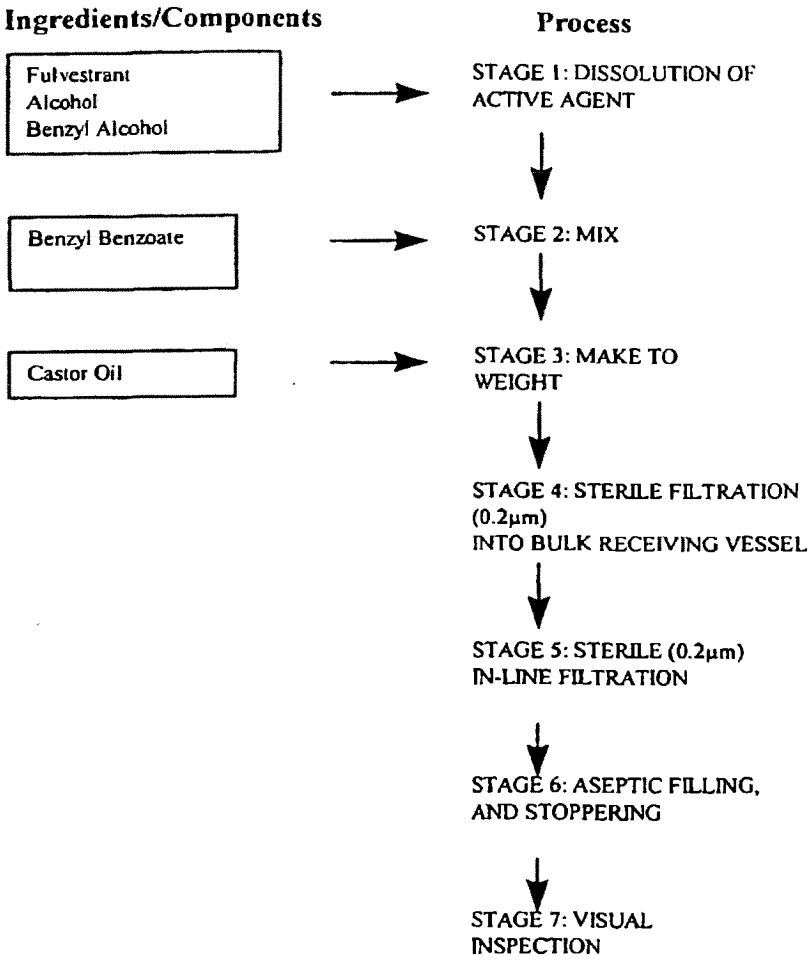
FLOW DIAGRAM OF MANUFACTURING



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3: 141-7.

Claims

1. A pharmaceutical formulation comprising fulvestrant in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intra-muscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

2. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

3. A pharmaceutical formulation as claimed in claim 1 or 2 wherein the blood plasma fulvestrant concentration attained is at least 2.5ngml^{-1} for at least 2 weeks..

4. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

5. A pharmaceutical formulation as claimed in claim 1 to 4 which contains 25% w/v or less of a pharmaceutically-acceptable alcohol.

6. A pharmaceutical formulation as claimed in claim 5 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

7. A pharmaceutical formulation as claimed in claim 5 which contains 15-25% w/v of a pharmaceutically acceptable alcohol.

8. A pharmaceutical formulation as claimed in claim 5 which contains 17-23% w/v of a pharmaceutically acceptable alcohol.

9. A pharmaceutical formulation as claimed in any claim from 1 to 8 which contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

10. A pharmaceutical formulation as claimed in claim 9 which contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

11. A pharmaceutical formulation as claimed in claim 9 which contains 45% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

12. A pharmaceutical formulation as claimed in claim 9 which contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

13. A pharmaceutical formulation as claimed in claim 9 which contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

14. A pharmaceutical formulation as claimed in claim 9 which contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

15. A pharmaceutical formulation as claimed in claim 9 which contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

16. A pharmaceutical formulation as claimed in claim 9 which contains 10-25% w/v of a pharmaceutically acceptable

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non-aqueous ester solvent.

17. A pharmaceutical formulation as claimed in claim 9 which contains 12-18% w/v of a pharmaceutically acceptable non-aqueous ester solvent.

18. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 15-25% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 10-25 % weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

19. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 17-23% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 12-18 % weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

20. A pharmaceutical formulation as claimed in any claim from 1 to 19 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

21. A pharmaceutical formulation as claimed in any claim from 1 to 20 wherein the pharmaceutically-acceptable non-aqueous ester solvent is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmitate or a mixture of any thereof.

22. A pharmaceutical formulation as claimed in any claim from 1 to 21 wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

23. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 15-25% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 10-25 % weight of benzyl benzoate in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

24. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 17-23% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 12-18 % weight of benzylbenzoate in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

25. A pharmaceutical formulation according to claim 23 or 24 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

26. A pharmaceutical formulation according to claim 25 wherein the ethanol and benzyl alcohol are present at about equal % weight per volume of formulation.

27. A pharmaceutical formulation as claimed in any claim from 1 to 26 wherein the total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least 45mgml^{-1}.

28. A pharmaceutical formulation as claimed in any claim from 1 to 27 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

29. A pharmaceutical formulation as claimed in claim 28 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5 to 5.25ml.

30. A pharmaceutical formulation as claimed in any of claims 1-29 wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation, and the formulation contains 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

31. A pharmaceutical formulation adapted for intramuscular injection, as defined in any claim from 1 to 30, for use in medical therapy.

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32. Use of fulvestrant in the preparation of a pharmaceutical formulation, as defined in any claim from 1 to 30, for the treatment of a benign or malignant disease of the breast or reproductive tract.

33. A syringe or vial containing a pharmaceutical formulation as defined in claim 30.

Patentansprüche

1. Pharmazeutische Formulierung, enthaltend Fulvestrant in einer Ricinoleat-Trägersubstanz, ein pharmazeutisch annehmbares nichtwässriges Esterlösungsmittel und einen pharmazeutisch annehmbaren Alkohol, wobei die Formulierung zur intramuskulären Anwendung und Erzielung einer mindestens 2 Wochen anhaltenden, therapeutisch signifikanten Fulvestrantkonzentration im Blutplasma geeignet ist.

2. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 30 Gew.-% oder weniger eines pharmazeutisch annehmbaren Alkohols und mindestens 1 Gew.-% eines in einer Ricinoleat-Trägersubstanz mischbaren, pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels, sowie eine zur Herstellung einer nach Injektion zur Erzielung einer mindestens 2 Wochen anhaltenden, therapeutisch signifikanten Fulvestrantkonzentration im Blutplasma geeigneten Formulierung ausreichende Menge einer Ricinoleat-Trägersubstanz.

3. Pharmazeutische Formulierung nach Anspruch 1 oder 2, bei der die im Blutplasma erzielte Fulvestrantkonzentration mindestens 2 Wochen lang mindestens 2,5 $ngml^{-1}$ beträgt.

4. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 30 Gew.-% oder weniger eines pharmazeutisch annehmbaren Alkohols und mindestens 1 Gew.-% eines in einer Ricinoleat-Trägersubstanz mischbaren, pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels, sowie eine zur Herstellung einer Formulierung mit mindestens 45 $mgml^{-1}$ Fulvestrant ausreichende Menge einer Ricinoleat-Trägersubstanz.

5. Pharmazeutische Formulierung nach Anspruch 1 bis 4, die 25% w/v oder weniger eines pharmazeutisch annehmbaren Alkohols enthält.

6. Pharmazeutische Formulierung nach Anspruch 5, die 20% w/v oder weniger eines pharmazeutisch annehmbaren Alkohols enthält.

7. Pharmazeutische Formulierung nach Anspruch 5, die 15-25% w/v eines pharmazeutisch annehmbaren Alkohols enthält.

8. Pharmazeutische Formulierung nach Anspruch 5, die 17-23% w/v eines pharmazeutisch annehmbaren Alkohols enthält.

9. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 8, die 60% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

10. Pharmazeutische Formulierung nach Anspruch 9, die 50% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

11. Pharmazeutische Formulierung nach Anspruch 9, die 45% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

12. Pharmazeutische Formulierung nach Anspruch 9, die 40% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

13. Pharmazeutische Formulierung nach Anspruch 9, die 35% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

14. Pharmazeutische Formulierung nach Anspruch 9, die 30% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

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15. Pharmazeutische Formulierung nach Anspruch 9, die 25% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

16. Pharmazeutische Formulierung nach Anspruch 9, die 10-25% w/v eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

17. Pharmazeutische Formulierung nach Anspruch 9, die 12-18% w/v eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

18. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 15-25 Gew.-% eines pharmazeutisch annehmbaren Alkohols und 10-25 Gew.-% eines in einer Ricinoleat-Trägersubstanz mischbaren, pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels, sowie eine zur Herstellung einer Formulierung mit mindestens 45 $mgml^{-1}$ Fulvestrant ausreichende Menge einer Ricinoleat-Trägersubstanz.

19. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 17-23 Gew.-% eines pharmazeutisch annehmbaren Alkohols und 12-18 Gew.-% eines in einer Ricinoleat-Trägersubstanz mischbaren, pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels, sowie eine zur Herstellung einer Formulierung mit mindestens 45 $mgml^{-1}$ Fulvestrant ausreichende Menge einer Ricinoleat-Trägersubstanz.

20. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 19, bei der es sich bei dem pharmazeutisch annehmbaren Alkohol um ein Gemisch aus Ethanol und Benzylalkohol handelt.

21. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 20, bei der das pharmazeutisch annehmbare nichtwässrige Esterlösungsmittel unter Benzylbenzoat, Ethyloleat, Isopropylmyristat, Isopropylpalmitat oder einem beliebigen Gemisch davon ausgewählt ist.

22. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 21, bei der es sich bei dem pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittel um Benzylbenzoat handelt.

23. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 15-25 Gew.-% eines pharmazeutisch annehmbaren Alkohols und 10-25 Gew.-% Benzylbenzoat in einer Ricinoleat-Trägersubstanz, sowie eine zur Herstellung einer Formulierung mit mindestens 45 $mgml^{-1}$ Fulvestrant ausreichende Menge einer Ricinoleat-Trägersubstanz.

24. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 17-23 Gew.-% eines pharmazeutisch annehmbaren Alkohols und 12-18 Gew.-% Benzylbenzoat in einer Ricinoleat-Trägersubstanz, sowie eine zur Herstellung einer Formulierung mit mindestens 45 $mgml^{-1}$ Fulvestrant ausreichende Menge einer Ricinoleat-Trägersubstanz.

25. Pharmazeutische Formulierung nach Anspruch 23 oder 24, bei der es sich bei dem pharmazeutisch annehmbaren Alkohol um ein Gemisch aus Ethanol und Benzylalkohol handelt.

26. Pharmazeutische Formulierung nach Anspruch 25, bei der der gew.-%ige Anteil an Ethanol und Benzylalkohol pro Volumen Formulierung jeweils etwa gleich ist.

27. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 26, bei der das Gesamtvolumen der Formulierung 6 ml oder weniger und die Fulvestrantkonzentration mindestens 45 $mgml^{-1}$ ausmachen.

28. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 27, bei der die Gesamtmenge an Fulvestrant in der Formulierung 250 mg oder mehr und das Gesamtvolumen der Formulierung 6 ml oder weniger ausmachen.

29. Pharmazeutische Formulierung nach Anspruch 28, bei der die Gesamtmenge an Fulvestrant in der Formulierung 250 mg und das Gesamtvolumen der Formulierung 5 bis 5,25 ml ausmachen.

30. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 29, bei der es sich bei dem pharmazeutisch annehmbaren Alkohol um ein Gemisch von, jeweils bezogen auf das Volumen der Formulierung, 10 Gew.-% Etha-

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nol und 10 Gew.-% Benzylalkohol handelt, und die Formulierung pro Volumen 15 Gew.-% Benzylbenzoat enthält, und es sich bei der Ricinoleat-Trägersubstanz um Rizinusöl handelt.

31. Pharmazeutische Formulierung zur intramuskulären Injektion gemäß Definition eines der Ansprüche 1 bis 30 zur Verwendung in der medizinischen Therapie.

32. Verwendung von Fulvestrant bei der Herstellung einer wie in einem der Ansprüche 1 bis 30 definierten pharmazeutischen Formulierung zur Behandlung gutartiger oder bösartiger Erkrankungen der Brust oder des Reproduktionstrakts.

33. Spritze oder Fläschchen, enthaltend eine wie in Anspruch 30 definierte pharmazeutische Formulierung.

Revendications

1. Préparation pharmaceutique comprenant du fulvestrant dans un véhicule de ricinoléate, un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique et un alcool acceptable d'un point de vue pharmaceutique, dans laquelle la préparation est adaptée à une administration intramusculaire et atteint une concentration en fulvestrant dans le plasma sanguin significative d'un point de vue thérapeutique pendant au moins 2 semaines.

2. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 30% ou moins en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, au moins 1% en poids d'un solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique et miscible dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation qui soit capable, après injection, d'atteindre une concentration en fulvestrant dans le plasma sanguin significative d'un point de vue thérapeutique pendant au moins 2 semaines.

3. Préparation pharmaceutique selon la revendication 1 ou 2, dans laquelle la concentration en fulvestrant dans le plasma sanguin atteinte est de 2,5 $ng.ml^{-1}$ au moins pendant 2 semaines au moins.

4. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 30% ou moins en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, au moins 1% en poids d'un solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique et miscible dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation à 45 $mg.ml^{-1}$ au moins de fulvestrant.

5. Préparation pharmaceutique, selon les revendications 1 à 4, qui contient 25% p/v ou moins d'un alcool acceptable d'un point de vue pharmaceutique.

6. Préparation pharmaceutique, selon la revendication 5, qui contient 20% p/v ou moins d'un alcool acceptable d'un point de vue pharmaceutique.

7. Préparation pharmaceutique, selon la revendication 5, qui contient de 15 à 25% p/v d'un alcool acceptable d'un point de vue pharmaceutique.

8. Préparation pharmaceutique, selon la revendication 5, qui contient de 17 à 23% p/v d'un alcool acceptable d'un point de vue pharmaceutique.

9. Préparation pharmaceutique, selon l'une quelconque des revendications 1 à 8, qui contient 60% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

10. Préparation pharmaceutique, selon la revendication 9, qui contient 50% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

11. Préparation pharmaceutique, selon la revendication 9, qui contient 45% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

12. Préparation pharmaceutique, selon la revendication 9, qui contient 40% p/v ou moins d'un solvant d'ester non

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aqueux acceptable d'un point de vue pharmaceutique.

13. Préparation pharmaceutique, selon la revendication 9, qui contient 35% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

14. Préparation pharmaceutique, selon la revendication 9, qui contient 30% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

15. Préparation pharmaceutique, selon la revendication 9, qui contient 25% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

16. Préparation pharmaceutique, selon la revendication 9, qui contient de 10 à 25% p/v d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

17. Préparation pharmaceutique, selon la revendication 9, qui contient de 12 à 18% p/v d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

18. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 15 à 25% en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, 10 à 25% en poids d'un solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique et miscible dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation à 45 $mg.ml^{-1}$ au moins de fulvestrant.

19. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 17 à 23% en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, 12 à 18% en poids d'un solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique et miscible dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation à 45 $mg.ml^{-1}$ au moins de fulvestrant.

20. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 19, dans laquelle l'alcool acceptable d'un point de vue pharmaceutique est un mélange d'éthanol et d'alcool benzylique.

21. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 20, dans laquelle le solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique, est choisi parmi : le benzoate de benzyle ; l'oléate d'éthyle ; le myristate d'isopropyle ; le palmitate d'isopropyle ; ou un mélange de n'importe lesquels d'entre eux.

22. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 21, dans laquelle le solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique, est le benzoate de benzyle.

23. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 15 à 25% en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, 10 à 25% en poids de benzoate de benzyle, dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation à 45 $mg.ml^{-1}$ au moins de fulvestrant.

24. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 17 à 23% en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, 12 à 18% en poids de benzoate de benzyle, dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation à 45 $mg.ml^{-1}$ au moins de fulvestrant.

25. Préparation pharmaceutique selon la revendication 23 ou 24, dans laquelle l'alcool, acceptable d'un point de vue pharmaceutique, est un mélange d'éthanol et d'alcool benzylique.

26. Préparation pharmaceutique selon la revendication 25, dans laquelle l'éthanol et l'alcool benzylique sont présents avec des % en poids environ égaux par volume de préparation.

27. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 26, dans laquelle le volume total de la préparation est de 6 ml ou moins et la concentration en fulvestrant est de 45 $mg.ml^{-1}$ au moins.

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28. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 27, dans laquelle la quantité totale de fulvestrant dans la préparation est de 250 mg ou plus et le volume total de la préparation est de 6 ml ou moins.

29. Préparation pharmaceutique selon la revendication 28, dans laquelle la quantité totale de fulvestrant dans la préparation est de 250 mg et le volume total de la préparation est de 5 à 5,25 ml.

30. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 29, dans laquelle l'alcool, acceptable d'un point de vue pharmaceutique, est un mélange de 10% en poids d'éthanol par volume de préparation, de 10% en poids d'alcool benzylique par volume de préparation, la préparation contient 15% en poids de benzoate de benzyle par volume de préparation et le véhicule de ricinoléate est de l'huile de castor.

31. Préparation pharmaceutique adaptée à une injection intramusculaire, selon l'une quelconque des revendications 1 à 30, à utiliser dans une thérapie médicale.

32. Utilisation de fulvestrant dans l'élaboration d'une préparation pharmaceutique, selon l'une quelconque des revendications 1 à 30, destinée au traitement d'une maladie bénigne ou maligne du sein ou de l'appareil reproducteur.

33. Seringue ou flacon contenant une préparation pharmaceutique, selon la revendication 30.

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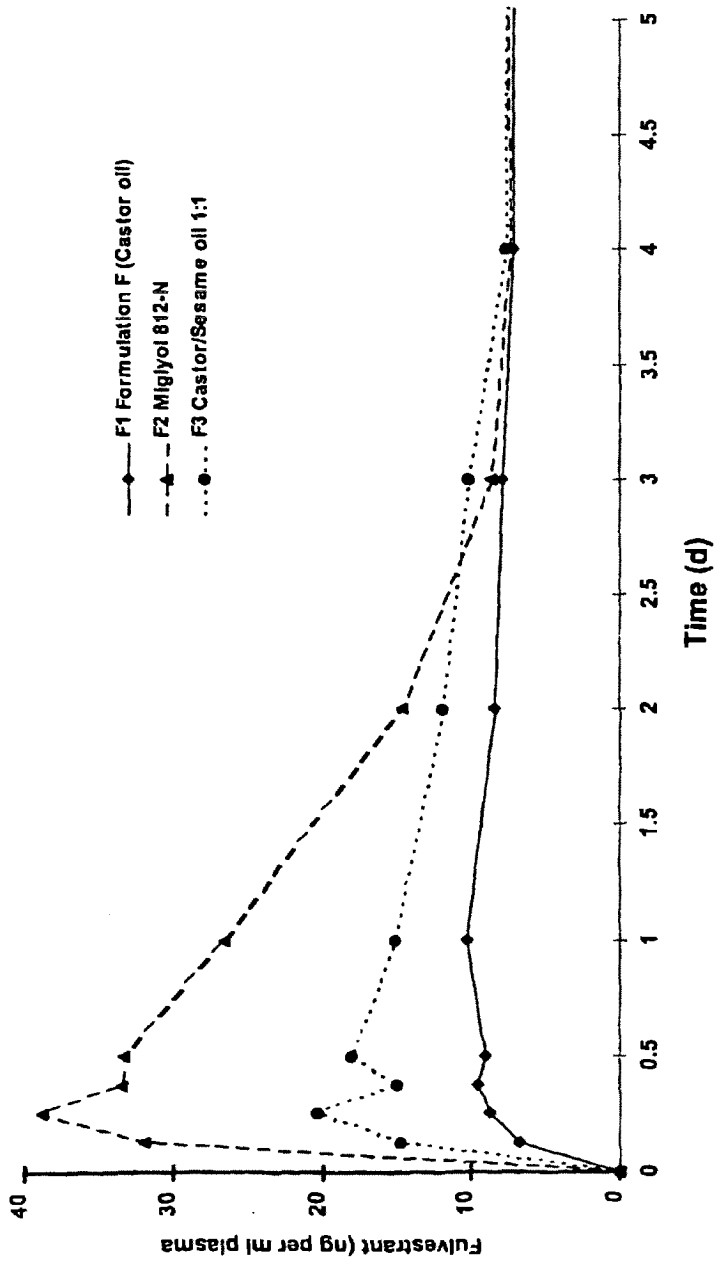

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Fourth IDS

Attachment II

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Date
16-05-2008

Reference	Application No./Patent No.
118 663 o2	01900186.6 - 2123 / 1250138

Applicant/Proprietor
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Communication pursuant to Rule 114(2) EPC

Please find enclosed observations by a third party concerning the patentability of the invention of the above-mentioned patent application. That person is not a party to the proceedings before the EPO (Art. 115 EPC).

Under Rule 114(2) EPC you may comment on the observations.

For the Opposition Division

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Reference	Application No./Patent No.
P/2FF22/BM/133.EP	01900186.6 - 2123 / 1250138
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Acknowledgment of receipt of observations by third parties (Article 115 EPC)

Receipt of your letter dated 06.05.08 is hereby acknowledged.

Under Article 115 EPC you will not be a party to the proceedings before the European Patent Office.

☐ In your letter the following documents are mentioned which were not enclosed, and which are not available in the EPO:

☐ The third party observations have not been filed in an official language of the EPO (R. 114(1) EPC).

You are requested to file copy(ies) and/or translation(s) in one of the official EPO languages within **two months** of notification of this communication if they are to be taken into account.

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Reference	Application No./Patent No.
M 2363 EP/OPP OPPO 01	01900186.6 - 2123 / 1250138
Applicant/Proprietor: AstraZeneca AB	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☒ Communication pursuant to R. 114(2) EPC

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☐ Letter from the opponent of
- ☒ Copy (copies) copy of F. 2022
- ☒ Communication: observations filed by third parties on 06.05.08

Please take note.

For the Opposition Division

Europäisches Patentamt · European Patent Office · Office européen des brevets

☐ **Registered letter**

EPO Form 2911O 12.07 13.05.08

HB21363

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(103)

DATE	YOUR REFERENCE	OUR REFERENCE
6 May 2008	--	P/2FF22/BM/133.EP

RE

Opposition against EP 1 250 138 01900186.6

OBSERVATIONS BY THIRD PARTIES

1. This is an observations by third parties in relation to the opposition against the European patent 1 250 138 (EP138), and the preliminary opinion of the Opposition Division.

INTRODUCTION

2. Claim 1 as granted relates to a pharmaceutical formulation comprising fulvestrant. The formulation comprises further a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol.

3. The formulation is adapted for intramuscular administration.

4. The ricinoleate vehicle is defined in [0035]. It is an oil being a triglyceride of ricinoleic acid. Conveniently it is castor oil.

5. The pharmaceutically acceptable non-aqueous ester solvent is defined [0029]. The non-aqueous ester solvent is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmytate or mixtures thereof.

6. Finally, the pharmaceutically acceptable alcohol is defined in [0028]. Practically, the alcohol is selected from ethanol, benzyl alcohol and mixtures thereof.

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7. It is noted that claim 1 does not comprise a limitation in relation to the (relative) amounts of the ingredients of the pharmaceutical formulation. Accordingly, any combination of ingredients which is adapted or suitable for intramuscular administration falls within the subject matter claimed in claim 1.

8. Claim 1 comprises further a description of the result to be attained with the pharmaceutical formulation. The result is that for at least two weeks a therapeutically significant blood plasma fulvestrant concentration is to be maintained. In [0041] the therapeutically significant blood plasma level of fulvestrant is defined as being at least 2.5 $ngml^{-1}$. However, the presence of this result-to-be-obtained-feature in claim 1 is considered incorrect. For reasons that claim 1 relates to a pharmaceutical formulation comprising various ingredients and that by properly claiming absolute or relative amounts of these ingredients this intramuscular pharmaceutical formulation could be properly claimed. This is the more true because the organism to be administered with the formulations is not included in claim 1. Neither is included the amount of fulvestrant administered. Such administration could follow any plasma concentration curve as visualized in the figure annexed to EP138.

II. LACK OF NOVELTY

9. D1 (EP 0 346 014) discloses a therapeutic product comprising a so called oestrogen component. A large variety of various oestrogen components are disclosed in page 3, lines 5 – page 4, line 1. Fulvestrant is one of these explicitly mentioned oestrogen components (page 3, lines 21-23) but a variety of other oestrogen components having a variety of possible ester groups are mentioned.

10. In page 5, lines 12-19 it is indicated that the pharmaceutical composition may have the form of a water emulsion. The oily phase may be a vegetable oil, such as castor oil, soja bean oil or arachis oil, or a mineral oil. The oily phase may comprise a suitable emulsifying agent. One of these emulsifying agents are esters or partial esters derived from fatty acids.

11. In page 7, lines 13-25 it is stated that the pharmaceutical composition may be formulated in an oily solution suitable for intramuscular injection. The oily solution or suspension may contain the oestrogen component. The oily solution is for example a solution containing arachis oil or castor oil, an alcohol, such as benzyl alcohol, and further 50 mg to 500 mg of the oestrogen component. By intramuscular injection the effect of the oestrogen component will last for one to six weeks.

12. The Patentee is of the opinion that the specified disclosure in page 5 may not be combined with the specified disclosure in page 7. For reasons that there is no explicit combination made in between these two disclosures in D1.

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13. However, in page 5 as from line 14 on it is stated that a suitable emulsifying agent may be added to the oily phase. This means to the skilled person that in order to improve the emulsifying character of the oily phase an emulsifying agent may be added. It goes without saying that in relation to the disclosure in page 7 (starting from line 21 on) it is straight forward to the skilled person that the oily solution or suspension disclosed may be supplemented with an emulsifying agent in order to improve the emulsifying character of the oily phase or suspension. This means that to the solution containing castor oil, alcohol and the oestrogen component an emulsifier may be added.

14. This would be different if in D1 it had been indicated that to a mixture of castor oil, alcohol and the oestrogen component the addition of an emulsifying agent is not wanted or considered superfluous.

15. Also the presence of example 3 disclosing the combination of fulvestrant, castor oil and benzyl alcohol will not change the allowed combination of the subject matter of page 5 and page 7.

16. Even, it is within the disclosure of D1 that for improving the emulsifying character of the castor mixture disclosed in example 3 an emulsifying agent could be added.

17. Accordingly, the position is taken that the combination of a ricinoleated vehicle, non-aqueous ester solvent, and a pharmaceutically acceptable alcohol is directly or implicitly disclosed in D1. Accordingly, claim 1 lacks novelty.

18. In the preliminary opinion the Opposition Division indicates that D1 discloses in example 3 a composition comprising fulvestrant, castor oil and benzyl alcohol for intramuscular administration. A non-aqueous ester solvent is not disclosed in example 3. Correctly, such non-aqueous ester solvents are mentioned in the description of D3 in page 5, line 16.

19. On the basis of this disclosure the Opposition Division is of the opinion that the combination of subject matter of claim 1 is not directly and unambiguously disclosed in D1.

20. However, the disclosure in relation to the subject matter of claim 1 is not limited to example 3 and to page 5, line 16. As indicated above it is disclosed in page 5, lines 12-16 that the oily phase which may be castor oil comprises an emulsifying agent such as the non-aqueous ester solvent. Example 3 describes such oily solution as a pharmaceutical composition according to the invention. Thus, it is directly contemplated to include in the oily solution of example 3 as an emulsifying agent a non-aqueous ester solvent identified in page 5, line 16.

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21. Accordingly, it is respectfully requested to reconsider the preliminary opinion in relation to novelty over D1.

III. LACK OF INVENTIVE STEP

22. In relation to discussion of the inventive step, the Patentee is of the opinion that the difference in between claim 1 and D1 is the presence of an ester solvent.

23. The problem solved (according to the Patentee) by the presence of a non-aqueous ester solvent would be a lowering of the alcohol concentration in the fulvestrant formulation while at the same time precipitation of fulvestrant from the formulation is prevented.

24. This rather specific and narrow problem is not in line with the original problem identified in EP138. In [0017] it is indicated that the inventors had found that in the best oil based solvent, castor oil, it is not possible to dissolve fulvestrant in a high enough concentration to dose a patient in a low volume injection and to achieve a therapeutically significant release rate.

25. In relation to this more general problem it is noted that claim 1 is not restricted to castor oil only. It is only conveniently that castor oil is selected. Furthermore, the high enough concentration of fulvestrant is not identified in claim 1 let alone the required volume to be injected and let alone that the injection has to occur via intramuscular injection.

26. The present problem solved by the Patentee suffers from the objection that in relation to the prevention of the precipitation of fulvestrant and in relation to a lowering of the alcohol concentration no specific amounts or ranges of amounts for fulvestrant and for the alcohol have been included in claim 1.

27. Thus, following the standard problem solution approach procedure the objective problem to be formulated in view of the alleged only difference in between claim 1 and D1, being the presence of the non-aqueous ester solvent, is the improvement of the solubility of fulvestrant in the pharmaceutical composition. If in a claim the additional ingredient is identified as a non-aqueous ester solvent, this implies that the additional ingredient is added for its property of improving the dissolution of fulvestrant in the solvent mixture.

28. In relation to this problem reference is made to D7. D7 relates to castor oil as a vehicle for parenteral administration of steroid hormones. In relation to the type of steroid hormones administered following D7 it is noted that D7 relates to any steroid hormone in general and that a variety of examples of contemplated steroid hormones or other hormones are identified in table 2 and further in the text in page 828.

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Mentioned are testosterone ester, a progesterone derivative and other hormones. In page 894, right column, last paragraph reference is made to estrogens and progestrogens. Finaly, the summary relates to parenteral steroid hormones as such and provides in point 3 examples of commercially available steroid hormones.

29. The examples given in table IV, V, VI and in the case reports (footnote 4 in page 895) comprise ternary mixtures of castor oil, benzyl alcohol and benzyl benzoate.

30. The only difference in between D7 and the subject matter of claim 1 is the selection of fulvestrant as the steroid hormone.

31. D7 indicates that for increasing the solvent power of the castor oil for steroid hormones, it is necessary to add a compatible and non-irritating co-solvent, in other words to add a pharmaceutically acceptable co-solvent. Examples are benzyl benzoate, benzyl alcohol, ethyl lactate and ethyl oleate (see page 892, left column, last paragraph). It is noted that in page 893, left column, last paragraph it is indicated that also combinations of benzyl alcohol and benzyl benzoate with both castor oil and sesame oil have been used.

32. Accordingly, D7 discloses that for increasing the solvent power of castor oil for steroid hormones one or two co-solvents are added. When two co-solvents are added, the co-solvents are benzyl benzoate and benzyl alcohol.

33. In this respect it is noted that the teaching of D7 relates to the increase of the solvent power of the castor oil. It is an increase of the solvent power in relation to steroid hormones. This is in line with the abstract in page 891 in which it is stated that for accommodating the demand for increasingly greater concentrations of hormones in solution, castor oil in combination with other suitable oil miscible solvents has been found to fulfill this need.

34. It is precisely this need which is identified in [0017] of EP138 (or the objective problem formulated above), that is, according to D7 solved by using castor oil in combination with other suitable oil miscible solvents, namely benzyl benzoate and benzyl alcohol.

35. Accordingly, the position is taken that in view of the combination of D1 and D7 the subject matter of claim 1 does not comprise an inventive step.

36. In his letter of 30 April 2007, the Patentee argues at length a difference in between the structures of the various steroid hormones inclusive fulvestrant.

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37. In this respect it is noted that in D1 a similar variety of oestrogen components have been mentioned and considered to fall within the disclosure of D1 (see in this respect page 3, line 5 – page 4, line 1).

38. The argument that due to the exotic structure of fulvestrant relative to the disclosure in D7 the skilled person would not contemplate to apply the teaching of D7 on a castor oil formulation comprising fulvestrant is not in line with the disclosure of D7. In this respect it is noted that the abstract of D7 and the teaching in page 892, left column, last paragraph does not in any respect limit the ability of the mixture of castor oil with one or two co-solvents (being benzyl benzoate and benzyl alcohol) to any particular type (or subtype) of hormone or steroid hormone.

39. The same is true for the disclosure of D1 in relation to the variety of types of oestrogen components disclosed.

40. Furthermore, the Patentee argues that fulvestrant has solubility properties very different from the other mentioned steroid hormones in D7.

41. In relation to the differences in solubility properties between steroids, such as fulvestrant, reference is made to table 2 of the patent and table II of D7. In table 2 in the patent it is indicated that fulvestrant is soluble in castor oil for 20mg/ml at 25°C. In table II in D7 the solubility of various steroids in castor oil at 25°C varies between 38.6 and 60.6.

42. But, it is the clear teaching in D7 that high concentrations of steroids hormones may be obtained in castor oil by combining castor oil with other suitable oil miscible solvents (see the abstract of D7 and page 892 left column last paragraph). This improvement in solubility of steroids is clearly demonstrated in the tables IV, V and VI of D7 showing that combining castor oil with benzyl alcohol and/or benzyl benzoate dramatically improves the solubility multifold.

43. In these referenced tables of D7 sesame oil was chosen as the standard vegetable oil only (page 893, right column, first paragraph). It is noted further that castor oil is less irritating than preparations containing sesame oil (page 895, left column, first paragraph). Thus, castor oil is the preferred oil for steroids.

44. In addition, a difference in solubility in castor oil in between steroid hormones is not relevant in relation to the question for inventive step. For reasons, that the disclosure in D7 for improving the solvent power of the castor oil by using pharmaceutically acceptable co-solvents is not restricted in any extent to particular types of steroid hormones. Thus, the skilled person when confronted with the objective problem of improving the solubility of a castor oil solution of fulvestrant would have been motivated by the disclosure of D7 to use in a fulvestrant castor oil mixture the co-

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solvents benzyl benzoate and benzyl alcohol. It is to be born in mind that D7 has not limitations in relation to the starting solubility of the steroid hormone in castor oil or sesame oil.

45. In addition, when the use of the combination of co-solvents (benzyl benzoate and benzyl alcohol) in a fulvestrant castor oil formulation is considered obvious, then any surprising effect in relation to the improvement in solvent power for a particular steroid hormone cannot contribute to an inventive step argument. For reasons, according to the standing Case Law, that when the application of a particular measurement is considered obvious, any (beneficial or surprising) result in relation to the application of that measure cannot contribute to the inventive step.

46. On the basis of the arguments given above it is considered that at least claim 1 of EP138 does not comprise an inventive step over D1 and D7.

The Representative,

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F. 2310 08.04.08

OPPO 01	Anmeldung Nr./Application No./Demande n° //Patent Nr./Patent No./ Brevet n°. 01900186.6 - 2123 / 1250138

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EPO - Munich 5
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01900186.6 2.1.23 OPPO I	08.04.08	2310

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An das

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HOFFMANN EITLE
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F 2376 08.04.08

OPPO A | Anmeldung Nr./Application No./Demande n° //Patent Nr./Patent No./ Brevet n°.
01900186.6 - 2123 / 1250138

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01900186.6 2.1.23 OPPO A	08.04.08	2310

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Siebertstrasse 3
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Formalities Officer
Name: Lausenmeyer J.
Tel.: 8074
or call:
+31 (0)70 340 45 00

Date
08-04-2008

Reference	Application No./Patent No.
M 2363 EP/OPP OPPO 01	01900186.6 - 2123 / 1250138
Applicant/Proprietor	
AstraZeneca AB	

POSTPONEMENT

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will be public, will take place before the opposition division

on 14.11.08 at 09.00 hrs in Room 2452
at the EPO, Bayerstr. 34, PschorrHöfe, D-80335 München

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 10/2000, 456).
If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC).
Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the OJ EPO 9/1991, 489, concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC), is 12.09.08.

You are requested to report in good time beforehand to the porter in the EPO foyer. Room 3473 and 3474 are available as waiting rooms. Parking is available free of charge in the underground car park. However, this applies only in the case of accessing the car park via the entrance "Zollstrasse".

1st Examiner:	2nd Examiner:	Chairman:
Bendl E	Paúl Soto R	Veronese A

For the Opposition Division

Annexes:
Confirmation of receipt (Form 2936)
Rule 4 EPC (EPO Form 2043)
Communication (EPO Form 2906)

Registered letter with advice of delivery
EPO Form 2310 12.07 [ORAL03=2452] 03.04.08

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Formalities Officer
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Tel.: 8074
or call:
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Date
08-04-2008

Reference	Application No./Patent No.
118 663 o2	01900186.6 - 2123 / 1250138

Applicant/Proprietor
AstraZeneca AB

POSTPONEMENT

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will be public, will take place before the opposition division

on 14.11.08 at 09.00 hrs in Room 2452
at the EPO, Bayerstr. 34, PschorrHöfe, D-80335 München

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If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC).
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1st Examiner:	2nd Examiner:	Chairman:
Bendl E	Paúl Soto R	Veronese A

For the Opposition Division

Annexes:
Confirmation of receipt (Form 2936)
Rule 4 EPC (EPC Form 2043)
Communication (EPO Form 2906)

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Formalities Officer
Name: Lausenmeyer, Jenny-Juergen
Tel.: 8074
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Date: 04-04-2008

Reference	Application No./Patent No.
M 2363 EP/OPP OPPO 01	01900186.6 - 2123 / 1250138
Applicant/Proprietor: AstraZeneca AB	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☒ ORAL PROCEEDINGS on 28.10.08

Enclosure(s):
- ☒ Letter from the proprietor of the patent of 31.03.08 with cited document
- ☐ Letter from the opponent of
- ☐ Copy (copies)
- ☐ Communication:

Please take note.

For the Opposition Division

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☐ **Registered letter**

EPO Form 2911O 12.07 02.04.08

JL20183

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Formalities Officer
Name: Lausenmeyer, Jenny-Juergen
Tel.: 8074
or call:
+31 (0)70 340 45 00

Date: 04-04-2008

Reference	Application No./Patent No.
118 663 o2	01900186.6 - 2123 / 1250138

Applicant/Proprietor: AstraZeneca AB

BY FAX AND POST

BRIEF COMMUNICATION

Oral Proceedings on 28.10.08

Subject:
- [x] Letter from the proprietor of the patent of 31.03.08
- [x] Letter from the opponent 01 of 05.03.08

Communication:
- [ ] The summons to attend oral proceedings / taking of evidence on 28.10.08 has been cancelled.
- [ ] The procedure will be continued in writing.
- [ ] The date fixed for oral proceedings is maintained.
- [ ] A new date will be set later.
- [x]

We would like to inform you that the date fixed for oral proceedings on 28.10.08 has been cancelled by the Opposition Division and is postponed to 14.11.08.
The new summons to attend oral proceedings will be communicated as soon as possible.

Please take note.

For the Opposition Division

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Formalities Officer
Name: Lausenmeyer, Jenny-Juergen
Tel.: 8074
or call:
+31 (0)70 340 45 00

Date
04-04-2008

Reference	Application No./Patent No.
M 2363 EP/OPP OPPO 01	01900186.6 - 2123 / 1250138
Applicant/Proprietor: AstraZeneca AB	

BY FAX AND POST

BRIEF COMMUNICATION

Oral Proceedings on 28.10.08

Subject:
- [X] Letter from the proprietor of the patent of 31.03.08
- [X] Letter from the opponent 01 of 05.03.08

Communication:
- [ ] The summons to attend oral proceedings / taking of evidence on 28.10.08 has been cancelled.
- [ ] The procedure will be continued in writing.
- [ ] The date fixed for oral proceedings is maintained.
- [ ] A new date will be set later.
- [X]

We would like to inform you that the date fixed for oral proceedings on 28.10.08 has been cancelled by the Opposition Division and is postponed to 14.11.08.
The new summons to attend oral proceedings will be communicated as soon as possible.

Please take note.

For the Opposition Division

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Anmeldenummer / Application No. / Demande N° 01900186.6

Terminverlegung/ Termin-aufhebung der mündlichen Verhandlung	**Change / Cancellation of date of oral proceedings**	**Report / annulation de date d'une procédure orale**
des vorgesehenen Termins:	arranged for:	date prévue :
Tag/ day/ jour :	28.10.08 Zeit/ at/ heure	09:00

I. An die Prüfungs- / Einspruchsabteilung	**To the Examining / Opposition Division**	**A la division d'examen / d'opposition**
1. ☐ Der Patentinhaber hat den Widerruf (oder dgl.) seines Patents beantragt. (Datum...)	The proprietor has requested the revocation (or the like) of his patent. (date....)	Le titulaire a requis la révocation (ou équivalent) de son brevet (date....)
2. ☐ Der Beteiligte/ Zeuge/ Sachverständige	The party/ witness/ expert	La partie / le témoin / l'expert
.....	the opponent 01	.....
hat mitgeteilt (Datum ....), dass er	has indicated (date ....) that he/ she 05.03.08	a fait savoir (date....)
☒ die Verlegung des Termins beantragt.	requests the date of oral proceedings to be changed.	qu'il requiert le report de la date de la procédure orale.
☐ die Änderung der Anfangszeit der mündlichen Verhandlung beantragt.	Requests the change of starting time of the oral proceeding.	qu'il requiert le report de l'heure de début de la procédure orale.
☐ den Antrag auf mündliche Verhandlung zurückzieht.	withdraws his request for oral proceedings.	qu'il retire sa requête de procédure orale.
☐ nicht erscheinen werde.	will not be attending.	qu'il ne comparaîtra pas.
☐ die Vernehmung vor einem nationalen Gericht wünscht.	wishes to be heard by national court.	qu'il souhaite que l'audience ait lieu devant un tribunal national.

05-03-2008
Datum/ Date

Lausenmeyer, Jenny-Jürgen
Unterstützungsdienst/ Support staff/ Service de soutien

JL20183

InnoPharma Exhibit 1046.0543

Anmeldenummer / Application No. / Demande N° 01900186.6

II. An die Formalprüfungsstelle:	**To the Formalities Section:**	**A la section des formalités:**
1. ☐ Der festgesetzte Termin zur mündlichen Verhandlung **bleibt bestehen.**	The date fixed for oral proceedings **is maintained.**	La date fixée pour la procédure orale **reste inchangée.**
2. ☐ **Auf Veranlassung der Abteilung** kann die mündliche Verhandlung aus folgenden Gründen zu dem vorgesehenen Zeitpunkt nicht stattfinden:	**At the instigation of the division** the oral proceedings cannot take place on the arranged date for the following reasons:	**A l'instigation de la division**, la procédure orale ne peut pas avoir lieu à la date prévue pour les raisons suivantes:
.....	.....	.....
.....	.....	.....
3. ☒ Die **Ladung** zur mündlichen Verhandlung/ Beweisaufnahme am: ..... **ist aufzuheben.** Die Beteiligten/ Zeugen/ Sachverständige und die internen Dienste und Personen des Amts sind entsprechend zu unterrichten.	The **summons** to attend oral proceedings/ taking of evidence on: 28.10.08 ..... should be **cancelled.** Notify the parties/ witnesses/ experts and those responsible within the EPO.	La convocation pour la procédure orale / l'instructions du: ..... doit être **annulée.** Les parties / témoins / experts, ainsi que les services internes et les personnes concernées de l'Office doivent être avisés en conséquence.
3.1 ☐ Das Verfahren wird **schriftlich** fortgesetzt.	The procedure will be continued in **writing.**	La procédure se poursuivra par voie **écrite.**
3.2 ☐ Ein **neuer Termin** wird zu einem **späteren** Zeitpunkt festgelegt.	A **new date** will be set **later.**	Une **nouvelle date** sera fixée **ultérieurement.**
3.3 ☒ Ein **neuer Termin** ist **wie folgt** festzulegen:	A **new date** is set **as follows:**	Une **nouvelle date** est fixée **comme suit** :
Tag/ day/ jour : 19.11.08 Zeit/ at/ heure : 09:00		
Absendung der Ladung mit Form 2008/ 2310 an die Beteiligten. Schriftsätze und Unterlagen der Beteiligten zur Vorbereitung der mündlichen Verhandlung können bis zu ..... Monat(en) vor der Tag der Verhandlung eingereicht werden (Übertrag auf Form 2008.1/ 2310.1)	Despatch Form 2008/ 2310 summoning the parties. Parties' written submissions and amendments in preparation for the oral proceedings, if any should be made not later than 2 month(s) before the date of oral proceedings (transfer to Form 2008.1/ 2310.1)	Envoi de la convocation au moyen du formulaire 2008 / 2310 aux parties. Des documents et / ou des pièces des parties en vue de la préparation de la procédure orale peuvent être produits jusqu'à ..... mois avant la date de la procédure (transfert au formulaire 2008.1 / 2310.1)

.....
Direktor/ Director/ Directeur

Datum/ Date

Saaldienst, Infostelle, Sprachendienst informiert/ room service, info. office, language service informed/ service des conférences, bureau d'information, service linguistique informé(s)
LA 03.04.08
Datum/ Date

ORAL 6
codiert/ coded/ codé
ROOMS
gelöscht/ cancelled/ annulé
LA 03.04.08
Datum/ Date
Zeichen/ Initials/ Initiales

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reserviert/ reserved/ réservée
ORAL 6
codiert/ coded/ codé
LA 03.04.08
Datum/ Date
Zeichen/ Initials/ Initiales

2.04.08
Datum/ Date

Vorsitzender Chairman Président	2. Prüfer 2nd examiner 2éme examinateur	1. Prüfer Primary examiner 1er examinateur	Rechtskundiges Mitglied Legal member Membre juriste

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European Patent Office

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EPO - Munich
86
31. März 2008

Munich, March 31, 2008

01 900 186.6

Our Ref.: 118 663 u8/bst
European Patent 1 250 138
AstraZeneca AB

This is in response to the summons to attend Oral Proceedings on 28.10.2008 and the Opponent's letter dated 5.3.2008.

It has meanwhile turned out that the undersigned is in the very same situation as the Opponent's representative. We have also been summoned by the EPO to attend Oral Proceedings on the 28.10.2008 in another case (Opposition against EP-B-1 272 195) which is in the same technical field as the current case and involves the same patent proprietor. A copy of the summons is enclosed for the Oppositions Division's quick reference.

We therefore join the Opponent's request for a postponement and would indeed be obliged if the Opposition Division deferred the hearing to another more convenient date.

Dr. Thorsten Bausch
European Patent Attorney
Association No. 151

Enc.: Communication by the EPO of 18.3.2008

PATENTANWÄLTE · MÜNCHEN
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Greg Sach, B.Sc. (U.C.L.) |1,3
Steffen Thomas, Dr., Dipl.-Chem. |2

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ATTORNEYS AT LAW
EUROPEAN TRADEMARK ATTORNEYS

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Isabelle Kuschel, LL.M.

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John F. Hardwick, B.Sc. (Hons)
Sabine Böhm, Ph.D. (London), B.Sc. |5,6

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|2 nicht/not European Patent Attorney
|3 nicht/not European Trademark Attorney
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InnoPharma Exhibit 1046.0545

Sos/20/3/08/oee

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Formalities Officer
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EINGEGANGEN
19. März 2008
HOFFMANN · EITLE. MÜNCHEN
PATENTANWÄLTE RECHTSANWÄLTE

Date
18-03-2008

Reference	Application No./Patent No.
118 664 u8/o2	01917289.9 - 2107 / 1272195

Applicant/Proprietor
AstraZeneca AB

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will be public, will take place before the opposition division

on 28.10.08 at 09.00 hrs in Room 2456
at the EPO, Bayerstr. 34, PschorrHöfe, D-80335 München

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 10/2000, 456).
If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC).
Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the OJ EPO 9/1991, 489, concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC), is 28.08.08.

You are requested to report in good time beforehand to the porter in the EPO foyer. Room 3473 and 3474 are available as waiting rooms. Parking is available free of charge in the underground car park. However, this applies only in the case of accessing the car park via the entrance "Zollstrasse".

1st Examiner:	2nd Examiner:	Chairman:
Escolar Blasco P	Nyeki A	Ludwig G

For the Opposition Division

Annexes:
Confirmation of receipt (Form 2936)
Rule 4 EPC (EPC Form 2043)
Communication (EPO Form 2906)

Registered letter with advice of delivery
EPO Form 2310 12.07 [ORAL03=2456] 13.03.08

ORAL4

to EPO postal service: 13.03.08

InnoPharma Exhibit 1046.0546

Europäisches Patentamt
European Patent Office
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Formalities Officer
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Tel.: 8074
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Date: 07-03-2008

Reference	Application No./Patent No.
118 663 o2	01900186.6 - 2123 / 1250138

Applicant/Proprietor: AstraZeneca AB

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☒ Letter from the opponent 01 of 05.03.08 (telecopy)
- ☐ Copy (copies)
- ☐ Communication:

Please take note.

For the Opposition Division

Europäisches Patentamt · European Patent Office · Office européen des brevets

☐ **Registered letter**

EPO Form 2911O 12.07 05.03.08

JL20183

InnoPharma Exhibit 1046.0547

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F. 2310 28.02.08

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OPPO 01	Anmeldung Nr./Application No./Demande n° //Patent Nr./Patent No./ Brevet n°. 01900186.6 - 2123 / 1250138

ntinhaber/Proprietor/Titulaire

Rückschein National

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28.2.08

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☒ Empfangsbevollmächtigter
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Datum 01.01.2008
Postmitarbeiter/Zusteller: Unterschrift
X

Empfänger der Sendung

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Tauchner, Paul
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Vossius & Partner,
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81675 Munich
ALLEMAGNE

Empfangsbestätigung

Name und Vorname in GROSSBUCHSTABEN

Ich bestätige, die Sendung am heutigen Tag erhalten zu haben.
Datum
Empfangsberechtigter: Unterschrift
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InnoPharma Exhibit 1046.0548

VOSSIUS & PARTNER

Patentanwälte Rechtsanwälte

3

Via telefax pages
Fax No. 2399-4465

VOSSIUS & PARTNER * POB 86 07 67 * 81634 München * Germany

European Patent Office
Attn.: Mr. J. Lausenmeyer
Formalities Officer
80298 MUNICH

Opposition against EP Patent 01 90 0186.6 / 1250138
Patentee: AstraZeneca AB
Opposition by: Gedeon Richter Ltd.
Our Ref.: M2363 EP/OPP

München, March 5, 2008
PT/ISS

I refer to the summons to attend oral proceedings issued on February 28, 2008.

As I already explained in my telephone conversation to the Formalities Officer (Mr. J. Lausenmeyer), the scheduled day for the oral proceedings (October 28, 2008) is unfortunately also a scheduled day for another oral proceedings where we have been summoned earlier. According to the Notice of the Vice Presidents of September 1, 2000 (O.J. 2000, 456, Section 2.3), a previously notified summons of the same party in other proceedings by a National Court represents a serious substantive reason to request the change of the date for oral proceedings.

I enclose a copy of the earlier summons for the Federal Patent Court in an unrelated case. Also, I have talked to the representative of the Patentee, my colleague Dr. Bausch, who accepted that there are no serious problems to postpone the hearing within next few weeks.

I have to add that our client (Gedeon Richter, Hungary) has expressedly made it clear that he wishes to be represented by myself and would not agree to be represented by any other colleague of this office.

PATENTANWÄLTE
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(bis 1992, danach in anderer Kanzlei)
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InnoPharma Exhibit 1046.0549

Furthermore, let me please inform the Opposition Division that in view of a scheduled trip abroad for October 30 and 31 and for another hearing date on November 5, 2008, it would be preferred if the postponed hearing could be at any date on or after Thursday, November 6 until the end of November 2008.

I would be pleased to discuss any further options, if necessary, with the Formalities Officer on the telephone.

Thank you for your consideration.

Dr. Paul Tauchner
European Patent Attorney

Encl.:
Summons to oral proceedings in the case before the Federal Patent Court (N1437 DE/NI)

Cc: Dr. Thorsten Bausch, Hoffmann Eitle (without enclosures)

Received at the EPO on Mar 05, 2008 13:10:08. Page 2 of 3

InnoPharma Exhibit 1046.0550

BUNDESPATENTGERICHT

EINGEGANGEN
Vossius & Partner
14. Dez. 2007 PT DH
Frist 28.10.08 mündl. Verhandlg. afr
beantr.: 28.5.
G

München, den 13. Dezember 2007

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81634 München

-Aktenzeichen und Beteiligte bitte stets angeben-

Aktenzeichen: 3 Ni 21/07 (EU)

Ihr Zeichen: N1437 DE/NI

Kläger(in): medac, Gesellschaft für klinische Spezialpräparate und 2 andere
Beklagte(r): Debiopharm S.A., Forum "aprés-demain"

Terminsladung

In dem Verfahren, betreffend das Patent

EP 0 567 438 (DE 693 22 992)

ist Termin zur mündlichen Verhandlung vor dem Bundespatentgericht

auf Dienstag, den 28. Oktober 2008 / 09:30 Uhr

im Sitzungssaal **2** anberaumt worden, zu der Sie hiermit geladen werden.

Anmeldung wird im **Dienstgebäude des Bundespatentgerichts** in 81549 München, Cincinnatistraße 64, 1. Obergeschoss, Kabine 4.10.02 (Sitzungsdienst), erbeten.

Es wird darauf hingewiesen, dass beim Ausbleiben eines Beteiligten auch ohne ihn verhandelt und entschieden werden kann.

Zusatz 1:

Der Berichterstatter gibt nach vorläufiger Prüfung der Sach- und Rechtslage zu bedenken, dass die Verbindung gemäß angegriffenem Patentanspruch 4 durch die Druckschriften Inorg.Chim. Acta 92 (1984) 279 - 284, J. Clin. Hematol. Oncol. 7 (1977) 197 - 209 sowie US 4 169 846, jeweils einzeln für sich betrachtet, vorbeschrieben ist.

BPatG 132 kH
Stand: 10.06

InnoPharma Exhibit 1046.0551

Europäisches Patentamt
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Anmeldenummer / Application No. / Demande N° 01900186.6

Terminverlegung/ Termin-aufhebung der mündlichen Verhandlung	**Change / Cancellation of date of oral proceedings**	**Report / annulation de date d'une procédure orale**
des vorgesehenen Termins:	arranged for:	date prévue :
Tag/ day/ jour :	28.10.08 Zeit/ at/ heure	09:00
I. An die Prüfungs- / Einspruchsabteilung	**To the Examining / Opposition Division**	**A la division d'examen / d'opposition**
1. ☐ Der Patentinhaber hat den Widerruf (oder dgl.) seines Patents beantragt. (Datum...)	The proprietor has requested the revocation (or the like) of his patent. (date....)	Le titulaire a requis la révocation (ou équivalent) de son brevet (date....)
2. ☐ Der Beteiligte/ Zeuge/ Sachverständige	The party/ witness/ expert	La partie / le témoin / l'expert
.....	the opponent 01	.....
hat mitgeteilt (Datum ....), dass er	has indicated (date ...) that he/ she 05.03.08	a fait savoir (date....)
☒ die Verlegung des Termins beantragt.	requests the date of oral proceedings to be changed.	qu'il requiert le report de la date de la procédure orale.
☐ die Änderung der Anfangszeit der mündlichen Verhandlung beantragt.	Requests the change of starting time of the oral proceeding.	qu'il requiert le report de l'heure de début de la procédure orale.
☐ den Antrag auf mündliche Verhandlung zurückzieht.	withdraws his request for oral proceedings.	qu'il retire sa requête de procédure orale.
☐ nicht erscheinen werde.	will not be attending.	qu'il ne comparaîtra pas.
☐ die Vernehmung vor einem nationalen Gericht wünscht.	wishes to be heard by national court.	qu'il souhaite que l'audience ait lieu devant un tribunal national.

05-03-2008
Datum/ Date

Lausenmeyer, Jenny-Jürgen
Unterstützungsdienst/ Support staff/ Service de soutien

JL20183

InnoPharma Exhibit 1046.0552

Anmeldenummer / Application No. / Demande N° 01900186.6

II. An die Formalprüfungsstelle: **To the Formalities Section:** **A la section des formalités:**

1. ☐ Der festgesetzte Termin zur mündlichen Verhandlung **bleibt bestehen.**

The date fixed for oral proceedings **is maintained.**

La date fixée pour la procédure orale **reste inchangée.**

2. ☐ **Auf Veranlassung der Abteilung** kann die mündliche Verhandlung aus folgenden Gründen zu dem vorgesehenen Zeitpunkt nicht stattfinden:

At the instigation of the division the oral proceedings cannot take place on the arranged date for the following reasons:

A l'instigation de la division, la procédure orale ne peut pas avoir lieu à la date prévue pour les raisons suivantes:

.....
.....

.....
.....

.....
.....

.....
Direktor/ Director/ Directeur

.....
Datum/ Date

3. ☐ Die **Ladung** zur mündlichen Verhandlung/ Beweisaufnahme am:

.....

ist aufzuheben. Die Beteiligten/ Zeugen/ Sachverständige und die internen Dienste und Personen des Amts sind entsprechend zu unterrichten.

The **summons** to attend oral proceedings/ taking of evidence on:

.....

should be **cancelled.** Notify the parties/ witnesses/ experts and those responsible within the EPO.

La convocation pour la procédure orale / l'instructions du:

.....

doit être **annulée**. Les parties / témoins / experts, ainsi que les services internes et les personnes concernées de l'Office doivent être avisés en conséquence.

Saaldienst, Infostelle, Sprachendienst informiert/ room service, info. office, language service informed/ service des conférences, bureau d'information, service linguistique informé(s)

.....
Datum/ Date

3.1 ☐ Das Verfahren wird **schriftlich** fortgesetzt.

The procedure will be continued in **writing.**

La procédure se poursuivra par voie **écrite.**

3.2 ☐ Ein **neuer Termin** wird zu einem **späteren** Zeitpunkt festgelegt.

A **new date** will be set **later.**

Une **nouvelle date** sera fixée **ultérieurement.**

ORAL 6
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ROOMS
gelöscht/ cancelled/ annulé

.....
Datum/ Date
Zeichen/ Initials/ Initiales

3.3 ☐ Ein **neuer Termin** ist **wie folgt** festzulegen:

A **new date** is set **as follows**:

Une **nouvelle date** est fixée **comme suit** :

Tag/ day/ jour : ..... Zeit/ at/ heure : .....

ROOMS
Saal Nr./ Room No./ Salle n°

.....
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ORAL 6
codiert/ coded/ codé

.....
Datum/ Date
Zeichen/ Initials/ Initiales

Absendung der Ladung mit Form 2008/ 2310 an die Beteiligten.
Schriftsätze und Unterlagen der Beteiligten zur Vorbereitung der mündlichen Verhandlung können bis zu

Despatch Form 2008/ 2310 summoning the parties.

Parties' written submissions and amendments in preparation for the oral proceedings, if any should be made not later than

Envoi de la convocation au moyen du formulaire 2008 / 2310 aux parties.
Des documents et / ou des pièces des parties en vue de la préparation de la procédure orale peuvent être produits jusqu'à

..... Monat(en)

.....month(s)

.....mois

vor der Tag der Verhandlung eingereicht werden (Übertrag auf Form 2008.1/ 2310.1)

before the date of oral proceedings (transfer to Form 2008.1/ 2310.1)

avant la date de la procédure (transfert au formulaire 2008.1 / 2310.1)

.....
Datum/ Date

.....	.....	.....	.....
Vorsitzender Chairman Président	2. Prüfer 2nd examiner 2ème examinateur	1. Prüfer Primary examiner 1er examinateur	Rechtskundiges Mitglied Legal member Membre juriste

InnoPharma Exhibit 1046.0553

VOSSIUS & PARTNER

Patentanwälte Rechtsanwälte

3

Via telefax pages
Fax No. 2399-4465

VOSSIUS & PARTNER * POB 86 07 67 * 81634 München * Germany

European Patent Office
Attn.: Mr. J. Lausenmeyer
Formalities Officer
80298 MUNICH

EPO - Munich
23
05. März 2008

op 28.10.08

Opposition against EP Patent 01 90 0186.6 / 1250138
Patentee: AstraZeneca AB
Opposition by: Gedeon Richter Ltd.
Our Ref.: M2363 EP/OPP

Confirmation Copy

München, March 5, 2008
PT/ISS

I refer to the summons to attend oral proceedings issued on February 28, 2008.

As I already explained in my telephone conversation to the Formalities Officer (Mr. J. Lausenmeyer), the scheduled day for the oral proceedings (October 28, 2008) is unfortunately also a scheduled day for another oral proceedings where we have been summoned earlier. According to the Notice of the Vice Presidents of September 1, 2000 (O.J. 2000, 456, Section 2.3), a previously notified summons of the same party in other proceedings by a National Court represents a serious substantive reason to request the change of the date for oral proceedings.

I enclose a copy of the earlier summons for the Federal Patent Court in an unrelated case. Also, I have talked to the representative of the Patentee, my colleague Dr. Bausch, who accepted that there are no serious problems to postpone the hearing within next few weeks.

I have to add that our client (Gedeon Richter, Hungary) has expressedly made it clear that he wishes to be represented by myself and would not agree to be represented by any other colleague of this office.

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EUROPEAN TRADEMARK ATTORNEYS
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AXEL STELLBRINK, Dipl.-Ing.
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DR. FRIEDERIKE STOLZENBURG, Dipl.-Biol
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DR. JÜRGEN MEIER, Dipl.-Biol.
DR. STEFAN FICKERT, Dipl.-Chem.
ARNOLD ASMUSSEN, Dipl.-Ing.(FH)
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InnoPharma Exhibit 1046.0554

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Thank you for your consideration.

Dr. Paul Tauchner
European Patent Attorney

Encl.:
Summons to oral proceedings in the case before the Federal Patent Court (N1437 DE/NI)

Cc: *Dr. Thorsten Bausch, Hoffmann Eitle (without enclosures)*

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BUNDESPATENTGERICHT

EINGEGANGEN
Vossius & Partner
14. Dez. 2007 PT DH
Frist 28.10.08 mündl. Verhandlung afr
bearb.: 28.9.
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München, den 13. Dezember 2007

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E-Mail: bundespatentgericht@bpatg.bund.de

Patentanwälte
Vossius & Partner
Postfach 86 07 67
81634 München

-Aktenzeichen und Beteiligte bitte stets angeben-

Aktenzeichen: 3 Ni 21/07 (EU)

Ihr Zeichen: N1437 DE/NI

Kläger(in): medac, Gesellschaft für klinische Spezialpräparate und 2 andere
Beklagte(r): Debiopharm S.A., Forum "aprés-demain"

Terminsladung

In dem Verfahren, betreffend das Patent

EP 0 567 438 (DE 693 22 992)

ist Termin zur mündlichen Verhandlung vor dem Bundespatentgericht

auf Dienstag, den 28. Oktober 2008 / 09:30 Uhr

im Sitzungssaal **2** anberaumt worden, zu der Sie hiermit geladen werden.

Anmeldung wird im **Dienstgebäude des Bundespatentgerichts** in 81549 München, Cincinnatistraße 64, 1. Obergeschoss, Kabine 4.10.02 (Sitzungsdienst), erbeten.

Es wird darauf hingewiesen, dass beim Ausbleiben eines Beteiligten auch ohne ihn verhandelt und entschieden werden kann.

Zusatz 1:

Der Berichterstatter gibt nach vorläufiger Prüfung der Sach- und Rechtslage zu bedenken, dass die Verbindung gemäß angegriffenem Patentanspruch 4 durch die Druckschriften Inorg.Chim. Acta 92 (1984) 279 - 284, J. Clin. Hematol. Oncol. 7 (1977) 197 - 209 sowie US 4 169 846, jeweils einzeln für sich betrachtet, vorbeschrieben ist.

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F. 2310 28. 02. 08

OPPO A

Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./ Brevet n°.
01900186.6 - 2123 / 1250138

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Empfangsbestätigung

Name und Vorname in GROSSBUCHSTABEN

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01900186.6	2.1.23 OPPO I	28. 02. 08	2310

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VOSSIUS & PARTNER
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SIEBERTSTR. 4
81675 MÜNCHEN

RAINER VIKTOR
EUROPEAN PATENT ATTORNEY
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Unter Bezugnahme auf die Mitteilung im ABl. des EPA 11/1991, 577, wird gebeten, die Empfangsbescheinigung mit **Empfangsdatum** und **Unterschrift** zu versehen und **umgehend** an das EPA zurückzusenden.

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An das

Europäische Patentamt

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Conformément à la communication parue au JO OEB 11/1991, 577, vous êtes prié de porter sur le récépissé la **date d'arrivée** du document, ainsi que votre **signature** et de le renvoyer **immédiatement** à l'OEB.

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01900186.6 2.1.23 OPPO A	28. 02. 08	2310

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Tauchner, Paul
Vossius & Partner,
Siebertstrasse 3
81675 Munich
ALLEMAGNE

Formalities Officer
Name: Lausenmeyer J.
Tel.: 8074
or call:
+31 (0)70 340 45 00

Date
28-02-2008

Reference	Application No./Patent No.
M 2363 EP/OPP OPPO 01	01900186.6 - 2123 / 1250138
Applicant/Proprietor: AstraZeneca AB	

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will be public, will take place before the opposition division

on 28.10.08 at 09.00 hrs in Room 2452
at the EPO, Bayerstr. 34, PschorrHöfe, D-80335 München

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 10/2000, 456).
If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC).
Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the OJ EPO 9/1991, 489, concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC), is 28.08.08.

You are requested to report in good time beforehand to the porter in the EPO foyer. Room 3473 and 3474 are available as waiting rooms. Parking is available free of charge in the underground car park. However, this applies only in the case of accessing the car park via the entrance "Zollstrasse".

1st Examiner:	2nd Examiner:	Chairman:
Bendl E	Paúl Soto R	Veronese A

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

Annexes:
Confirmation of receipt (Form 2936)
Rule 4 EPC (EPC Form 2043)
Communication (EPO Form 2906)

Registered letter with advice of delivery
EPO Form 2310 12.07 [ORAL03=2452] 25.02.08

ORAL4

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ALLEMAGNE

Formalities Officer
Name: Lausenmeyer J.
Tel.: 8074
or call:
+31 (0)70 340 45 00

Date
28-02-2008

Reference	Application No./Patent No.
118 663 o2	01900186.6 - 2123 / 1250138

Applicant/Proprietor
AstraZeneca AB

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

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The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

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1st Examiner:	2nd Examiner:	Chairman:
Bendl E	Paúl Soto R	Veronese A

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Annexes:
Confirmation of receipt (Form 2936)
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Wichtige Hinweise zur mündlichen Verhandlung

Das Europäische Patentamt verfügt über keine eigenen Dolmetscher. Diese müssen im Bedarfsfall von außerhalb, teilweise sogar aus anderen Ländern, beigezogen werden, was mit einem hohen Aufwand an Kosten und organisatorischen Vorbereitungen verbunden ist. Muss ein Verhandlungstermin kurzfristig abberaumt werden, können Kosten für bestellte Dolmetscher nicht mehr vermieden werden.

Es wird daher gebeten, eine Simultanübersetzung nur bei wirklichem Bedarf in Anspruch zu nehmen. Es wäre wünschenswert, wenn sich die Beteiligten (zweckmäßigerweise gleichzeitig mit der Terminabstimmung) auf die Benutzung einer Amtssprache einigen könnten. Bei Verständigungsschwierigkeiten sind die Mitglieder der Einspruchsabteilung bereit zu helfen.

Die von den Verfahrensbeteiligten bevorzugte (abgestimmte) Verhandlungssprache und ggf. eine notwendige Simultanübersetzung sind dem Amt möglichst vor der in Regel 4(1) EPÜ angegebenen Frist mitzuteilen.

☐ Verfahrenssprache ist **Deutsch**

Von der/dem/den Einsprechenden wurde

☐ Englisch

☐ Französische

benutzt.

Es wird um eilige Mitteilung - möglichst per telefax an den zuständigen Formalprüfer - gebeten,

möglichst bis

Datum **16.09.2008**

(bitte umblättern)

Important information concerning oral proceedings

The European Patent Office has no interpreters of its own. When interpreters are needed they have to be brought in from outside, sometimes even from other countries, which is costly and involves considerable organisation. If oral proceedings have to be cancelled at short notice, the cost of interpreters already engaged still has to be borne.

Please therefore make use of simultaneous interpreting facilities only where strictly necessary. If possible the parties should agree on an official language for the proceedings, preferably at the time when they arrange a date. The members of the Opposition Division will be willing to help should any communication problems arise.

The EPO should be told if possible before the period mentioned in Rule 4 (1) EPC which language the parties prefer (agree on) and whether simultaneous interpreting facilities are required.

☒ Language of the proceedings is **English**

The langauge used by the opponent/s was

☐ German

☐ French.

Please inform us urgently - where possible by fax addressed to the formalities officer concerned -

if possible by

Date **16.09.2008**

(please see overleaf)

Très important Procédure orale

L'Office européen des brevets ne dispose pas de son propre service d'interprètes. Aussi faut-il appel le cas échéant à des interprètes de l'extérieur, qui viennent même parfois de l'étranger, ce qui occasionne de frais élevés et demande un grand travail d'organisation. Si la date d'une procédure orale doit être annulée au dernier moment, il n'est plus possible d'éviter les frais d'interprètes.

Les parties à une procédure sont donc priées de ne demander une traduction simultanée qu'en cas de réel besoin. Il serait souhaitable qu'elles puissent se mettre d'accord en même temps qu'elles conviennent de la date sur l'utilisation d'une langue officielle comme langue des débats. Si les parties éprouvent des difficultés de compréhension lors des débats, les membres de la division d'opposition sont disposés à leur prêter leur assistance.

L'Office doit être avisé si possible avant le début du délai mentionné dans la règle 4(1) CBE de la langue préférée par les parties pour le déroulement des débat (et sur laquelle elles se sont préalablement mises d'accord) et de la nécessité éventuelle d'une traduction simultanée.

☐ La langue de la procédure est le **français**

La langue utilisée par l'opposant/les opposants était

☐ l'allemand

☐ l'anglais.

Prière d'indiquer d'urgence à l'agent des formalités compétent si possible par téléfax

si possible jusquâu

Date **16.09.2008**

(voir au verso)

InnoPharma Exhibit 1046.0563

1. welche Sprache(n) Sie in der mündlichen Verhandlung verwenden (**Sprechen**)

2. aus welcher Sprache Sie eine Simultanübersetzung benötigen (**Hören**).

Sollten Sie Ihren Antrag auf mündliche Verhandlung zurückziehen oder zum anberaumten Verhandlungstermin nicht erscheinen wollen bzw. aus wichtigem Grund daran gehindert sein, werden Sie gebeten,

- **unverzüglich das Amt - möglichst per Telefax - davon zu benachrichtigen, wobei das Schriftstück mit einem deutlichen Vermerk "Dringend, mündliche Verhandlung am ..." oder sinngemäß gekennzeichnet sein sollte;**

- **in dringenden Fällen** (weniger als 1 Monat vor dem Verhandlungstermin) zusätzlich **auch dem/die anderen Verfahrensbeteiligten** bzw. ihre(n) Vertreter auf schnellstem Weg **direkt zu unterrichten.**

In jedem solchen Fall obliegt der Einspruchsabteilung die Entscheidung, ob die Verhandlung durchgeführt oder abberaumt wird. Es wird jedoch darauf hingewiesen, dass einem Verfahrensbeteiligten, der eine nicht rechtzeitige oder unterbliebene Benachrichtigung zu verantworten hat, die dadurch den anderen Beteiligten verursachten Kosten auferlegt werden können (Art. 104 EPÜ).

Hinweis auf Regel 4 EPÜ

Regel 4
Sprache im mündlichen Verfahren

1. which language(s) you intend to use during the oral proceedings (**Speaking**)

2. from which language you need simultaneous interpretation (**Listening**).

Should you decide to withdraw your request for oral proceedings or not wish to attend on the date set, or if for some special reason you are unable to do so, you are requested

- **to notify the EPO immediately, where possible by fax, marking the document clearly with the words "Urgent, oral proceedings on ..." or similar;**

- **in urgent cases** (less than one month before the date set for the proceedings), additionally to **notify the other party/parties** and/or their representative(s) **direct as rapidly as possible.**

In all such cases the Opposition Division will decide whether the proceedings are to go ahead or be cancelled. You should however note that costs incurred by the other parties may be charged to a party who either fails to notify them or does not do so in good time (Article 104 EPC).

Attention is drawn to Rule 4 EPC

Rule 4
Language in oral proceedings

1. quelle(s) langue(s) vous utiliserez au cours de la procédure orale (**pour parler**)

2. à partir de quelle langue vous aurez besoin d'une traduction simultanée (**pour écouter**).

Si vous retirez votre requête tendant à recourir à la procédure orale ou si vous ne souhaitez pas vous présenter à la date fixée pour la procédure orale ou ne pouvez vous y présenter pour une raison sérieuse, veuillez

- **en faire avis sans retard à l'Office, si possible par téléfax, en partant sur votre communication clairement la mention "Urgent, procédure orale le ..." ou une indication similaire;**

- **dans les cas urgents** (moins d'un mois avant la date fixée pour la procédure orale) **en faire avis également directement** pas la voie la plus rapide à **l'autre/aux autres partie(s)** ou bien à son/leurs mandataire(s)

Il appartient alors à la division d'opposition de décider si la procédure orale aura lieu ou non. Il est néanmoins souligné que les frais causés aux autres parties par une partie qui est responsable de l'omission d'un tel avis ou de ce que cet avis n'a pas été fait en temps utile peuvent être mis à la charge de cette partie (art. 104 CBE)

Rappel de la Règle 4 CBE

Règle 4
Langues admissibles lors de la procédure orale

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(1) Jeder an einem mündlichen Verfahren vor dem Europäischen Patentamt Beteiligte kann sich anstelle der Verfahrenssprache einer anderen Amtssprache des Europäischen Patentamts bedienen, sofern er dies dem Europäischen Patentamt spätestens einen Monat vor dem angesetzten Termin mitgeteilt hat oder selbst für die Übersetzung in die Verfahrenssprache sorgt. Jeder Beteiligte kann sich einer Amtssprache eines Vertragsstaats bedienen, sofern er selbst für die Übersetzung in die Verfahrenssprache sorgt. Von diesen Vorschriften kann das Europäische Patentamt Ausnahmen zulassen.

(1) Any party to oral proceedings before the European Patent Office may use an official language of the European Patent Office other than the language of the proceedings, if such party gives notice to the European Patent Office at least one month before the date of such oral proceedings or provides for interpretation into the language of the proceedings. Any party may use an official language of a Contracting State, if he provides for interpretation into the language of the proceedings. The European Patent Office may permit derogations from these provisions.

(1) Toute partie à une procédure orale devant l'Office européen des brevets peut utiliser une langue officielle de l'Office européen des brevets autre que la langue de la procédure, à condition soit d'en aviser l'Office européen des brevets un mois au moins avant la date de la procédure orale, soit d'assurer l'interprétation dans la langue de la procédure. Toute partie peut utiliser une langue officielle de l'un des Etats contractants à condition d'assurer l'interprétation dans la langue de la procédure. L'Office européen des brevets peut autoriser des dérogations aux présentes dispositions.

(2) Die Bediensteten des Europäischen Patentamts können sich im mündlichen Verfahren anstelle der Verfahrenssprache einer anderen Amtssprache des Europäischen Patentamts bedienen.

(2) In the course of oral proceedings, employees of the European Patent Office may use an official language of the European Patent Office other than the language of the proceedings.

(2) Au cours de la procédure orale, les agents de l'Office européen des brevets peuvent utiliser une langue officielle de l'Office européen des brevets autre que la langue de la procédure.

(3) In der Beweisaufnahme können sich die zu vernehmenden Beteiligten, Zeugen oder Sachverständigen, die sich in einer Amtssprache des Europäischen Patentamts oder eines Vertragsstaats nicht hinlänglich ausdrücken können, einer anderen Sprache bedienen. Erfolgt die Beweisaufnahme auf Antrag eines Beteiligten, so werden die Beteiligten, Zeugen oder Sachverständigen mit Erklärungen, die sie in einer anderen Sprache als in einer Amtssprache des Europäischen Patentamts abgeben, nur gehört, sofern dieser Beteiligte selbst für die Übersetzung in die Verfahrenssprache sorgt. Das Europäische Patentamt kann jedoch die Übersetzung in eine seiner anderen Amtssprachen zulassen.

(3) Where evidence is taken, any party, witness or expert to be heard who is unable to express himself adequately in an official language of the European Patent Office or of a Contracting State may use another language. Where evidence is taken upon request of a party, parties, witnesses or experts expressing themselves in a language other than an official language of the European Patent Office shall be heard only if that party provides for interpretation into the language of the proceedings. The European Patent Office may, however, permit interpretation into one of its other official languages.

(3) Lors de l'instruction, les parties, témoins ou experts appelés à être entendus, qui ne possèdent pas une maîtrise suffisante d'une langue officielle de l'Office européen des brevets ou d'un Etat contractant, peuvent utiliser une autre langue. Si la mesure d'instruction est ordonnée sur requête d'une partie, les parties, témoins ou experts qui s'expriment dans une langue autre qu'une langue officielle de l'Office européen des brevets ne sont entendus que si cette partie assure l'interprétation dans la langue de la procédure. L'Office européen des brevets peut toutefois autoriser l'interprétation dans l'une de ses autres langues officielles.

(4) Mit Einverständnis aller Beteiligten und des Europäischen Patentamts kann jede Sprache verwendet werden.

(4) If the parties and the European Patent Office agree, any language may be used.

(4) Sous réserve de l'accord des parties et de l'Office européen des brevets, toute langue peut être utilisée.

InnoPharma Exhibit 1046.0565

I. Facts and Submissions

1. The European patent application with the application number 01900186.6 (International application number PCT/GB2001/000049) was filed on 08.01.2001, claiming the priorities of 10.01.2000 (GB0000313) and 12.04.2000 (GB0008837).

2. The International application was published on 19.07.2001 (WO2001/051056, Gazette 2001/29), the European application was published on 23.10.2002 (Bulletin 2002/43).

3. The date of publication and mention of the grant of the patent was 19.10.2005 (Bulletin 2005/42).

4. The following contracting states were designated: AT, BE, CH, CY, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE, TR

5. The proprietor of the patent is:

AstraZeneca AB
151 85 Södertälje (SE)

6. On 19.07.2006 with a letter dated the same day an opposition was filed by

Gedeon Richter Ltd.
P.O. Box 27
H-1475 Budapest 10 (HU)

7. In the letter of opposition revocation of the opposed patent in its entirety based on the grounds as defined in Article 100 (a) EPC (lack of novelty and lack of inventive step) was requested. As a subsidiary request the Opponent asked for oral proceedings.

With regard to novelty the Opponent focused on document D1, in particular on Example 3 and a passage on page 5, line 16, which mentions esters or partial esters derived from fatty acids and hexitol anhydrides. He argued that the blood concentration defined in Claim 1 represents a result to be achieved. This feature was furthermore described to be mentioned in D1 on page 7, lines 24/25.

InnoPharma Exhibit 1046.0566

Having regard to inventive step combinations of D1 with either of D5, D2/D6 and D7 were mentioned.

8. In his letter of reply, the Proprietor requested maintenance of the patent in its form as granted as rejection of the opposition. On an auxiliary basis oral proceedings were requested.

The Proprietor explained that the combination of Example 3 of D3 with the passages of the description cited mean a combination of different embodiments. He also considered the inventive step objections based on the combinations of documents cited by the Opponent as unfounded.

9. In the course of the procedure the following documents have been cited so far. The parties are requested to adhere to this numbering throughout the procedure:

D1 = EP 0 346 014
D2 = WO 96/19997
D3 = WO 96/21440
D4 = Waterton et al, Laboratory Animal Science 43(3) 247-251, 1993
D5 = US 4 388307
D6 = EP 0 310 542
D7 = Riffkin et al, J Pharm Sci 53(8) 891-895, 1964
D8 = US 3164520

All documents have been published prior to the present priority date.

InnoPharma Exhibit 1046.0567

II. Preliminary, non-binding opinion of the Opposition Division

1. Oral proceedings

Since both parties requested oral proceedings, summons are attached to the present communication. The topics to be discussed will be the grounds for opposition and the requirements of Article 123(2)/(3) EPC in case of any amendments.

The preliminary, non-binding opinion of the Opposition Division is as follows:

2. Novelty

Document D1 discloses in Example 3 a composition comprising fulvestrant, castor oil and benzyl alcohol for the intramuscular administration. As confirmed by the Opponent, a non-aqueous ester solvent has not been disclosed in the example.

Although such esters are mentioned in the description (e.g. see page 5, line 16), the combination of features has not been directly and unambiguously disclosed in D1. Thus, the requirements for novelty are considered to be met.

3. Inventive step

It will have to be discussed during the oral proceedings whether the claimed subject-matter involves an inventive step. It currently seems that D1 is the closest prior art document (this has also been confirmed by the Opponent and the Proprietor).

The analysis will be made by using the so-called problem-solution approach.

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European Patent Office
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European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Application No.: 01 900 186.6

Patent No.: EP-B-1250138

Preparation for oral proceedings - Instructions to Support Service

Oral proceedings are to be held in connection with the above patent application

1. The matters to be discussed are set out in the annex (Form 2906)

2. Dispatch the summons using Form 2008/2310 and Form 2906 for the parties to attend on:

Day 28.10.2008 Time 09:00

ROOMS

Room 2 452 booked

ORAL 01, 02, 03 and 05 coded

Date LA 25.02.08 Initials

2.1 If no room is available, notify the division on Form 2088

2.2 Parties' submissions in preparation for the oral proceedings, if any, should be made no later than

2 month(s)

before the date of the oral proceedings
(transfer to Form 2008.1 / 2310.1)

2.3 Encode ORAL(04) coded

Date LA 25.02.08 Initials

2.4 Dispatch Form 2008.7 / 2310.7 to division

Date LA 25.02.08 Initials

InnoPharma Exhibit 1046.0569

Europäisches Patentamt
European Patent Office
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European Patent Office
80298 MUNICH
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Fax: +49 89 2399 4465

3. ☐ Arrange for the following special equipment to be provided in the conference room:

Date Initials

4. Request language service to provide simultaneous interpretation facilities as necessary

LA 25.02.08
Date Initials

5. Return the dossier to primary examiner with Form 2041 (15 days before the oral proceedings)

LA 25.02.08
Date Initials

6. Check that summons has been received (Form 2936 / advice of delivery)

7. 15 days before the oral proceedings:
- dispatch the dossier to the primary examiner and
- dispatch Form 2041 with copies for the other members of the examining division.

20.02.08
Date

Veronese, Andrea	Paul Soto, Raquel	Bendl, Ernst	
Chairman	2nd examiner	1st examiner	Legal member

InnoPharma Exhibit 1046.0570

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MÜNCHEN LONDON

EPO - Munich
32
08. Juni 2007

HOFFMANN · EITLE • Postfach 81 04 20 • D-81904 München
European Patent Office

80298 Munich

Munich, June 8, 2007

Our Ref.: 118 663 o2/kbo
Opposition ./. EP 1 250 138 (Application No. 01 900 186.6)
Patentee: AstraZeneca

As we have taken over representation of the above-mentioned opposition case, we herewith file a signed Power of Attorney.

Very truly yours,

Dr. Thorsten Bausch
European Patent Attorney
Association No. 151

Enc.:
Power of attorney

PATENTANWÄLTE · MÜNCHEN
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|3 nicht/not European Trademark Attorney
|4 Dutch Patent Attorney
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02

InnoPharma Exhibit 1046.0571

Vollmacht[1]
Authorisation[1]
Pouvoir[1]

Bitte vor dem Ausfüllen des Formblatts Rückseite beachten. / Please read the notes overleaf before completing the form. / Veuillez lire les remarques au verso avant de remplir le formulaire

Zeichen des Vertreters (der Vertreter) / Representative's reference / Référence du (des) mandataire(s) (max. 15 Positionen / max. 15 spaces / 15 caractères au maximum)

118 663 o2

Nr. der Anmeldung (des Patents) / Application/Patent No. / N° de la demande (du brevet)

EP 1 250 138 B1 (EP Application No. 01900186.6)

Ich (Wir) / I (We) / Je (Nous)[2]

AstraZeneca AB
151 85 Södertälje (SE)

bevollmächtige(n) hiermit / do hereby authorise / autorise (autorisons) par le présente[3]

HOFFMANN · EITLE
PATENT- UND RECHTSANWÄLTE
D-81925 MÜNCHEN · ARABELLASTRASSE 4
Association No. 151

☐ Weitere Vertreter sind auf einem gesonderten Blatt angegeben. / Additional representatives indicated on supplementary sheet. / D'autres mandataires sont mentionnés sur une feuille supplémentaire.

mich (uns) zu vertreten als / to represent me (us) as / à me (nous) représenter en tant que

☒ Anmelder oder Patentinhaber, / applicant(s) or patent proprietor(s), / demandeur(s) ou titulaire(s) du brevet,

☐ Einsprechenden (Einsprechende), / opponent(s), / opposant(s),

für mich (uns) zu handeln in den durch das Europäische Patentübereinkommen geschaffenen Verfahren in der (den) folgenden europäischen Patentenmeldung(en) oder dem (den) folgenden europäischen Patent(en)[4] und Zahlungen für mich (uns) in Empfang zu nehmen: / to act for me (us) in all proceedings established by the European Patent Convention concerning the following European patent application(s) or patent(s)[4] and to receive payments on my (our) behalf: / à agir en mon (notre) nom dans toute procédure instituée par la Convention sur le brevet européen et concernant la (les) demande(s) de bravet ou le (les) brevet(s) européen(s)[4] suivant(s) et à recevoir das paiaments en mon (notre) nom:

EP 1250 138 B1

☐ Weitere Anmeldungen oder Patente sind auf einem gesonderten Blatt angegeben. / Additional applications or patents indicated on supplementary sheet. / D'autres demandes ou brevets sont mentionnés sur une feuille supplémentaire.

☐ Die Vollmacht gilt auch für Verfahren nach dem Vertrag über die internationale Zusammenarbeit auf dem Gebiet des Patentwesens. / This authorisation shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty. / Ce pouvoir s'applique également à touta procédure instituée par le Traité de coopération en matière de brevets.

☒ Diese Vollmacht gilt auch für eventuelle europäische Teilanmeldungen. / This authorisation also covers any European divisional applications. / Le présent pouvoir vaut également pour les demandes divisionnaires européennes qui pourraient être déposées.

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☐ Ich (Wir) widerrufe(n) hiermit frühere Vollmachten in Sachen der obenbezeichneten Anmeldung(en) oder des obenbezeichneten Patents (der obenbezeichneten Patente)[5]. / I (We) hereby revoke all previous authorisations in respect of the above application(s) or patent(s)[5] / Je révoque (Nous révoquons) par la présente tout pouvoir antérieur, donné pour la (les) demande(s) ou le (les) brevet(s) mentionné(s) ci-dessus[5].

Ort/Place/Lieu: ALDERLEY PARK, MACCLESFIELD, CHESHIRE. ENGLAND Datum/Date: 10 MAY 2007

Unterschrift(en) / Signature(s)[6]

Das Formblatt muß vom (von den) Vollmachtgeber(n) (bei juristischen Personen vom Unterschriftsberechtigten) eigenhändig unterzeichnet sein. Nach der Unterschrift bitte den (die) Namen des (der) Unterzeichneten in Druckschrift wiederholen (bei juristischen Personen die Stellung des Unterschriftsberechtigten innerhalb der Gesellschaft angeben). / The form must bear the personal signature(s) of the authorisor(s) (in the case of legal persons, that of the officer empowered to sign). After the signature, please print the name(s) of the signatory(ies) adding, in the case of legal persons, his (their) position within the company. / Le formulaire doit être signé de la propre main du (des) mandant(s) (dans le cas de personnes morales, de la personne ayant qualité pour signer). Veuillez ajouter en caractères d'imprimerie, après la signature, le (les) nom(s) du (des) signataire(s) en mentionnant, dans le cas de personnes morales, ses (leurs) fonctions au sein de la société.

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Europäisches Patentamt | **European Patent Office** | **Office européen des brevets**

Giles, Allen Frank
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Global Intellectual Property
151 85 Södertälje
SUEDE

Formalities Officer
Name: Sleex
Tel.: 8044

Date
14-05-2007

Reference	Application No./Patent No.
DUF/AFG/70635/E	01900186.6 - 2123 / 1250138

Applicant/Proprietor
AstraZeneca AB

Communication pursuant to Art. 1(2) of the decision of the President of the EPO dated 19.07.1991 concerning the filing of authorisations (OJ EPO 1991, 489)

Concerning the above-mentioned European patent application/patent the EPO has been notified of the appointment of a new representative for the

☒ applicant.

☐ proprietor of the patent.

☐ opponent _____ .

☒ A copy of the authorisation/the letter of the new representative is enclosed.

☐ The new representative _____

has referred to his general authorisation No. _____ .

The EPO will communicate with the new representative directly from now on.

Transfer Service
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InnoPharma Exhibit 1046.0573

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ALLEMAGNE

Formalities Officer
Name: Sleex
Tel.: 8044

Date 14.05.07

Reference	Application No./Patent No.
118 663 o2	01900186.6 - 2123 / 1250138

Applicant/Proprietor
AstraZeneca AB

Communication of amended entries concerning the representative (Rule 92(1)h) EPC)

As requested, for the above-mentioned European patent application/European patent the entries concerning the representative have been amended as follows:

HOFFMANN EITLE
Patent- und Rechtsanwälte
Arabellastrasse 4
81925 München
DE

The amendment will be recorded in the Register of European Patents.

Transfer Service
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InnoPharma Exhibit 1046.0574

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Formalities Officer
Name: Lausenmeyer J.
Tel.: 8074

Date 14-05-2007

Reference	Application No./Patent No.
M 2363 EP/OPP OPPO 01	01900186.6 - 2123 / 1250138
Applicant/Proprietor: AstraZeneca AB	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☐ Letter from the opponent of
- ☒ Copy(copies) EPO f. 2548 dated 14.5.2007
- ☐ Communication:

Please take note.

For the Opposition Division

Europäisches Patentamt · European Patent Office · Office européen des brevets

☐ **Registered letter**

EPO Form 2911O 05.02 09.05.07

MG21202

InnoPharma Exhibit 1046.0575

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Europäisches Patentamt | European Patent Office | Office européen des brevets

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Formalities Officer
Name: Lausenmeyer J.
Tel.: 8074

Date: 08-05-2007

Reference	Application No./Patent No.
M 2363 EP/OPP OPPO 01	01900186.6 - 2123 / 1250138
Applicant/Proprietor: AstraZeneca AB	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☒ Letter from the proprietor of the patent of 30.04.07 with cited document
- ☐ Letter from the opponent of
- ☐ Copy(copies)
- ☐ Communication:

Please take note.

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

☐ **Registered letter**

EPO Form 2911O 05.02 03.05.07

JL20183

InnoPharma Exhibit 1046.0576

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EPO - Munich
20
30. April 2007

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European Patent Office

80298 Munich

Munich, April 30, 2007

Our Ref.: 118 663 o2
Opposition ./. EP 1 250 138 B1 (Application No. 01 900 186.6)
Patentee: AstraZeneca

We herewith take over representation of this case. It is requested that future correspondence be sent to our Munich office.

This is in response to the communication dated August 24, 2006 and the opposition as filed by Gedeon Richter Ltd.

It is requested that the opposition be rejected and the opposed patent be maintained as granted. Only on an auxiliary basis, oral proceedings are requested.

In our opinion, the opposed patent is both novel and involves an inventive step. The opponent's arguments are not convincing for the following reasons.

PATENTANWÄLTE · MÜNCHEN
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InnoPharma Exhibit 1046.0577

1.) Subject-matter of the opposed patent

The opposed patent relates to a novel pharmaceutical formulation as defined in the claims as granted. According to the feature analysis presented by the opponent, claim 1 reads:

(1.1) A pharmaceutical formulation, comprising
(1.2) fulvestrant in
(1.3) a ricinoleate vehicle;
(1.4) a pharmaceutically acceptable non-aqueous ester solvent, and
(1.5) a pharmaceutically acceptable alcohol
wherein the formulation is adapted for
(1.6) intra-muscular administration and
(1.7) attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

The opponent is of the opinion that feature 1.7 does not represent a technical feature which is able to effectively distinguish the claimed subject-matter from any prior art teaching. According to the opponent, feature 1.7 has to be regarded as a mere result to be achieved (desideratum).

First of all, it is unclear to us which objection against a feature that arguably represents "a result to be achieved" the opponent is trying to make here. If the opponent is trying to raise a clarity objection, this must be rejected, as lack of clarity is not an opposition ground.

Furthermore, a feature that defines "a result to be achieved" is *a priori* neither unallowable under the EPC nor unclear nor non-technical (see Guidelines of Examination in the European Patent Office, Part C, Chapter III 4.7). In the present case, there can be no doubt that feature 1.7 is of a technical character.

As a general rule, a feature must be directly and positively verifiable by tests or procedures adequately specified in the description or known to the person skilled in the art and which do not require undue experimentation (T 68/85). Feature 1.7 of claim 1 of the opposed patent defines the blood plasma level over an extended period of time which is characteristic for an extended release formulation. In paragraph [0041] of the opposed patent the meaning of "therapeutically significant levels" is clearly defined. Also, the skilled person has no difficulty in determining the blood plasma level after two weeks.

InnoPharma Exhibit 1046.0578

Therefore, feature 1.7 is clearly a technical feature which is suitable to distinguish the claimed subject-matter from the prior art.

2.) Novelty

Referring to D1 (US 5,183,814) the opponent has argued that the pharmaceutical formulation of claim 1 of the opposed patent would lack novelty. However, in doing so, the opponent has combined a specific Example, i.e. Example 3 of D1, with different disclosures of the general description, namely page 5, line 16 of D1 and the paragraph starting in line 20 of page 5.

The opponent has combined separate items of D1 belonging to different embodiments. This is not permissible (T 305/87) and does not represent a fair reading of D1 as a whole. In effect, the Opponent has formed an arbitrary selection of features *ex post* and with the benefit of knowing the invention of the opposed patent.

As mentioned in the opposed patent itself (paragraph [0014]) in Example 3 of D1 an oil based injection formulation of fulvestrant is described which comprises 50 mg of fulvestrant, 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. However, the formulation of Example 3 does not contain a non-aqueous ester solvent.

The opponent has relied on page 5, line 16 of D1 where esters or partial esters derived from fatty acids and hexitol anhydrides (e.g. sorbitan monooleate) are mentioned as emulsifying agents used in the pharmaceutical formulations of D1 on the basis of a vegetable oil (page 5, line 13 of D1). The opponent ignores though that the paragraph of D1 to which reference was made, only relates to emulsifying agents in oil-in-water emulsions (page 5, line 13).

Example 3 however does not relate to an oil-in-water emulsion such that the skilled person has no reason to add an emulsifying agent to the pharmaceutical composition of Example 3. In addition, it is to be noted that D1 teaches that a sweetening agent or flavouring agent may be added to the oil-in-water emulsions (page 5, line 18). Therefore, it can be assumed that these oil-in-water emulsions are rather intended for oral administration than for intramuscular administration. This understanding is confirmed by the subsequent paragraph on page 5, lines 20-25 where injectable aqueous or oily suspensions are mentioned.

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Although it is disclosed in this paragraph that these suspensions may be formulated using "one or more of the appropriate dispersing or wetting agents and suspending agents which have been mentioned above" (page 5, lines 21-22), this paragraph does neither disclose nor suggest to specifically use an ester solvent in an injectable oil-based formulation.

In addition, all esters mentioned in D1 are commonly used non-ionic surfactants and are used in that capacity to enable a better suspension or dispersion of a solid phase in a solvent phase; however, these surfactants are not "ester solvents" by themselves.

In summary, D1 does not directly and unambiguously disclose a pharmaceutical composition comprising fulvestrant in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol. The pharmaceutical formulation as claimed in granted claim 1 of the opposed patent is thus new vis-à-vis D1.

3.) Inventive step

In the following, we will show that the subject-matter claimed in claim 1 of the opposed patent also involves an inventive step in view of a combination of

- D1 with D5
- D1 with D2/D6
- D1 with D7.

The Opponent's arguments are thus unfounded.

In each of the above approaches the opponent considered D1, in particular Example 3 of D1, as closest prior art. We agree, and this is also in line with paragraph [0014] of the opposed patent where Example 3 of D1 is discussed.

The pharmaceutical formulation of claim 1 differs from the pharmaceutical composition of Example 3 of D1 in that it contains a pharmaceutically acceptable non-aqueous ester solvent.

The presence of the non-aqueous ester solvent has the effect that the alcohol concentration in fulvestrant formulations can be lowered whilst preventing precipitation of fulvestrant from the formulation.

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The objective problem underlying the opposed patent can thus be seen as the prevention of the precipitation of the active ingredient fulvestrant when lowering the alcohol concentration. Lowering the alcohol concentration is advantageous for formulation on a commercial scale [0014]. Insofar, there seems to be no disagreement with the Opponent.

3.1) Combination of D1 with D5

The opponent is of the opinion that the skilled person would have learned from D5 that esters are generally suitable as solubilizing agents in oily solutions also in combination with alcohols.

However, it is to be noted that D5 refers to galenic compositions containing cyclosporin A (see for example claim 1 of D5 or the examples). Even in its most general aspect, D5 at best discloses that the compositions "are particularly suitable for hydrophobic and/or lipophilic peptides which are insoluble or difficultly soluble in conventional pharmaceutical vehicles, in particular cyclosporin, ..." (column 1, lines 3rd line from the bottom to column 2, line 2).

However, fulvestrant is not a peptide.

The skilled person thus had no motivation to consult a document relating to galenic compositions containing peptides, in particular cyclosporin A, when aiming at lowering the alcohol content in a fulvestrant-containing formulation. D5 neither discloses, nor teaches nor suggests that the pharmaceutical vehicles described in this document may also be suitable for a pharmaceutical formulation containing a compound of a completely different chemical and pharmacological class, i.e. fulvestrant. For these reasons the skilled person had no motivation to combine Example 3 of D1 with the teaching of D5. The opponent's combination of these two references is clearly based on hindsight.

3.2) Combination of D1 with D2/D6

The opponent made particular reference to Example 5 of D2/D6, disclosing a formulation of tamoxifen as a solution in castor oil and benzyl benzoate. The opponent's conclusions, however, are again made with the benefit of knowledge of the invention underlying the opposed patent.

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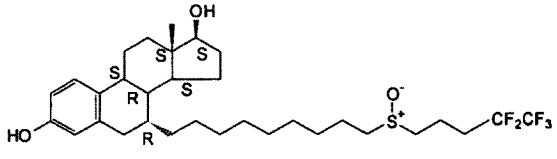
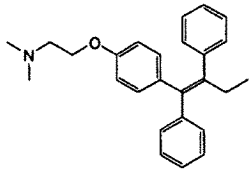
Although both tamoxifen and fulvestrant act as an antiestrogenic agent, they are structurally completely different. While fulvestrant is a steroid, tamoxifen is a nonsteroidal agent. Solubility refers to the ability for a given substance, the solute, to dissolve in a solvent. The solubility of one substance dissolving in another is determined by the balance of intermolecular forces between the solvent and solute and the entropy change that accompanies the solvation. Therefore, regarding solubility it is not the question whether tamoxifen and fulvestrant may have similar biological effects in the human body, but whether they are similar on a molecular level. However, as shown by the chemical formulas below, tamoxifen and fulvestrant are completely different molecules such that it is impossible to apply any knowledge about the solubility of the compound tamoxifen to the solubility of fulvestrant.

Fulvestrant



Tamoxifen



The same is true with regard to Example 8 of D6 where a composition containing 11β-[(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one is described.

The opponent has argued that since the use of an ester compound as a solubilizing agent for an antioestrogenic steroid in castor oil is disclosed in both D2 and D6, the skilled person would have tried out such an ester as a solubilizer when being faced with the above-mentioned objective technical problem relating to the antioestrogenic steroid fulvestrant. However, it is respectfully submitted that both D2 and D6 merely disclose formulations of certain pharmaceutical ingredients without mentioning their individual functions or effects. A skilled person would not have generalized the teaching of these examples to formulations of a quite different entity, i.e. fulvestrant. Moreover, D2/D6 do not give the slightest hint that the use of benzyl benzoate would allow less alcohol to be used in the formulation of fulvestrant.

In summary, it is to be noted that the opponent referred to two isolated Examples, namely Example 5 of D2/D6 and Example 8 of D6, that are not further explained in the description

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of these references. Merely from the fact that in D2/D6 two Examples are disclosed which use castor oil in combination with benzyl benzoate to solubilize a different chemical entity, the skilled person would not have taken any teaching or expectation that the addition of benzyl benzoate would have any beneficial effect in a fulvestrant-containing formulation that additionally contains an alcohol solvent. Therefore, the skilled person had no motivatation to combine Example 3 of D1 with Example 5 of D2/D6 or Example 8 of D6. There is no reason apparent why the skilled person would have combined these particular references in the expectation of an advantage or improvement.

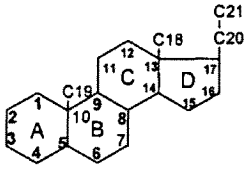
Thus, the opponent's argument does not pass the "could-would-test" generally applied by the EPO in the evaluation of inventive step since Decision T 2/83.

3.3) Combination of D1 with D7

The opponent refers to D7 relating to castor oil vehicle systems for prolonged action of the injected active ingredient (which form the basis of the claimed oily solutions). D7 relates to pharmaceutical formulations of steroid hormones, i.e. the same chemical family as fulvestrant. The opponent refers to left column on page 892 of D7, where it is stated that in order "to increase the solvent power of the oil it was necessary to add compatible and non-irritating cosolvents. Such additions consisted of benzyl benzoate, benzyl alcohol, ethyl acetate, ethyl oleate, etc.". Furthermore, in right column of page 894 of D7, various oily formulations are exemplified which comprise certain steroids, castor oil, benzyl alcohol and benzyl benzoate. However, these examples seem to show quite contradictory results.

It is to be noted that D7 is a document from 1964 and thus refers only to those steroid hormones known at this time. Fulvestrant was not known in 1964. Furthermore, the only steroids for which D7 contains data are 17-hydroxyprogesterone caproate, testosterone, estradiol valerate and progesterone (see Table II on page 892 of D7).

The steroids mentioned in the D7 and fulvestrant have in common the steroidal framework:



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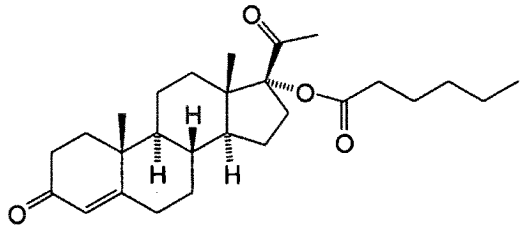
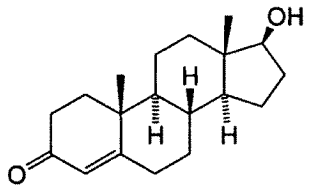
However, the steroidal framework is not alone responsible for the solubility properties. In fact, the solubility of a steroid is of course also strongly influenced by the substituents present at the steroidal framework. On the molecular level, the steroids mentioned in D7 have the following structures:

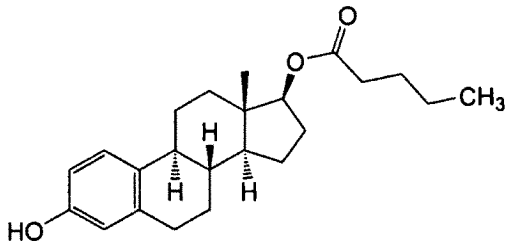
17-Hydroxyprogesterone caproate:



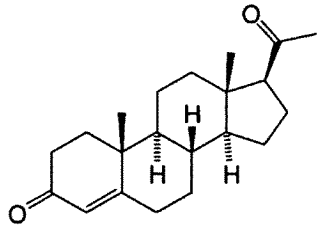
Testosterone:



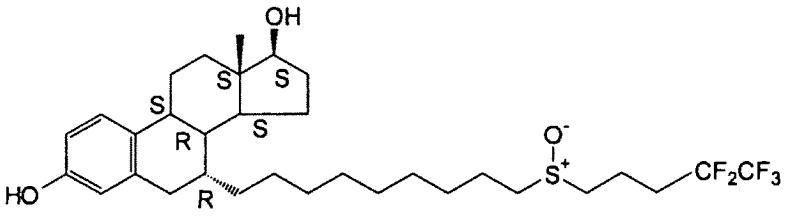
Estradiol valerate:



Progesterone:



On the other hand, fulvestrant has the following structure:



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Testosterone and progesterone as well as 17-hydroxyprogesterone caproate and estradiol valerate, respectively, have relatively similar constitutional units such that similar solubility properties could be assumed. Fulvestrant, however, has a completely different substituent at the steroidal framework such that a prediction of its solubility based on solubility data of testosterone, progesterone, 17-hydroxyprogesterone caproate and estradiole valerate is impossible.

Indeed, the solubility properties of Fulvestrant are very different from those of the four steroids mentioned in D7. This may be seen when comparing the solubility data regarding castor oil and sesame oil (data taken from Table II on page 892 of D7 and Table 2 on page 6 of the opposed patent):

Steroid	Solubility [mg/ml] at 25°C	
	Castor oil	Sesame oil
Fulvestrant	20	0.58
17-Hydroxyprogesterone caproate	55.5	23.4
Testosterone	38.6	5.4
Estradiol valerate	60.6	16.1
Progesterone	52.0	22.9

From the above table one can take that the solubility of fulvestrant in castor oil and sesame oil respectively, is much lower than the solubility of the other steroids in the same oils. That is, fulvestrant presents a much more difficult formulation problem when used in an oil-based formulation.

Furthermore, the steroids mentioned in D7 and fulvestrant do not only show very different solubility properties in oily substances, but also in ester solvents. In this regard it is referred to new document D8 (US 3,164,520). D8 was published around the same time as D7 and is concerned with injectable steroid compositions containing at least 75% benzyl benzoate. Column 1, lines 20-27 lists compounds employed in D8, such as 17-hydroxyprogesterone and the esters thereof, testosterone, estradiol and the acids thereof, progesterone and its derivatives. In other words, similar steroids as mentioned in D7. These steroidal compounds have a very high solubility in benzyl benzoate, although specific solubility limits are not given. In the Examples of D8 the following compositions are described:

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Example	Steroid	Steroid concentration in benzyl benzoate [mg/ml]
1	16,17-dihydroxyprogesterone	200
2	testosterone palmitate	200
3	progesterone	250
4	Progesterone + 17-hydroxyprogesterone caproate	250 + 250
5	Testosterone enanthate	400

It is to be noted that the above solubility data do not even refer to the solubility limits. It is assumed that the solubility limits are considerably higher. In contrast, fulvestrant shows a solubility maximum in benzyl benzoate of 6.15 mg/ml, i.e. orders of magnitude lower than the steroids mentioned in D8 or D7.

The question regarding the inventive step is whether the skilled person, when intending to solve the above objective problem underlying the invention, i.e. lowering the alcohol concentration in Example 3 of D1 while preventing fulvestrant from precipitation, would have applied the teaching of D7 to fulvestrant. We respectfully submit that he/she would not have done so for the following reasons:

From D7 and D8 the skilled person knew that specific classical steroids show a good solubility in benzyl benzoate. Thus, it might have been a rational choice to add the "good solvent" benzyl benzoate to these steroids in the hope of improving the solubility in the solvent mixture. On the other hand, the skilled person at the priority date of the opposed patent was aware of the quite different molecular structures of fulvestrant and the classical steroids mentioned in D7. Therefore, the skilled person had no reason to assume that a solvent system used for the classical steroids of D7 would also be successful in the case of fulvestrant showing a quite different chemical structure and solubility profile.

In view of this unpredictability, the skilled person would have proceeded cautiously and step-by-step. Step 1 would be to determine the solubility of fulvestrant in various solvents in order to find out which one of them might be appropriate for solving the objective problem. The result of such a series of experiments is shown in Table 2 of the opposed patent. From such solubility data with the actual compound of interest, the skilled person takes that the solubility of fulvestrant in an ester solvent is much lower than in an alcohol solvent. Therefore, the skilled person must have assumed that the replacement of part of the

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alcohol solvent in Example 3 by an ester solvent will deteriorate the solubility of fulvestrant.

Indeed, from a chemical point of view it is completely surprising that, although the solubility of fulvestrant in an ester solvent alone is very low, the presence of an ester solvent in a composition containing a ricinoleate vehicle and an alcohol solvent eases in fact the solubility of fulvestrant and allows part of the alcohol to be omitted. Such an effect is not at all derivable from D7 as the steroids described in D7 have already a good solubility in an ester solvent alone, contrary to fulvestrant.

The preparation of an intra-muscular formulation of fulvestrant had to occur under certain boundary conditions which were quite difficult to comply with. On the one hand, a depot formulation that achieves therapeutically significant levels over a period of 14 days must contain an appreciable amount of fulvestrant, typically 250 mg or more [0025]. Moreover, the administration volume is limited to relatively small volumes, typically in the order of 5 ml [0025] and [0026]. This results in a solubility requirement of at least about 50 mg/ml fulvestrant in the oil-based pharmaceutical formulation. Given that the solubility of fulvestrant in ethyl oleate only is 1.25 mg/ml, in benzyl benzoate 6.15 mg/ml, and in isopropyl myristate 0.80 mg/ml, respectively, a skilled person would have had no incentive to add these relatively poor solvents for fulvestrant to a composition such as the one of Example 3 of D1.

For the above reasons, the claimed pharmaceutical formulations were not derivable in an obvious way from the combination of Example 3 of D1 with D7.

3.4) Comment on the alleged breadth of claim 1

In item "3.2 d) Remarks" (paragraph on page 9 of the opposition writ) the opponent mentions that claim 1 is allegedly extraordinarily broad by not further defining the definition of the alcohol and the ester component.

First of all, patentee would like to note that opponent's objection is very vague. Even a "broad" claim as such is not objectionable under the EPC. Opponent fails to provide any evidence showing that claim 1 is unjustifiably broad. Secondly, patentee would like to point out that claim 1 is in fact not really a broad, but rather a narrow and quite specific claim. First of all, claim 1 only refers to pharmaceutical formulations that contain the

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specific steroid fulvestrant. Furthermore, the opponent overlooks that the alcohol and the ester solvent are very limited as only "pharmaceutically acceptable" solvents are comprised. In addition, it is to be noted that claim 1 comprises only such formulations which fulfil the feature "attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks". This also limits the composition of the claimed pharmaceutical formulation.

3.5) Independent claims 2 and 4

The subject-matters of independent claim 2 and 4 are patentable for the same reasons as presented with regard to the pharmaceutical formulation of claim 1.

4.) Summary

For the above reasons, we respectfully submit that our request to reject the opposition is justified.

Dr. Thorsten Bausch
EUROPEAN PATENT ATTORNEY
Association No. 151

Enc.: D8 (US 3,164,520)

1 copy for the opponent

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United States Patent Office

3,164,520

Patented Jan. 5, 1965

3,164,520

INJECTABLE STEROID COMPOSITIONS CONTAINING AT LEAST 75% BENZYL BENZOATE

Raymond Charles Huber, Martinsville, N.J., assignor to Olin Mathieson Chemical Corporation, New York, N.Y., a corporation of Virginia

No Drawing. Filed Oct. 29, 1962, Ser. No. 233,931
4 Claims. (Cl. 167—58)

This invention relates to compositions of matter and more particularly to new parenterally administrable pharmaceutical compositions comprising one or more active medicaments and a physiologically acceptable non-toxic pharmaceutical vehicle, comprised essentially of benzyl benzoate.

The active medicament which may be incorporated in the novel compositions of this invention may be any one which is administered for use in comparatively large unit dosages, for example, 10 mg./ml. to 500 mg./ml. and which is soluble in benzyl benzoate. Examples of the medicaments which may be employed in this invention include inter alia, steroid hormones, especially those steroid hormones which exhibit anabolic, estrogenic, androgenic and progestational activity, for example, 17-hydroxyprogesterone and the esters thereof, testosterone, estradiol and the acid esters thereof, progesterone and its derivatives and Δ^1-testololactone and its derivatives. In the most preferable embodiment of this invention the active medicament is a steroid hormone although other pharmaceutically active compounds may also be employed, with satisfactory results.

Heretofore it has been well recognized in the preparation of parenterally administrable pharmaceutical compositions that a suitable solvent must be employed to render the composition injectable. However, as the science of medicine has progressed it has been found that increasingly higher dosages of certain medicaments must be employed in the treatment of certain ailments in order to achieve several advantages. Among these advantages can be numbered the prolongation of activity of the medicaments involved and the lessening of the total number of individual injections which are needed to obtain the same results.

Additionally, it has been found that new chemical modifications of medicaments are continually being discovered and the solubility of these modified medicaments in the solvents commonly employed, appears to be more and more limited and it has therefore become increasingly difficult to dissolve these new modified medicaments in parenterally acceptable vehicles. It is well-known that certain pharmaceutical vehicles yield satisfactory results at low level medicament concentrations when employed in compositions for parenteral administration. Such vehicles are the vegetable oils such as cotton seed oil, peanut oil, sesame oil, or corn oil, in combination with small amounts of benzyl benzoate. However, when an increased dosage level of the medicaments is employed, along with a correspondingly necessary increased amount of pharmaceutical vehicle it has been found that certain undesirable disadvantages exist.

The undesirable disadvantages which are present when the prior art vehicles are employed with a high dosage level of medicaments, are many. In addition to the prior art vehicles being incapable of solubilizing any great quantities of the medicaments, it has been found that the compositions heretofore employed produce an undue amount of irritation at the site of injection, when parenterally administered into the animal being treated.

It has now been found that the disadvantages encountered in the parenteral administration of high dosage levels of the medicaments of this invention can be avoided by employing the novel pharmaceutical compositions of

this invention. It has been found that these disadvantages can be overcome by employing benzyl benzoate as the essential component of the pharmaceutical vehicle of parenterally administrable compositions. The benzyl benzoate has been found to be capable of dissolving great quantities of the medicaments of this invention and the resulting parenterally administrable composition employing this vehicle does not produce undue irritation when injected into the animals being treated.

The amount of benzyl benzoate which may be employed in the compositions of this invention while still yielding satisfactory results has been found to range from about 75% to 100% by volume of the pharmaceutical vehicle employed. Thus the ratio of benzyl benzoate present in the pharmaceutical vehicle as compared to any other ingredients therein must be at least 3 to 1. In the most preferable embodiment of this invention it has been found that a pharmaceutical vehicle consisting essentially of pure benzyl benzoate yields the best results although at lower levels satisfactory results are also obtained.

As is common in the art of preparing parenterally administrable pharmaceutical compositions other additives such as preservatives, antioxidants or anesthetics, such as benzyl alcohol and the other like well known additives may also be included in the pharmaceutical compositions of this invention. However, their use herein is permissive and not mandatory as their incorporation or omission in the final product of this invention does not substantially affect the results herein obtained.

The compositions of this invention are easily prepared by merely taking the desired amount of medicament and dissolving it in the pharmaceutical vehicle of this invention by any means known in the art, for example, by mere stirring.

The final compositions of this invention are parenterally administrable to the animal being treated. The administration of the composition may be accomplished intramuscularly, subcutaneously or in any other manner known to the art as may be determined in the individual cases wherein this invention is employed. It has been generally found that the most preferable results are obtained when an intramuscular route of administration is employed, although other methods of administration will also give satisfactory results.

The invention is more particularly illustrated by the following examples:

Example 1

Two g. of the acetophenone derivative of 16,17-dihydroxyprogesterone are dissolved in 10 ml. of benzyl benzoate with stirring and warming. The resultant solution is then filled in vials of 5 ml. each and sterilized by autoclaving at 121° C. for two hours.

0.25 ml. of the resulting solution is then injected into the vastus lateralis muscle of a rabbit producing a lesion at the site of the injection having the size of about 640 cubic millimeters after two days.

When 2 g. of the acetophenone derivative of 16,17-dihydroxyprogesterone are dissolved in 4.5 ml. of benzyl benzoate and 5.5 ml. of castor oil in accordance with the procedure of Example 1 and 0.25 ml. of the resultant solution is injected intramuscularly into the rabbit a lesion at the site of injection having a size of 967 cubic millimeters after two days.

Example 2

The procedure of Example 1 is followed except that 2 g. of testosterone palmitate are substituted for the acetophenone derivative of 16,17-dihydroxyprogesterone of Example 1.

0.25 ml. of the resultant solution is injected intramus-

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cularly into a rabbit producing a lesion at the site of injection having the size of about 420 cubic millimeters after two days. When 2 g. of testosterone palmitate are dissolved in a vehicle consisting of 40% castor oil and 60% benzyl benzoate and the resultant solution is injected intramuscularly into the rabbit, a lesion at the site of injection having a size of 610 cubic millimeters is produced after two days.

Example 3

A 25% solution of progesterone is prepared by dissolving 2.5 g. of progesterone in benzyl benzoate to make 10 ml. Sterilization is obtained by autoclaving the solution at 121° C. for 2 hours. When 0.25 mg. of this solution is injected into the vastus lateralis muscle of the rabbit, a lesion is produced which, after 2 days, measures 672 cubic millimeters.

When 2.5 g. of progesterone are dissolved to make 10 ml. in a mixture of 50% benzyl benzoate and 50% castor oil as the vehicle, and 0.25 ml. of this solution is injected into the rabbit muscle, a lesion size of 898 cubic millimeters is produced after two days.

Example 4

A 50% solution of hormones is prepared by dissolving 2.5 g. of progesterone and 2.5 g. of 17-hydroxyprogesterone caproate in benzyl benzoate to make 10 ml. of final product. After autoclaving at 121° C. for 2 hours to sterilize, 0.25 ml. of the solution is injected into a rabbit muscle and the lesion size is measured after 2 days. A lesion consisting of 572 cubic millimeters was produced. When this same hormone combination in the same proportions was dissolved in a vehicle consisting of 46% benzyl benzoate and 54% castor oil, a rabbit muscle lesion size of 1047 cubic millimeters is produced 2 days after injection of 0.25 ml. of test material.

Example 5

A 40% solution of testosterone enanthate is prepared by dissolving 4.0 g. in benzyl benzoate to make 10 ml. of final volume. After autoclaving at 121° C. for 2 hours to sterilize, 0.25 ml. of the solution is injected into the vastus lateralis muscle of the rabbit and the lesion size is measured after 2 days. A lesion consisting of 847 cubic millimeters is produced.

When this same quantity of hormone is dissolved in a vehicle consisting of 20% benzyl benzoate and 80% sesame oil and 0.25 ml. is injected a lesion size of 1441 cubic millimeters is produced.

Example 6

A 5% solution of Δ^1-testololactone is prepared by dissolving 50 mg./ml. in benzyl benzoate and after autoclaving to sterilize, 0.25 ml. of the solution is injected into a rabbit muscle. After 2 days a lesion size of only 483 cubic millimeters is produced.

Example 7

15 mg. of Δ^1-testololactone is dissolved in a solution comprised of 7.5 ml. of benzyl benzoate and 2.5 ml. of castor oil. The resultant solution is sterilized, then filled in vials of 5 ml. each and sterilized by autoclaving at 121° C. for 2 hours. The injectable solution may then be administered to the patient being treated.

This invention may be variously otherwise embodied within the scope of the appended claims.

What is claimed is:

1. A parenterally administrable pharmaceutical composition comprising the acetophenonide of 16,17-dihydroxyprogesterone and a physiologically acceptable non-toxic pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

2. A parenterally administrable pharmaceutical composition comprising testosterone palmitate and a physiologically acceptable non-toxis pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

3. A parenterally administrable pharmaceutical composition comprising testosterone enanthate and a physiologically acceptable non-toxic pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

4. A method of administering a large single dosage of a steroid which comprises parenterally administering to the patient being treated a composition comprising a steroid selected from the group consisting of 17-hydroxyprogesterone, the caproate ester of 17-hydroxyprogesterone, testosterone, the enanthate ester of testosterone, the palmitate ester of testosterone, estradiol, progesterone, and Δ^1-testololactone, and a pharmaceutical carrier, said carrier being at least 75% by volume of benzyl benzoate.

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DUF/AFG/70635/E	01900186.6 - 2123 / 1250138

Applicant/Proprietor
AstraZeneca AB

Extension of time limit pursuant to Rule 84 EPC

Opposition procedure

With reference to your request, the time limit for replying to the communication dated 24.08.06 has been extended

by 02 months

to a total of 08 months [MAXIMUM] *

from the date of notification of the above-mentioned communication.

Please note: To the extent that your request exceeded the above extension, your request has been refused.

Note:
The granting of extensions to time limits is governed by the implementing Regulations to the EPC and the Guidelines for Examination in the EPO, part E-VIII, 1.6.

If no reply to the communication is received in due time, the procedure will be continued. Attention is drawn to Article 114(2) EPC.

Opposition Division

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* see Guidelines for Examination in the EPO, part E-VIII, 1.6

InnoPharma Exhibit 1046.0591

European Patent Office
80298 MUNICH
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Tel.: +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Europäisches Patentamt | **European Patent Office** | **Office européen des brevets**

Tauchner, Paul
Vossius & Partner,
Siebertstrasse 3
81675 Munich
ALLEMAGNE

Formalities Officer

Name: Lausenmeyer J.

Tel.: 8074

Date
01-02-2007

Reference	Application No./Patent No.
M 2363 EP/OPP OPPO 01	01900186.6 - 2123 / 1250138
Applicant/Proprietor: AstraZeneca AB	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☐ Letter from the opponent of
- ☒ Copy(copies) EPO Form 2944
- ☐ Communication:

Please take note.

For the Opposition Division

Europäisches Patentamt · European Patent Office · Office européen des brevets

☐ **Registered letter**

EPO Form 2911O 05.02 29.01.07

JL20183

InnoPharma Exhibit 1046.0592

AstraZeneca

26 January 2007

European Patent Office
Directorate General 2
Erhardtstraße 27
D-80331 MÜNCHEN
Germany

EPO - Munich
37
30. Jan. 2007

Our Ref :Z70635-1X EP

VIA FAX & COURIER

Re: European Application No. 01 900 186.6-2123

Dear Sirs,

We refer to the Communication of a notice of opposition (R57(1)EPC) dated 24 August 2006 and hereby request a further extension of time for filing our observations to a total of 8 months. Please advise us of the new date accordingly.

Yours faithfully,

Allen F Giles
Authorised Representative
General Authorisation No. 19489

Direct Tel +44 1625 516573
Fax +46 8553 28820

InnoPharma Exhibit 1046.0593

AstraZeneca

26 January 2007

European Patent Office
Directorate General 2
Erhardtstraße 27
D-80331 MÜNCHEN
Germany

Our Ref :Z70635-1X EP

VIA FAX & COURIER

Re: European Application No. 01 900 186.6-2123

Dear Sirs,

We refer to the Communication of a notice of opposition (R57(1)EPC) dated 24 August 2006 and hereby request a further extension of time for filing our observations to a total of 8 months. Please advise us of the new date accordingly.

Yours faithfully,

Allen F Giles
Authorised Representative
General Authorisation No. 19489

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AstraZeneca
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Reg No 556011-7482
VAT No SE556011748201

Received at the EPO on Jan 26, 2007 17:17:52. Page 1 of 1

AZ38

InnoPharma Exhibit 1046.0594

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Giles, Allen Frank
AstraZeneca AB,
Global Intellectual Property
151 85 Södertälje
SUEDE

Formalities Officer
Name: Lausenmeyer J.
Tel.: 8074

Date 27-12-2006

Reference	Application No./Patent No.
DUF/AFG/70635/E	01900186.6 - 2123 / 0012501

Applicant/Proprietor
AstraZeneca AB

Extension of time limit pursuant to Rule 84 EPC

Opposition procedure

With reference to your request, the time limit for replying to the communication dated 24.08.06 has been extended

by 02 months

to a total of 06 months

from the date of notification of the above-mentioned communication.

Please note: To the extent that your request exceeded the above extension, your request has been refused.

Note:
The granting of extensions to time limits is governed by the implementing Regulations to the EPC and the Guidelines for Examination in the EPO, part E-VIII, 1.6.

If no reply to the communication is received in due time, the procedure will be continued. Attention is drawn to Article 114(2) EPC.

Opposition Division

InnoPharma Exhibit 1046.0595

European Patent Office
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Vossius & Partner,
Siebertstrasse 3
81675 Munich
ALLEMAGNE

Formalities Officer
Name: Lausenmeyer J.
Tel.: 8074

Date: 27-12-2006

Reference	Application No./Patent No.
M 2363 EP/OPP OPPO 01	01900186.6 - 2123 / 0012501
Applicant/Proprietor: AstraZeneca AB	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☐ Letter from the opponent of
- ☒ Copy(copies) EPO Form 2944
- ☐ Communication:

Please take note.

For the Opposition Division

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☐ **Registered letter**

EPO Form 2911O 05.02 20.12.06

JL20183

InnoPharma Exhibit 1046.0596

AstraZeneca

19 December 2006

EPO - Munich
73
22. Dez. 2006

Our Ref :Z70635-1X EP

European Patent Office
Directorate General 2
Erhardtstraße 27
D-80331 MÜNCHEN
Germany

VIA FAX & COURIER

Re: European Application No. 01 900 186.6-2123

Dear Sirs,

We refer to the Communication of a notice of opposition (R57(1)EPC) dated 24 August 2006 and hereby request an extension of time for filing our observations. Please advise us of the new date accordingly.

Yours faithfully,

Allen F Giles
Authorised Representative
General Authorisation No. 19489

Direct Tel +44 1625 516573
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InnoPharma Exhibit 1046.0597

AstraZeneca

19 December 2006

European Patent Office
Directorate General 2
Erhardtstraße 27
D-80331 MÜNCHEN
Germany

Our Ref :Z70635-1X EP

VIA FAX & COURIER

Re: European Application No. 01 900 186.6-2123

Dear Sirs,

We refer to the Communication of a notice of opposition (R57(1)EPC) dated 24 August 2006 and hereby request an extension of time for filing our observations. Please advise us of the new date accordingly.

Yours faithfully,

Allen F Giles
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General Authorisation No. 19489

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Reg No 556011-7488
VAT No SE556011748801

Received at the EPO on Dec 19, 2006 16:58:00. Page 1 of 1

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Giles, Allen Frank
AstraZeneca AB,
Global Intellectual Property
151 85 Sodertalje
SUEDE

Formalities Officer
Name: Lausenmeyer J.
Tel.: 8074

Date 24-08-2006

Reference	Application No./Patent No.
DUF/AFG/70635/E	01900186.6 - 2123 / 1250138

Applicant/Proprietor
AstraZeneca AB

Communication of notices of opposition (R. 57(1) EPC)

Notice of opposition has been filed within the opposition period by:

01. Gedeon Richter Ltd./P.O. Box 27/1475 Budapest 10/HONGRIE//

The notice of opposition indicated above has been already communicated to you.

You are requested to file your observations within a period of **4 months** from notification of this communication.

You may also file amendments, where appropriate, to the description, claims and drawings within the period specified. One set of these documents is to be filed.

If you introduced documents which have not yet been mentioned during the proceedings, your attention is drawn to Rule 59 EPC.

Enclosures:

For the Opposition Division

Europäisches Patentamt · European Patent Office · Office européen des brevets

Registered letter
EPO Form 2317A 07.02 18.08.06 OBSO

InnoPharma Exhibit 1046.0599

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Tauchner, Paul
Vossius & Partner,
Siebertstrasse 3
81675 Munich
ALLEMAGNE

Formalities Officer
Name: Lausenmeyer J.
Tel.: 8074

Date
24-08-2006

Reference	Application No./Patent No.
M 2363 EP/OPP OPPO 01	01900186.6 - 2123 / 1250138
Applicant/Proprietor: AstraZeneca AB	

Communication of further notices of opposition pursuant to Rule 57(2) EPC

No further opposition has been filed.

A copy of the communication pursuant to Rule 57(1) EPC sent to the proprietor of the patent is also enclosed for your information.

The patent proprietor's(proprietors') observations on the notice of opposition to the above-mentioned patent will be communicated to the opponent without delay. A time limit for reply will be fixed if the Opposition Division considers this expedient.

If no reply to a communication is received within the time limit set, the proceedings will be resumed forthwith. Your attention is drawn to Article 114(2) EPC.

Enclosures: copy of the communication pursuant to Rule 57(1) EPC(Form 2317)

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InnoPharma Exhibit 1046.0600

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Giles, Allen Frank
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Global Intellectual Property
151 85 Sodertalje
SUEDE

Formalities Officer
Name: Lausenmeyer J.
Tel.: 8074

Date 27-07-2006

Reference	Application No./Patent No.
DUF/AFG/70635/E	01900186.6 - 2123 / 1250138

Applicant/Proprietor
AstraZeneca AB

Communication of a notice of opposition

Enclosed herewith is a copy of a notice of opposition to the European patent specified above.

An invitation to file observations and to file amendments, where appropriate, to the description, claims and drawings (Rule 57(1) EPC) will be issued separately.

The period within which such observations may be filed will not be fixed until the following conditions are met:

(a) the opposition period has expired;

(b) the notice of opposition has been examined for certain formal requirements (Rule 56 EPC).

Enclosure: Notice of opposition O I - Gedeon Richter Ltd.
(with cited documents)

For the Opposition Division

InnoPharma Exhibit 1046.0601

EPO - Munich
37

19. Juli 2006 To the European Patent Office

Notice of Opposition to a European Patent

Tabulation Marks

for EPO use only

I. Patent opposed

Opp. No. OPPO (1)

Patent No.	1 250 138
Application No.	01 90 0186.6
Date of mention of the grant in the European Patent Bulletin (Art. 97(4), 99(1) EPC)	19.10.2005

Title of the invention:
Fulvestrant formulaltion

II. Proprietor of the Patent

first named in the patent specification: AstraZeneca AB

Opponent's or representative's reference (max. 15 spaces): M 2363 EP/OPP OREF

III. Opponent

OPPO (2)

Name: Gedeon Richter Ltd.

Address: P.O. Box 27
H-1475 Budapest 10
Hungary

State of residence or of principle place of business: Hungary

Telephone/Telex/Fax:

Multiple opponents: ☐ further opponents see additional sheet

IV. Authorisation

1. **Representative**
(Name only one representative to whom notification is to be made)

OPPO (9)

Name: Vossius & Partner

Address of place of business: European Patent Attorneys
Siebertstraße 4
81675 München
(No. 31)

Telephone/Telex/Fax: +49 89 413040 +49 89 41304111

Additional representative(s): ☐ (on additional sheet/see authorisation) OPPO (5)

2. **Employee(s)** of the opponent authorised for these opposition proceedings under act. 133(3) EPC: Name(s):

Authorisation(s)

To 1./2.

☒ not considered necessary

☐ has/have been registered under No.

☐ is/are enclosed

Zur Kasse 635 € (A)

InnoPharma Exhibit 1046.0602

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V. Opposition is filed against

— the patent as a whole ☒

— claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

— it is not new (Art. 52(1); 54 EPC) ☒

— it does not involve an inventive step (Art.52(1); 56 EPC) ☒

— patentability is excluded on other grounds, i.e. Art. ☐

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). ☐

(c) the subject-matter of the patent opposed extends beyond the content of the application/ of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). ☐

VII. Facts and arguments

(Rule 55(c) EPC)
presented in support of the opposition are submitted herewith on a separate sheet (annex 1) ☒

VIII. Other requests:

As an auxiliary request oral proceedings according to Art. 116 EPC are to be held.

InnoPharma Exhibit 1046.0603

IX. Evidence presented

for EPO use only

Enclosed = ☒

will be filed at a later date = ☐

A. **Publications:** | Publication date

1 EP 0 346 014 A1

Particular relevance (page, column, line, fig.):

2 WO 96/19997

Particular relevance (page, column, line, fig.):

3 WO 96/21440

Particular relevance (page, column, line, fig.):

4 Waterton et al., Laboratory Animal Science, vol. 43, no. 3, 1993, p. 247-251

Particular relevance (page, column, line, fig.):

5 US 4,388,307

Particular relevance (page, column, line, fig.):

6 EP 0 310 542 A1

Particular relevance (page, column, line, fig.):

7 Riffkin et al.: J. Pharm. Sci. (1964), 53(8), 891-895

Particular relevance (page, column, line, fig.):

Continued on additional sheet ☐

B. **Other evidence**

Continued on additional sheet ☐

InnoPharma Exhibit 1046.0604

X. Payment of the opposition fee is made

for EPO use only

☒ as indicated in the enclosed voucher for payment of fees and costs (EPO Form 1010)

☐

XI. List of documents:

Enclosure No.:			No. of copies	
0	☒	Form for notice of opposition	1 (min. 2)	
1	☒	facts and arguments (see VII.)	1 (min. 2)	
2		Copies of documents presented as evidence (see IX.)		
2a	☒	— Publications	1 (min. 2 of each)	
2b	☐	— Other documents	(min.2 of each)	
3	☐	Signed authorisation(s) (see IV.)		
4	☒	Voucher of payment of fees and costs (see X.)	1	
5	☐	Cheque		
6	☐	Additional sheet(s))	(min. 2 of each)	
7	☐	Other (please specify here):		

XII. Signature of opponent or representative

Place Munich

Date July 19, 2006

Dr. Paul Tauchner
European Patent Attorney

Please print name under signature. In the case of legal persons, the position which the person signing holds within the company should also be printed.

InnoPharma Exhibit 1046.0605

D1

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 346 014 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 89305563.2

(22) Date of filing: 02.06.89

(51) Int. Cl.[4]: A61K 31/565 , //(A61K31/565, 31:165)

Claims for the following Contracting States: ES + GR.

(30) Priority: 06.06.88 GB 8813353

(43) Date of publication of application: 13.12.89 Bulletin 89/50

(84) Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Applicant: IMPERIAL CHEMICAL INDUSTRIES PLC
Imperial Chemical House Millbank
London SW1P 3JF(GB)

(72) Inventor: Dukes, Michael
54 Styal Road
Wilmslow Cheshire, SK9 4AQ(GB)

(74) Representative: Slatcher, Reginald Peter et al
Imperial Chemical Industries PLC Legal Department: Patents PO Box 6
Welwyn Garden City Herts, AL7 1HD(GB)

(54) **Therapeutic product.**

(57) The invention relates to a therapeutic product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions; to a process for the manufacture of said product and to a pharmaceutical composition containing said product. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to a process for the manufacture of said composition.

EP 0 346 014 A1

InnoPharma Exhibit 1046.0606

THERAPEUTIC PRODUCT

This invention relates to a therapeutic product for use in a new method of medical treatment and, more particularly, it relates to a product comprising an oestrogen and a pure antioestrogen for use in a new method for the treatment or prophylaxis of perimenopausal or postmenopausal conditions, particularly perimenopausal or postmenopausal osteoporosis. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to the use thereof in the manufacture of a new medicament for use in the treatment or prophylaxis of perimenopausal or postmenopausal conditions.

When a female animal, particularly a human female, enters the perimenopausal stage the animal's ovaries begin to secrete less of the female sex hormones, particularly oestradiol. Symptoms in women at this stage include the following: vasomotor disturbances (hot flushes), urogenital atrophy (particularly affecting the vagina and distal urethra), psychosomatic complaints, changes in lipid metabolism and osteoporosis. The rate of decline of ovarian function and the severity of the above-mentioned symptoms are highly variable between individual women but in a substantial number of individuals the symptoms are sufficiently severe that treatment is required. Oestrogen replacement therapy has been used in women and it is generally recognised to be effective in combatting the typical perimenopausal and post-menopausal symptoms (British Medical Journal, 1987, 295, 914; American Journal of Obstet. and Gynecol., 1987, 156, 1298 and 1347). However oestrogen replacement therapy can also cause uterine hyperplasia, irregular vaginal menstruation and, in a small proportion of women, endometrial cancer (American Journal of Obstet. and Gynecol., 1987, 156, 1313).

To combat the continuous unopposed stimulation of oestrogen-responsive tissues an oestrogen and a progestogen are normally co-administered for part of each treatment period thereby causing regular vaginal menstruation. (American Journal of Obstet. and Gynecol., 1987, 156, 1304). However the continuation of menstrual periods is unattractive to many postmenopausal women and, in addition, progestogens can cause side effects, for example oedema, premenstrual irritability and breast tenderness.

Alternative therapies are therefore required.

It has recently been shown that compounds demonstrating a mixture of oestrogenic and antioestrogenic properties in warm-blooded animals, including humans, may be of use in the treatment of postmenopausal conditions (European Patent Specification No. 0178862). Particular compounds stated to have such activity include clomiphene and tamoxifen. Comprehensive reviews of the clinical usage of these compounds are available, for example a review of clomiphene by Clark et al. in Pharmacology and Therapeutics, 1982, Volume 15, pages 467 to 519, and a review of tamoxifen by Furr et al. in Pharmacology and Therapeutics, 1984, Volume 25, pages 127-205.

It has also recently been shown that a treatment regime comprising the dosing of a small amount of an oestrogen, for example oestrone sulphate or natural conjugated oestrogens, followed by the dosing of an antioestrogen, for example tamoxifen or clomiphene led to the partial inhibition of the maximum oestrogen-induced stimulation of uterine endometrial tissue (A. Kauppila et al., Gynecol. obstet. Invest., 1988, 25, 58 and Arch. Gynecol., 1983, 234, 49).

It has now been found that administration of an oestrogen and a pure antioestrogen, whether simultaneously, sequentially or separately, results in the oestrogen being selectively effective in some oestrogen-responsive tissues, for example bone, and being selectively opposed in other oestrogen-responsive tissues, for example the endometrium of the uterus, and this is the basis of the present invention.

A pure antioestrogen is a compound which possesses antioestrogenic activity and no oestrogenic activity. This may be demonstrated in rats by the effect of the compound in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when each of a pure antioestrogen and oestradiol benzoate are administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate alone. Unlike the known antioestrogens tamoxifen and clomiphene, when a pure antioestrogen is administered alone to a rat no increase in uterine weight whatsoever is observed.

It is disclosed in European Patent Specification No. 138504 that certain preferred steroidal antioestrogens are pure antioestrogens. It is also disclosed in European Patent No. 124369 that certain preferred non-steroidal antioestrogens are pure antioestrogens.

According to the present invention there is provided a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

InnoPharma Exhibit 1046.0607

In a particular product of the invention the oestrogen component of a product of the invention is oestradiol, ethinyloestradiol, oestriol, oestrone, natural conjugated oestrogens, piperazine oestrone sulphate, mestranol, chlorotrianisene, dienoestrol, stilboestrol or hexoestrol or a pharmaceutically-acceptable ester thereof.

A pharmaceutically-acceptable ester of the oestrogen component of a product of the invention is, for example, an alkyl or aryl ester each of up to 12 carbon atoms. It will be appreciated that an ester of a steroidal oestrogen may be formed at the 3-position, the 17-position or at both of these positions. It will also be appreciated that an ester may be formed at one or both of the phenolic groups in some non-steroidal oestrogens, for example stilboestrol and hexoestrol. A suitable alkyl ester of up to 12 carbon atoms is, for example, an acetate, propionate, butyrate, valerate, hexanoate, heptanoate, octanoate, cyclopentylpropionate, nonanoate, decanoate, undecanoate or dodecanoate. A suitable aryl ester of up to 12 carbon atoms is, for example, a benzoate, toluate or naphthoate. A preferred pharmaceutically-acceptable ester of the oestrogen component of a product of the invention includes, for example, oestradiol benzoate, oestradiol cyclopentylpropionate, oestradiol dipropionate, oestradiol heptanoate, oestradiol undecanoate, oestradiol valerate and stilboestrol dipropionate.

In a further particular product of the invention the pure antioestrogen is

N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl- or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;

N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-triene-7α-yl)butyl]-phenylpropionamide;

7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)triene-3,17β-diol; or

7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

In a further particular product of the invention the pure antioestrogen is a compound of the formula:-

NU-A-X-R^1

wherein NU is 6-hydroxy-2-p-hydroxyphenylnapth-1-yl and A is -$(CH_2)_{10}$-, -$(CH_2)_{11}$- or -$(CH_2)_5$-(1,4-phenylene)-$(CH_2)_2$-;

or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnapth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is -$(CH_2)_{10}$-, -$(CH_2)_{11}$- or -$(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2$-;

or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is -$(CH_2)_{10}$-, -$(CH_2)_{11}$- or -$(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2$-;

and wherein XR^1 is -CONR^{1}R^2 wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is -SR^1, -SOR^1 or -SO_2R^1 wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

In a further particular product of the invention the pure antioestrogen is

N-n-butyl-, N-n-butyl-N-methyl-, N-n-pentyl, N-(1H,1H-heptafluorobutyl)-or N-(1H,1H-heptafluorobutyl)-N-methyl-3-p-[5-(6-hydroxy-2-p-hydroxyphenylnaphth-1-yl)pentyl]phenylpropionamide;

N-methyl-N-(1H,1H-heptafluorobutyl)-p-[4-[(1RS,2RS)-6-hydroxy-2-p-hydroxphenyl-2-methyl-1,2,3,4-tetrahydronaphth-1-yl]-butyl]phenylpropionamide;

(1RS,2RS)-1-[4-[p-(2-n-hexylthioethyl)phenyl]butyl]-2-p-hydroxyphenyl-1,2,3,4-tetrahydronaphth-6-ol or the corresponding 4,4,5,5,5-pentafluoropentylthio derivative, or the corresponding hexylsulphinyl, hexylsulphonyl or pentafluoropentylsulphinyl derivatives;

2-p-hydroxyphenyl-1-[5-[p-(2-n-hexylthioethyl)phenyl]pentyl]naphth-6-ol or the corresponding hexylsulphinyl derivative; or

(1RS,2RS)-1-[4[p-(2-n-hexylthioethyl)phentyl]butyl]-2-p-hydroxyphenyl-2-methyl-1,2,3,4-tetrahydronaphth-6-ol or the corresponding 4,4,5,5,5-pentafluoropentylthio derivative, or the corresponding hexylsulphinyl or pentafluoropentylsulphinyl derivative, or the corresponding (1RS,2SR) isomers of both the hexylthio and hexylsulphinyl derivatives.

A preferred product of the invention comprises an oestrogen and a pure antioestrogen for use as stated above wherein the oestrogen is oestradiol or ethinyloestradiol, or a pharmaceutically-acceptable ester thereof, and the pure antioestrogen is 7α-[9-(4,4,5,5,5- pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol or (1RS,2RS)-2-p-hydroxyphenyl-2-methyl-1-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-1,2,3,4-tetrahydronaphth-6-ol.

A particularly preferred product of the invention comprises an oestrogen and a pure antioestrogen for use as stated above wherein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-

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oestra-1,3,5(10)-triene-3,17β-diol.

According to a further feature of the invention there is provided a process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing together said oestrogen and said pure antioestrogen.

In a further feature of the invention there is provided a process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing into admixture said oestrogen and said pure antioestrogen.

A product of the invention may be administered to a warm-blooded animal, including a human, in the form of a pharmaceutical composition. Thus according to a further feature of the present invention there is provided a pharmaceutical composition which comprises the product of the invention together with a pharmaceutically-acceptable diluent or carrier.

As mentioned above a product of the invention is useful for selective oestrogen therapy of perimenopausal or postmenopausal conditions. It will be understood that there is no absolute requirement that the oestrogen and pure antioestrogen components of the product of the invention must be dosed simultaneously. Sequential or separate use of these components may also provide selective oestrogen therapy and such use is to be understood to fall within the definition of a product of the invention. Thus it will be appreciated that a pharmaceutical composition according to the present invention includes a composition comprising an oestrogen, a pure antioestrogen and a pharmaceutically-acceptable diluent or carrier. Such a composition conveniently provides the product of the invention for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions. A pharmaceutical composition according to the present invention also includes separate compositions comprising a first composition comprising an oestrogen and a pharmaceutically-acceptable diluent or carrier, and a second composition comprising a pure antioestrogen and a pharmaceutically-acceptable diluent or carrier. Such a composition conveniently provides the product of the invention for sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, capsules, aqueous or oily suspensions, emulsions or dispersible powders or granules), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions; for example for use within a transdermal patch), for parenteral administration (for example as a sterile aqueous or oily solution or suspension for intravenous, subcutaneous, intramuscular or intravascular dosing), or as a suppository for rectal dosing or as a pessary for vaginal dosing.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as gelatin or starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

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Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, castor oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as castor oil, soya bean oil or arachis oil, or a mineral oil, such as, for example, liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

The pharmaceutical compositions may also be in the form of sterile injectable aqueous or oily suspensions, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol, in a vegetable oil (such as arachis oil, castor oil or coconut oil) or in a mineral oil (such as liquid paraffin).

Conveniently the subcutaneous or intramuscular injection of an aqueous suspension or an oily solution or suspension of a pharmaceutical composition of the invention provides a depot of the active ingredients at the injection site from which those ingredients may leach out over a period of time to provide the sustained release thereof.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

According to a further feature of the invention there is provided a process for the manufacture of a pharmaceutical composition as defined above which comprises bringing into admixture a product as defined above together with a pharmaceutically-acceptable diluent or carrier.

The invention also provides a method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering simultaneously, sequentially or separately to a warm-blooded animal an effective amount of a product as defined above. The invention also provides the use of a product as defined above for the manufacture of a new medicament for use simultaneously, sequentially or separately in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

It will be appreciated that the definition of the product of the invention and the pharmaceutical composition of the invention includes only those products or compositions which are useful in a new method for the treatment or prophylaxis of perimenopausal or postmenopausal condition. Pharmaceutical compositions comprising an oestrogen and a pure antioestrogen, together with a pharmaceutically-acceptable diluent or carrier, are novel. In European Patent Sepcifications Nos. 138504 and 124369 it is disclosed that the antioestrogenic activity of the compounds disclosed therein may be demonstrated by the co-administration of a test compound and oestradiol benzoate to an immature female rat. Antioestrogenic activity is demonstrated by antagonism of the increase in weight of the uterus of the rat which is produced when oestradiol benzoate alone is administered to said rat. It is to be noted that, during those tests, the oestradiol benzoate was given by subcutaneous injection whereas the test compound was given separately either orally or subcutaneously.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

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The pharmaceutical compositions of this feature of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the are such as, for example, those disclosed above.

This aspect of the invention also provides a process for the manufacture of a pharmaceutical composition as defined immediately above which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

This aspect of the invention also provides a method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering to a warm-blooded animal an effective amount of a pharmaceutical composition as defined immediately above. The invention also provides the use of a pharmaceutical composition as defined immediately above for the manufacture of a new medicament for use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

As stated above a product of the invention is of use in selective oestrogen therapy of perimenopausal or postmenopausal conditions. Selective oestrogen therapy may be demonstrated using the standard procedure set out below:-

a) an in vivo assay measuring the antioestrogenic activity of a compound and any oestrogenic activity possessed by that compound. This may be demonstrated in rats by the effect of the compound in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when each of a pure antioestrogen and oestradiol benzoate are administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate without the pure antioestrogen. Unlike the known antioestrogens tamoxifen and clomiphene, when a pure antioestrogen is administered alone to a rat no increase in uterine weight whatsoever is observed.

The oestrogenic activity of a compound may be demonstrated in rats by the effect of the compound when it is administered alone to said rat on the uterine weight of the animal.

b) An in vivo assay in mature rats measuring the antioestrogenic activity of a compound by the effect of the compound when dosed during a test period of 28 days in antagonising the protective effect on the animals' bone density of their endogenous oestrogens. The bone density of a group of ovariectomised rats in which endogenous oestrogen levels are much reduced serves as a control for the effect expected to be produced by a fully effective antioestrogen.

The antioestrogenic activity of the compound in mature rats can also be measured in the same assay by measuring the effect of the compound in antagonising the effect of the animals' endogenous oestrogens which serve to increase the weight of their uteri.

A comparison of the potencies of the antioestrogenic effects of a compound as measured by its effects on the animals' bone density and uterine weights allows the selectivity of the antioestrogenic effects of the compound to be measured.

Although the pharmacological properties of a product of the invention vary with the structures of the oestrogenic and antioestrogenic components and with the route of administration, in general a product of the invention comprises:-

(i) an oestrogen which possesses oestrogenic activity in the above test (a) at doses in the range, for example, 0.002-2.0 mg/kg orally or in the range, for example, 0.0001-0.1 mg/kg subcutaneously;

(ii) a pure antioestrogen which possesses antioestrogenic activity in the above tests (a) and (b) at doses in the range, for example, in test (a): ED_{50} 0.05-5 mg/kg orally or ED_{50} 0.01-1.0 mg/kg subcutaneously;

in test (b): antiuterotrophic effect:- ED_{50} < 20 mg/kg/day orally, < 2 mg/kg/day subcutaneously or intramuscularly and < 10 mg/kg/injection when dosed as an intramuscular depot injection; reduction in bone density:- ED_{50} > 20 mg/kg/day orally, > 5 mg/kg/day subcutaneously or intramuscularly and > 10 mg/kg/injection when dosed as an intramuscular depot injection.

A product of the invention is thereby seen to be surprisingly selective as the activity of the pure antioestrogen component is expressed to a high degree within uterine tissue but to a lesser degree on bone.

The size of the dose, for therapeutic or prophylatic purposes, of a product of the invention as defined above will naturally vary according to the nature and severity of the conditions presented, the age and menopausal state of the animal and the route of administration.

In general the minimum quantity of the oestrogenic component of a product of the invention as defined above will be chosen so as to provide a beneficial effect with regard to the nature and severity of the conditions presented. The quantity of the pure antioestrogenic component is then chosen to antagonise to a substantial degree the effect of the oestrogenic component on the uterine tissue. Methods of evaluating the

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condition of uterine tissue are well known to the man skilled in the art, for example, by examination of a specimen of endometrial tissue taken by, for example, suction or, for example, by way of a biopsy.

So far as the oestrogenic component of a product of the invention as defined above is concerned the size of the dose and routes of administration conventionally utilised in oestrogen replacement therapy may be used. Thus, for example, a tablet containing, for example, 0.5 to 2 mg of oestradiol, oestradiol benzoate, natural conjugated oestrogens or oestradiol valerate may be administered daily. Alternatively a tablet containing 10 to 100 µg of ethinyloestradiol may be administered daily. Alternatively the oestrogenic component may be administered by, for example, intramuscular injection utilising, for example, 1 to 10 mg of oestradiol benzoate dissolved in an oil such as ethyl oleate; for example, transdermal means utilising, for example, 10-100 µg of oestradiol contained within a transdermal patch; or, for example, vaginal application utilising, for example, daily application of 0.5 to 2 mg of natural conjugated oestrogens contained within 0.5 to 5 ml of a cream.

So far as the antioestrogenic component of a product of the invention as defined above is concerned the size of the dose is chosen such that the effect of the oestrogenic component on uterine tissue is antagonised to a substantial degree whereas the beneficial effect of the oestrogenic component on bone is substantially unopposed.Thus, for example, the antioestrogenic component may be formulated in like manner to the oestrogenic component, for example as a tablet, an oily solution suitable for intramuscular injection, within a transdermal patch, or within a cream suitable for vaginal application. The daily administration of one or more tablets containing conveniently 50 mg to 5 g, and preferably 50 mg to 500 mg, of a pure antioestrogen may be used. Preferably the pure antioestrogen may be administered by the periodic intramuscular injection of, for example, an aqueous suspension or an oily solution or suspension containing 50 mg to 5 g of the pure antioestrogen. Preferably an oily solution, for example a solution containing arachis or castor oil, an alcohol such as benzyl alcohol and 50 mg to 500 mg of the pure antioestrogen is employed. Such an injection provides a depot of the pure antioestrogen which thereafter leaches out from the injection site to provide a selective antioestrogenic effect for a period of, for example, one to six weeks.

As mentioned above a product of the invention is useful for selective oestrogen therapy of perimenopausal or postmenopausal conditions. As previously mentioned perimenopausal and postmenopausal conditions include, for example, vasomotor disturbances (hot flushes), urogenital atrophy (particularly affecting the vagina and the distal urethra), psychosomatic complaints, changes in the lipid metabolism and oesteoporosis. The selective antioestrogenic effect of the pure antioestrogenic component of a product of the invention, as demonstrated by a greater antioestrogenic effect on the uterus of a rat than on the bone of the rat, allows the beneficial effect of the oestrogenic component of the product of the invention to be selectively applied to the bone and prevents the detrimental effect of an unopposed oestrogenic effect on the uterus. The utero-selective effect of the pure antioestrogenic component of a product of the invention will allow the beneficial effect of the oestrogenic component of a product of the invention to be applied to other oestrogen-responsive tissues, for example those causing vasomotor disturbances, pyschosomatic complaints and changes in lipid metabolism.

The invention will now be illustrated in the following non-limiting Examples.

Example 1

Assay in Mature Rats of the Selective Antioestrogenic Activity of a Pure Antioestrogen

The pure antioestrogen used was (1RS,2RS)-2-p-hydroxyphenyl-2-methyl-1-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-1,2,3,4-tetrahydronaphth-6-ol.

The compound was given subcutaneously as a solution in arachis oil at doses of 2 mg/kg/day and 10 mg/kg/day to two groups of 5 mature rats for a total of 28 days. Further groups of 5 mature rats served as an untreated control group. A further group of 5 mature rats was ovariectomised to serve as another control group. At the end of the treatment period the weights of the uteri of the test and control groups of rats were determined. In addition the femurs were dissected, weighed and their volumes were determined using Archimedes Principle. The femurs were then burned and the residual ash was weighed. From these data, gross femur density and bone mineral density were calculated as follows:-

Gross Femur Density = Femur Weight/Femur Volume

Bone Mineral Density = Femur Ash Weight/Femur Volume

The results shown below in Tables I and II demonstrate that at a dose of 2 mg/kg/day subcutaneously

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the test compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri (90% inhibition of uterine weight) whereas there was no significant inhibition of either bone mineral density or of gross femur density.

TABLE I

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	382 ± 34	
Ovariectomised Controls	111 ± 14	
Test Compound at 2 mg/kg/day s.c.	135 ± 8	91%
Untreated Controls	369 ± 47	
Ovariectomised Controls	99 ± 5	
Test Compound at 10 mg/kg/day s.c.	125 ± 4	90%

TABLE II

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition	Bone Mineral Density (g/ml)	Calculated Inhibition
Untreated Controls	1.612 ± 0.010		0.742 ± 0.009	
Ovariectomised Controls	1.569 ± 0.010		0.685 ± 0.010	
Test Compound at 2 mg/kg/day s.c.	1.604 ± 0.006	19%*	0.730 ± 0.007	21% *
Untreated Controls	1.629 ± 0.014		0.766 ± 0.005	
Ovariectomised Controls	1.571 ± 0.007		0.704 ± 0.005	
Test Compound at 10 mg/kg/day s.c.	1.580 ± 0.004	84%	0.727 ± 0.005	63%

* This level of inhibition was not statistically significant.

Example 2

The experiment described in Example 1 was repeated except that the pure antioestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol. This compound was given at a series of doses as a daily intramuscular injection, the compound having been dissolved in a mixture of propylene glycol: ethanol: water: poloxamer 407. The formulation contained 25 mg of test compound, 100 mg of ethanol (96%), 100 mg of water, 20 mg of poloxamer 407 and sufficient propylene glycol to bring the solution to a volume of 1 ml.

The results shown below in Tables III and IV demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas there was no significant inhibition of gross femur density.

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TABLE III

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	302 ± 36	
Ovariectomised Controls	70 ± 1.3	
Test Compound (mg/kg)		
0.1	208 ± 17	41
0.3	174 ± 16	55
1	94 ± 9	90
3	103 ± 2	86

TABLE IV

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Untreated Controls	1.523 ± 0.008	
Ovariectomised Controls	1.491 ± 0.006	
Test Compound at (mg/kg)		
0.1	1.528 ± 0.005	0%
0.3	1.528 ± 0.008	0%
1	1.532 ± 0.005	0%
3	1.533 ± 0.005	0%

Example 3

The pure antioestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

Each of a series of selected doses of this compound was dissolved in a mixture of castor oil and benzyl alcohol and given by intramuscular injection to a group of 5 mature rats. The formulation contained 50 mg of the test compound, 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. In each case a second dose was administered two weeks after the first dose. Two weeks after the second dose the weights of the uteri of the test groups of rats were determined. In addition the femurs were dissected and analysed for Gross Femur Density as in Example 1.

A further group of rats, given two injections of castor oil separated by a two week period, served as an intact control group. A further group of rats was ovariectomised to serve as another control group.

The results shown below in Tables V and VI demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas at the two higher test doses there was no significant inhibition of gross femur density.

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TABLE V

Treatment	Uterine Weight (mg)	Calculated Inhibition
Intact Controls	318 ± 31	
Ovariectomised Controls	76 ± 4	
Test Compound (mg/rat/dose)		
0.75	202 ± 23	48
1.25	180 ± 15	57
2.5	123 ± 12	81

TABLE VI

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Intact Controls	1.584 ± 0.007	
Ovariectomised Controls	1.521 ± 0.005	
Test Compound (mg/rat/dose)		
0.75	1.562 ± 0.004	35
1.25	1.576 ± 0.004	13*
2.5	1.569 ± 0.007	23*

* This level of inhibition was not statistically significant.

Claims

1. A product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

2. A product as claimed in claim 1 wherein the pure antioestrogen is
N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl- or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;
N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)butyl]-phenylpropionamide;
7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)-triene-3,17β-diol; or
7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

3. A product as claimed in claim 1 wherein the pure antioestrogen is a compound of the formula:-
NU-A-X-R^1
wherein NU is 6-hydroxy-2-p-hydroxyphenylnaphth-1-yl and A is -$(CH_2)_{10}$-, -$(CH_2)_{11}$- or -$(CH_2)_3$-(1,4-phenylene)-$(CH_2)_2$-;
or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is -$(CH_2)_{10}$-, -$(CH_2)_{11}$-or -$(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2$-;
or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is -$(CH_2)_{10}$-, -$(CH_2)_{11}$-or-$(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2$-;

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and wherein XR^1 is $-CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $-SR^1$, SOR^1 or $-SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

4. A product as claimed in claim 1 wherein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)-nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

5. A process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing together said oestrogen and said pure antioestrogen.

6. A pharmaceutical composition comprising a product as claimed in any one of claims 1 to 4 together with a pharmaceutically-acceptable diluent or carrier.

7. The use of a product as claimed in any one of claims 1 to 4 for the manufacture of a new medicament for use simultaneously, sequentially or separately in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

8. A pharmaceutical composition comprising an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

9. A process for the manufacture of a pharmaceutical composition as claimed in claim 8 which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

10. The use of a pharmaceutical composition as claimed in claim 8 for the manufacture of a new medicament for use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

Claims for the following Contracting States: GR, ES.

1. A process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal condition, which process is characterised by bringing together said oestrogen and said pure antioestrogen.

2. A process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process is characterised by bringing into admixture said oestrogen and said pure antioestrogen.

3. A process as claimed in claim 1 or claim 2 wherein the pure antioestrogen is
N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl- or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;
N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)butyl]-phenylpropionamide;
7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)-triene-3,17β-diol; or
7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

4. A process as claimed in claim 1 or 2 wherein the pure antioestrogen is a compound of the formula:-
NU-A-X-R^1
wherein NU is 6-hydroxy-2-p-hydroxyphenylnaphth-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$, or $-(CH_2)_5-$(1,4-phenylene)$-(CH_2)_2-$;
or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$or $-(CH_2)_4-$(1,4-phenylene)$-(CH_2)_2-$;
or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$or $-(CH_2)_4-$(1,4-phenylene)$-(CH_2)_2-$;
and wherein XR^1 is $-CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $-SR^1$, SOR^1 or $-SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

5. A process as claimed in claim 1 or claim 2 wherein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

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6. A process for the manufacture of a pharmaceutical composition which comprises bringing into admixture a product as defined in any one of claims 1 to 5 together with a pharmaceutically-acceptable diluent or carrier.

7. A process for the manufacture of a pharmaceutical composition which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

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EUROPEAN SEARCH REPORT

Application Number

EP 89 30 5563

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,X	EP-A-0 124 369 (IMPERIAL CHEMICAL INDUSTRIES PLC) * Page 15, lines 4-6 * ---	1-10	A 61 K 31/565// (A 61 K 31/565 A 61 K 31:165)
D,X	EP-A-0 138 504 (IMPERIAL CHEMICAL INDUSTRIES PLC) * Page 14, lines 2-5 * ---	1-10	
A	CHEMICAL ABSTRACTS, vol. 109, no. 3, 18th July 1988, page 73, abstract no. 17199p, Columbus, Ohio, US; N. FROEHLANDER et al.: "Growth hormone and somatomedin C during post-menopausal replacement therapy with estrogen alone and in combination with an antiestrogen", & MATURITAS 1988, 9(4), 297-302 * Abstract * -----	1-10	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	20-09-1989	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

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D2

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Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: COMPOUNDS WITH PROGESTERONE-ANTAGONISTIC AND ANTI-OESTROGEN PROPERTIES INTENDED FOR COMBINED USE IN FEMALE CONTRACEPTION

(54) Bezeichnung: PROGESTERONANTAGONISTISCH- UND ANTIÖSTROGEN WIRKSAME VERBINDUNGEN ZUR GEMEINSAMEN VERWENDUNG FÜR DIE WEIBLICHE KONTRAZEPTION

(57) Abstract

The invention concerns the use of at least one compound with progesterone-antagonistic properties and at least one compound with anti-oestrogen properties, each in a dose which would not in itself inhibit ovulation, in a single dosing unit, in order to prepare medicaments female contraception.

(57) Zusammenfassung

Die vorliegende Erfindung beschreibt die Verwendung mindestens einer Verbindung mit progesteronantagonistischer (PA) und mindestens einer Verbindung mit antiöstrogener (AÖ) Wirkung, jeweils in nicht-ovulationshemmender Dosierung in einer einzelnen Dosiseinheit, zur Herstellung von Arzneimitteln zur weiblichen Kontrazeption.

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LEDIGLICH ZUR INFORMATION

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Progesteronantagonistisch- und antiöstrogen wirksame Verbindungen zur gemeinsamen Verwendung für die weibliche Kontrazeption

Die vorliegende Erfindung betrifft die Verwendung mindestens einer Verbindung mit progesteronantagonistischer (PA) und mindestens einer Verbindung mit antiöstrogener (AÖ) Wirkung, jeweils in nicht-ovulationshemmender Dosierung in einer einzelnen Dosiseinheit, zur Herstellung von Arzneimitteln zur weiblichen Kontrazeption.

Die erfindungsgemäß hergestellten Arzneimittel entfalten ihre empfängnisverhütende Wirkung auf der Basis der Rezeptivitätshemmung, indem eine Einnistung einer befruchteten Eizelle in die Uterusschleimhaut verhindert wird, ohne daß die Ovulation bzw. der Zyklus gestört wird.

Bereits auf der ganzen Welt hat sich der Gebrauch von oralen Kontrazeptiva zu einem gesellschaftlichen Faktor entwickelt, der nicht mehr wegzudenken ist. Besonders unter dem Aspekt der sich nach wie vor rasant entwickelnden Weltbevölkerung ist eine Weiterentwicklung der bislang bewährten Methoden zur Fertilitätskontrolle unbedingt erforderlich.

Der Einsatz von kompetitiven Progesteronantagonisten in der weiblichen Fertilitätskontrolle wird sowohl bei diversen Tierspezies als auch am Menschen schon seit einigen Jahren diskutiert, wie den nachfolgend aufgeführten Publikationen entnommen werden kann, wobei insbesondere der Einsatz von RU 486 (11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(1-propinyl)estra-4,9-dien-3-on; EP-A-0057115) in diesem Zusammenhang aufgeführt wurde:

Collins et al., Blockade of the spontaneous mid-cycle gonadotropin surge in monkeys by RU 486; A progesterone antagonist or agonist. J. Cli. Metab., 63:1270-1276 (1986);

Croxatto, H.B., Salvatierra 1990 Cyclic use of antigestagens for fertility control. IIIrd International Symposium on Contraception, Heidelberg, June 19-23, 1990;

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Danford et al., Contraceptive potential of RU 486 by ovulation inhibition. III. Preliminary observations on once weekly administration. Contraception 40: 195-200 (1989);

Kekkonen et al., Lähteoenmäki P 1990 Interference with ovulation by sequential treatment with the antiprogesterone RU 486 and synthetic progestin. Fertil Steril [Fertile Sterile] 53: 4747 (1990);

Puri et al., Gonadal and pituitary responses to progesterone antagonist ZK 98 299 during the follicular phase of the menstral cycle in bonnet monkeys. Contraception 39(2): 227-243 (1989);

Puri et al., Contraceptive potential of a progesterone antagonist ZK 98 734 ((Z)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estra-4,9-dien-3-on): Effect on folliculogenesis, ovulation and corpus luteum function in bonnet monkeys. In Moudgal et al., (eds) (1990).

Der kontrazeptive Effekt eines Progesteronantagonisten ist einerseits von der ovulationshemmenden Wirkung anderseits von direkten Effekten auf das Endometrium bedingt.

Hierbei ist zu erwähnen, daß diejeniege Dosierung eines kompetitiven Progesteronantagonisten, welche einen ovulationsinhibierenden Effekt hervorruft, sehr stark von dem jeweiligen kompetitiven Progesteronantagonisten abhängt:

Bei Progesteronantagonisten vom RU 486-Typ handelt sich um wenig-dissozierte Verbindungen mit einer stark ausgeprägten ovulationshemmenden Wirkung.

Bei Progesteronantagonisten vom Onapriston-Typ handelt sich um endometriumsspezifische (stark-dissozierte) Verbindungen, die die Ovulation erst bei hohen Dosierungen hemmen. Eine chronische Behandlung mit derartigen Progesteronantagonisten führt zur Wachstumsretardierung des Endometriums, wobei der ovarielle und menstruelle Zyklus nicht gestört wird. Im Endometrium kommt es zur Degeneration von endometrialen Drüsen und zur Verdichtung des Stromas, so daß die Implantation eines befruchteten Eies verhindert wird (Hemmung der Rezeptivität).

Die Klasse von 11β-Aryl- oder 11β,19-Arylen-substituierten Steroiden wird pharmakologisch nach ihrem stark progesteron- bzw. glukocortikoid-antagonistischen Effekt unterschieden. So kann RU 468 einerseits für einen therapeutisch induzierten Schwangerschaftsabbruch (die humane abortive Dosis in Kombination mit einem

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Prostaglandin liegt bei 200-600 mg; EP-A 0 139 608), andererseits aber auch über seine antagonistische Wirkung am Glucocortikoid-Rezeptor zur Therapie des Cushing-Syndroms eingesetzt werden.

Eine andere Möglichkeit der Verwendung kompetitiver Progesteronantagonisten für die weibliche Fertilitätskontrolle, die sogenannte "LH+2"-Behandlung, wird von Swahn et al. [The effect of RU 486 administration during the early luteal phase on bleeding pattern, hormonal parameters and endometrium, Human Reproduction 5(4): 402-408 (1990)] vorgeschlagen, indem 2 Tage nach dem Anstieg des luteinisierenden Hormons (LH) im Menstruationszyklus der Frau (das ist im allg. am Tag 14, 15 oder 16) einmalig eine ovulationshemmende Dosiseinheit RU 486 verabreicht wird (luteale Kontrazeption). Eine Behandlung mit RU 486 in diesem Abschnitt des Menstruationszyklus führt nicht zur Störung des Zyklus. Applikation von RU 486 in anderen Phasen des Zyklus führt bei Dosierungen oberhalb von 1 mg/Tag entweder zur Amenorrhoe bzw. zu einer Abbruchblutung. Allerdings besitzt dieses Verfahren keine praktische Bedeutung, da die einfache und genaue zeitliche Bestimmung des LH-Peaks immer noch ein Problem darstellt.

Von Glasier et al. [Mifepristone (RU 486) compared with high-dose estrogen and progestogen for emergency postcoital contraception, The New England J. of Med. 327: 1041-1044 (1992)] wird auch die Verwendung von RU 486 für die postkoitale Kontrazeption (emergency postcoital contraception) beschrieben. Die Methode zeigt neben einer hohen Wirksamkeit ein geringes Ausmaß von Nebenwirkungen. Bei einem hohen Prozentsatz der Frauen dieser Studie trat eine Verlängerung des Zyklus auf. Dieser Effekt ist primär auf die antiovulatorische Wirkung von RU 486 zurückzuführen.

Des weiteren wird in WO 93/23020 beschrieben, daß kompetitive Progesteronantagonisten in einer Dosis, die sowohl unterhalb der abortiven als auch ovulationsinhibierenden Dosierung liegt, zur weiblichen Fertilitätskontrolle verwendet werden können. Es handelt sich hier um eine im allgemeinen wöchentliche, bzw. mehrfache und damit regelmäßige Applikation.

Ebenso beschreibt die EP-A 0 219 447, welche Effekte die tägliche Gabe eines Progesteronantagonisten während der follikulären, bzw. optional auch der lutealen Phase des weiblichen Zyklus in einem Zeitraum von bis zu 4 Tagen in einer Dosierung

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von 10-200 mg bezüglich des endometrialen Differenzierungszustandes auslöst. Die hierbei resultierenden Veränderungen am Endometrium werden hinsichtlich des Nidationszeitpunktes für die in-vitro-Fertilisation genutzt.

Von Batista et al. [Daily administration of the progesterone antagonist RU 486 prevents implantation in the cycling guinea pig. Am. J. Obstet. Gynecol. 165: 82-86 (1991)] wird auch die Verwendung von RU 486 für die weibliche Fertilitätskontrolle beschrieben, welche durch tägliche Einnahme, präkoital und den gesamten weiteren Zyklus hindurch, in einer ovulationshemmenden Dosis die Nidation beim Meerschweinchen verhindert.

Von Kawano et al. [Effect of RU 486 on Glycogen Metabolism in Endometrium. Acta Obstetrica et Gynaecologica Japonica, 41: 1507-1511, (1989)] wird am Rattenmodell der Einfluß von RU 486 in einer Dosierung von 30 mg/kg Körpergewicht auf den endometrialen Glykogen-Metabolismus beschrieben, so daß eine erfolgreiche Eiimplantation gestört wird. Die Applikation erfolgt allerdings am Tag 2 oder 4 der Schwangerschaft.

Die hormonelle Steuerung der Implantation ist speziesabhängig. Bei allen bisher untersuchten Säugetieren ist die Anwesenheit des ovariellen Progesterons für eine erfolgreiche Implantation notwendig. Bei postkoital ovariektomierten Ratten und Mäusen, die mit Progestron substituiert werden, kommt es allerdings ohne Östrogengabe zu keiner Implantation (Finn CA, Porter DG [1975] Implantation of ova [Chapter 6] and The control of implantation and the decidual reaction [Chapter 8]; In Finn CA and Porter [eds] The Uterus, Elek Science, London, pp 57-73; 86-95). Wird bei diesen Tierspezies Östrogen injiziert, kommt es sofort zur Implantation der Blastocyste (delayed implantation model). Diese Beobachungen deuten darauf hin, daß das ovarielle Östrogen bei Anwesenheit des Progesterons die Implantation bei Nagetieren induziert. Es war bereits bekannt, daß beim Meerschweinchen und Primaten die ovariellen Östrogene für die Implantation nicht essentiel sind. Bei Meerschweinchen, die nach Anpaarung ovariektomiert wurden, findet die Implantation nur nach einer Progesteronsubstitution (ohne zusätzlicher Östrogenbehandlung) statt (Deansley R [1972] Retarded embryonic development and pregnancy termination in ovariectomized guinea pigs: progesterone deficiency and decidual collapse; J Reprod Fert [1972] 28:241-247).

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Sowohl Antiöstrogene als auch Östrogene in hoher Dosierung hemmen die Implantation bei Ratten und Mäusen (Martin L, Cox RJ, Emmens CW [1963] Further studies in the effects of estrogens and antiestrogens on early pregnancy in mice. J Reprod Fertil 5:239-247; Singh MM Kamboj VP [1992] Fetal resoption in rats treated with an antiestrogen in relation to luteal phase nidatory estrogen secretion. Acta endocrinol 126:444-50). Die implantationshemmende Wirkung von Antiöstrogenen mit östrogenen Partialwirkungen (Nafoxidine, Centchroman, Tamoxifen) wurde auch beim Meerschweinchen beschrieben (Wisel MS, Datta JK, Saxena RN [1994] Int J Fertil 39:156-163). Es ist unklar, ob die implantationshemmende Wirkung der oben genannten Antiöstrogene auf die antagonistische oder agonistische Wirkung zurückzuführen ist, da auch hochdosierte Östrogene die Implantation beim Meerschweinchen verhindern.

Die Verwendung von Östrogenantagonisten (Centchroman) zur Kontrazeption beim Menschen ist ebenfalls beschrieben (Nittyanand S, Kamboj VP [1992] Centchroman: contraceptive efficacy and safety profile. International Conference on Fertility Regulation, November 5-8, 1992 Bombay, India, Programme and abstracts). Allerdings treten bei wirksamen Dosierungen unerwünschte Nebenwirkungen vor, die auf die systemische Wirkung der Östrogenantagonisten zurückzuführen sind. Die Östrogendeprivation, die nach einer Langzeitbehandlung mit einem Antiöstrogen auftreten kann, limitiert zumindest deren regelmäßige Anwendung zur Kontrazeption.

Schließlich geht aus der DE-A 42 13 005 die Verwendung von Aromatasehemmern zur Empfängnisverhütung bei weiblichen Primaten im fortpflanzungsfähigen Alter in einer Dosierung, bei der der menstruelle Zyklus des weiblichen Primaten im wesentlichen unbeeinflußt bleibt, hervor. Aromatasehemmer blockieren die Biosynthese von Estrgenen aus deren metabolischen Vorstufen. Die Absoluthöhe der für die kontrazeptive Wirkung erforderlichen Tagesdosen hängt dabei ganz von der Art des verwendeten Aromatasehemmers ab. Für hochaktive Aromatasehemmer liegen die Tagesdosen in der Regel zwischen etwa 0,05 bis etwa 30 mg. Bei weniger aktiven Aromatasehemmern können die Tagesdosen auch höher liegen.

Der vorliegenden Erfindung liegt die Aufgabe zugrunde, ein Präparat für die endometriale Kontrazeption bereitzustellen (Hemmung der endometrialen Rezeptivität, postkoitale Anwendung, "Bedarfspille"), welches die oben genannte unerwünschte Nebenwirkung nicht zeigt und gleichzeiting eine höhere kontrazeptive

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Sicherheit aufweist als die getrennte Applikation der entsprechenden Einzelkomponenten.

Unter "Bedarfspille" soll ein oral zu verabreichendes Arzneimittel verstanden werden, welches bei vorzugsweise einmaliger und praekoitaler bedarfsweiser Anwendung eine Konzeption verhindert. Ein derartiges Mittel, hergestellt unter ausschließlicher Verwendung eines kompetitiven Progesteronantagonisten, ist in der nicht veröffentlichten deutschen Patentanmeldung P 44 38 820.9 beschrieben.

Diese Aufgabe wird dadurch gelöst, daß mindestens eine Verbindung mit progesteronantagonistischer (PA) und mindestens eine Verbindung mit antiöstrogener (AÖ) Wirkung, jeweils in nicht-ovulationshemmender Dosierung in einer einzelnen Dosiseinheit, gemeinsam zur Herstellung von Arzneimitteln zur weiblichen Kontrazeption verwendet werden.

Es wurde nunmehr gefunden, daß die Kombination eines Progesteronantagonisten und Antiöstrogens synergistisch die Endometriumsproliferation und -differenzierung hemmt, so daß der antifertile Effekt der Einzelkomponenten bei entsprechender Dosierung in der Kombination entweder verstärkt wird oder zur Erzielung eines mit den Einzelkomponenten bei deren separaten Anwendung vergleichbaren Effektes die Einzelkomponenten in der Kombination entsprechend niedriger dosiert werden können.

Mittel, enthaltend mindestens eine Verbindung mit antigestagener und mindestens eine Verbindung mit antiöstrogener Wirkung, insbesondere zur Geburtseinleitung und zum Schwangerschaftsabbruch sowie zur Behandlung gynäkologischer Störungen sowie die Verwendung mindestens einer Verbindung mit antigestagener und mindestens einer Verbindung mit antiöstrogener Wirkung zur Herstellung von Arzneimitteln für die angegebenen Indikationen, sind bereits Gegenstand der EP-A 0 310 541.

Pharmazeutische Zusammensetzungen zur postkoitalen Fertilitätskontrolle, die einen kompetitiven Progesteronantagonisten (Antigestagen) sowie einen Progesteron- und Östrogensyntheseblocker enthalten, sind bereits im US-Patent 4,670,426 beschrieben. Als typische Vertreter für den zu verwendenden kompetitiven Progesteronantagonisten sind Fluocinolonacetonid, Triamcinolonacetonid, Steroide mit einem zyklischen 16,17-Acetal mit Aceton und 11β-[4-(Dimethylamino)phenyl]-17β-

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hydroxy-17α-(1-propinyl)estra-4,9-dien-3-on (RU 38 486) und äquivalente Derivate erwähnt. Der typische Gehalt liegt dabei zwischen 20 und 50 mg. Als Beispiele für den Progesteron- und Östrogensyntheseblocker sind Aminoglutethimid, 4β,17α-Dimethyl-17β-hydroxy-3-oxo-4α,5-epoxy-5α-androstan-2α-carbonitril, 20,25-Diazocholesterol und Verbindungen mit äquivalenter Aktivität angeführt und zwar in einer Dosis von 300 bis 1000 mg. Die Anwendung der Zusammensetzung hat gemäß US-Patent 4,670,426 möglichst früh innerhalb der ersten Woche nach dem Geschlechtsverkehr über einen Zeitraum von 3 Tagen zu erfolgen; am besten sollte die Behandlung 2 bis 6 Tage fortgesetzt werden. Die Verhinderung der Nidation und somit einer Schwangerschaft wird durch den synergistischen Effekt bei der gemeinsamen Anwendung der beiden Bestandteile der Zusammensetzung bewirkt, und zwar mit einer Erfolgsrate in der Größenordnung von 90% oder mehr.

Es wurde nunmehr gefunden, daß neben Antigestagenen (kompetitiven Progesteronantagonisten) auch reine Östrogenantagonisten, wie 7α-[9-[(4,4,5,5,5-Pentafluorpentyl)sulfinyl]nonyl]estra-1,3,5(10)-trien-3,17β-diol (ICI 182780), die Implantation beim Meerschweinchen hemmen. Dieser Befund deutet darauf hin, daß beim Meerschweinchen, anders als bisher angenommen, auch Östrogene eine wichtige Rolle bei der Implantation spielen.

Weiter wurde gefunden, daß beim Meerschweinchen überraschenderweise eine kombinierte Behandlung mit Progesteronantagonisten und Antiöstrogenen während der Periimplantationsphase (Tag 1-7 post coitum) eine synergistische Wirkung aufweisen. Diese Beobachtungen deuten darauf hin, daß bei dieser Spezies die Östrogene in der Blastozyste gebildet werden. Eine ähnliche Situation kann beim Menschen existieren.

Die wesentlichen Vorteile der vorliegenden Erfindung liegen nicht zuletzt in der niedrigen Dosierung der Wirkstoffe begründet, einerseits durch die mögliche Verringerung der bei einer Monotherapie erforderlichen wirksamen Mengen durch den synergistischen Effekt, andererseits durch die Verwendung niedrigerer, nicht-ovulationsinhibierender Dosierungen. So wird der weibliche Menstruationszyklus in keiner Weise in seiner Zyklizität beeinträchtigt (wie durch ovulationshemmende Substanzen wie RU 486 verursacht) und der Organismus nicht durch unnötig hohe Mengen des kompetitiven Progesteronantagonisten bzw. des Antiöstrogens belastet. Die Verwendung einer solchen Progesteronantagonisten/Antiöstrogen-Kombination

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bietet eine sichere Empfängnisverhütung, d.h. die regelmäßige Einnahme eines derartigen Medikamentes (täglich, regelmäßig alle 3 bis 7 Tage) verhindert die Einnistung der Blastozyste ohne Beeinflußung des Zyklus. Ferner wird die kontrazeptive Sicherheit nach einer einmaligen, bedarfsorientierten präkoitalen Einahme unabhängig von dem Einnahmetag im Zyklus ("Bedarfspille") bzw. nach einer postkoitalen Behandlung erhöht.
Durch die Dosisreduktion des Antiöstrogens ist nicht mit einer Östrogendeprivation zu rechnen. Es kann so eine endometriumselektive Wirkung des Antiöstrogens erreicht und eine ungünstige Wirkung aufgrund einer Östrogendeprivation an anderen Organen, beispielsweise am Knochen, vermieden werden.

Das Gewichtsverhältnis beider Komponenten in dem neuen Arzneimittel kann dabei in weiten Grenzen variiert werden. So können sowohl gleiche Mengen PA und AÖ als auch ein Überschuß einer der beiden Komponenten eingesetzt werden. PA und AÖ werden gemeinsam, getrennt, gleichzeitig in einem Gewichtsverhältnis von im wesentlichen 50:1 bis 1:50, vorzugsweise 25:1 bis 1:25, und insbesondere 10:1 bis 1:10 verwendet. Die gleichzeitige Gabe ist bevorzugt. Vorzugsweise können PA und AÖ kombiniert in einer Dosiseinheit appliziert werden.

Die beiden Komponenten können einmal täglich oder intermittierend alle 3-6 Tage über den gesamten Zyklus appliziert werden. Sie können auch einmalig präkoital (nach Bedarf; "Bedarfs-Pille") unabhängig vom Zeitpunkt des Menstruationszyklus oder postkoital angewandt werden. Bei der präkoitalen Anwendung wird der Progesteronantagonist höher dosiert, allerdings unterhalb der ovulationshemmenden Dosierung.

Als kompetitive Progesteronantagonisten kommen alle Verbindungen in Frage, die die Wirkung des Progesterons am Gestagenrezeptor (Progesteronrezeptor) kompetitiv blockieren und dabei keine eigene gestagene Aktivität zeigen; die Blockade kann durch die verabreichte Substanz selbst oder durch deren Metaboliten bewirkt werden.

Bei den kompetitiven Progesteronantagonisten handelt sich gemäß vorliegender Erfindung vorzugsweise um endometriumsspezifische (dissozierte) Verbindungen die höchstenfalls eine schwache antiovulatorische Aktivität aufweisen. Es können auch nicht-dissozierte Progesteronantagonisten angewandt werden, wobei dann deren

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Dosierung unterhalb der ovulationsinhibierenden Dosis liegt. Beispielsweise kommen folgende Steroide infrage:

11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(1-propinyl)estra-4,9-dien-3-on (RU 38 486),
11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(1-propinyl)-18a-homoestra-4,9-dien-3-on und
11β-[4-(Dimethylamino)phenyl]-17aβ-hydroxy-17aα-(1-propinyl)-17a-homoestra-4,9,16-trien-3-on (alle EP-A 0 057 115),
17α-Ethinyl-17β-hydroxy-11β-(4-methoxyphenyl)estra-4,9-dien-3-on (Steroids 37 (1981), 361-382),
11β-(4-Acetylphenyl)-17β-hydroxy-17α-(1-propinyl)estra-4,9-dien-3-on (EP-A 0 190 759),
4',5'-Dihydro-11β-[4-(dimethylamino)phenyl]-6β-methylspiro[estra-4,9-dien-17β,2'(3'*H*)-furan]-3-on
4',5'-Dihydro-11β-[4-(dimethylamino)phenyl]-7β-methylspiro[estra-4,9-dien-17β,2'(3'*H*)-furan]-3-on
11β-(4-Acetylphenyl)-19,24-dinor-17,23-epoxy-17α-chola-4,9,20-trien-3-on (alle US-A 4,386,085)
sowie
die in der EP-A 0 277 676 beschriebenen 11ß-Aryl-14ß-estradiene und -triene, die 19,11ß-überbrückten Steroide, die Gegenstand der EP-A-0 283 428 sind, die aus der EP-A-0 289 073 hervorgehenden 11ß-Aryl-6-alkyl (bzw. 6-Alkenyl oder 6-alkinyl)-estradiene und -pregnadiene und die aus der EP-A-0 321 010 bekannten 11ß-Aryl-7-methyl (bzw. 7-ethyl)-estradiene sowie die 10ß-H-Steroide der EP-A-0 404 283, beispielsweise (*Z*)-11β-[4-(Dimethylamino)phenyl]-17α-(3-hydroxy-1-propenyl)estr-4-en-17β-ol.

Weiterhin seien als typische Vertreter erfindungsgemäß zu verwendender, kompetitiver Progesteronantagonisten beispielsweise genannt:
11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on (EP-A-0 129 499);
(*Z*)-11β-(4-Acetylphenyl)-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estra-4,9-dien-3-on (EP-A-0 190 759);
(*Z*)-6'-(4-Cyanphenyl)-9,11α-dihydro-17β-hydroxy-17α-(3-hydroxy-1-propenyl)-4'*H*-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-on und

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(*Z*)-9,11α-Dihydro-17β-hydroxy-17α-(3-hydroxy-1-propenyl)-6'-(3-pyridinyl)-4'*H*-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-on
17α-Hydroxy-17β-(3-hydroxypropyl)-11β-[4-(1-methylethenyl)phenyl]-13α-estra-4,9-dien-3-on (**ZK 131 535**)
11β-[4-(3-Furanyl)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on (**ZK 135 695**)
(*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estr-4-en-3-on
(*E*)-11β-[4-[[(Acetyloxy)imino]methyl]phenyl]-17β-methoxy-17α-(methoxymethyl)estra-4,9-dien-3-on
(*E*)-11β-[4-[[[(Ethoxycarbonyl)oxy]imino]methyl]phenyl]-17β-methoxy-17α-(methoxymethyl)estra-4,9-dien-3-on

Bei den letztgenannten PAs handelt es sich um solche vom dissoziierten Typ, bei denen bei einer bestimmten Schwellendosis Veränderungen des Endometriums beobachtet werden, während die Ovulation (zentrale Wirkung) nicht gehemmt wird. Der Quotient aus ovulationshemmender und abortiver Dosis (Dissoziationsfaktor) kann als ein Maß für die Dissoziation dienen. Dissoziierte PAs sind im Rahmen vorliegender Erfindung bevorzugt.

Die Aufzählung der PAs ist nicht abschließend; auch andere in den genannten Veröffentlichungen beschriebene kompetitive Progesteronantagonisten sowie solche aus hier nicht genannten Veröffentlichungen sind geeignet. Neuerdings sind auch nicht-steroidale, am Progesteronrezeptor als Antagonisten wirksame Verbindungen bekannt geworden (WO-A 93/21145), die für die Zwecke der vorliegenden Erfindung verwendet werden können.

Die kompetitiven Progesteronantagonisten können zum Beispiel lokal, topisch, enteral, transdermal oder parenteral appliziert werden. Für die bevorzugte orale Applikation kommen insbesondere Tabletten, Dragèes, Kapseln, Pillen, Suspensionen oder Lösungen in Frage, die in üblicher Weise mit den in der Galenik gebräuchlichen Zusätzen und Trägersubstanzen hergestellt werden können. Für die lokale oder topische Anwendung kommen beispielsweise Vaginalzäpfchen, Vaginalgels, Implantate, Vaginalringe, intrauterine Freisetzungssysteme (IUDs) oder transdermale Systeme wie Hautpflaster in Frage.

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Eine Dosierungseinheit enthält etwa 0,25 bis 50 mg 11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on oder eine biologisch äquivalente Menge eines anderen kompetitiven Progesteronantagonisten.
Wirkäquivalente Mengen werden im Niditationshemmtest am Meerschweinchen (Behandlung Tag 1-7 post coitum) ermittelt.

Erfolgt die Applikation des erfindungsgemäß hergestellten pharmazeutischen Mittels durch ein Implantat, einen Vaginalring, ein IUD oder ein transdermales System, so müssen diese Applikationssysteme derart ausgebildet sein, daß die durch sie täglich freigesetzte Dosis des kompetitiven Progesteronantagonisten in diesem Bereich von 0,25 bis 50 mg liegt.

Die erfindungsgemäß zu applizierende Dosis eines kompetitiven Progesteronantagonisten kann im nicht-ovulationshemmenden sowie nicht-abortauslösenden Dosisbereich des betreffenden Progesteronantagonisten liegen.

Als antiöstrogen wirkende Verbindungen kommen erfindungsgemäß in erster Linie Östrogenantagonisten (kompetitive Antiöstrogene) infrage. Östrogenantagonisten gemäß vorliegender Erfindung können sowohl von Steroiden abgeleitet oder nicht-steroidale Verbindungen sein. Unter Östrogenantagonisten gemäß vorliegender Erfindung sollen nur solche Verbindungen verstanden werden, die möglichst selektiv wirken, d.h. die im wesentlichen nur die Wirkung von Östrogenen hemmen und/oder deren Konzentration senken.
Die Östrogenantagonisten wirken, indem sie Östrogen vom Rezeptor verdrängen.

Als Östrogenantagonisten kommen alle gebräuchlichen Verbindungen mit kompetitiver antiöstrogener Wirkung am Rezeptor in Betracht. Sie können etwa in gleichen Mengen eingesetzt werden wie die bereits im Handel befindlichen Östrogenantagonisten, das heißt die tägliche Dosis beträgt etwa 5-100 mg für Tamoxifen oder die biologisch äquivalente Menge eines anderen Östrogenantagonisten.

Als nicht-steroidale Östrogenantagonisten seien beispielsweise genannt:
(*Z*)-*N*,*N*-Dimethyl-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]ethanamin (Tamoxifen),
1-[2-[4-(3,4-Dihydro-6-methoxy-2-phenyl-1-naphthalinyl)phenoxy]ethyl]pyrrolidin-hydrochlorid (Nafoxidin),

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α-[4-[2-(Diethylamino)ethoxy]phenyl]-4-methoxy-α-phenylbenzenethanol (Mer-25), [6-Hydroxy-2-(4-hydroxyphenyl)-3-benzothienyl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanon-hydrochlorid (Raloxifen), (3*R-trans*)-3,4-Dihydro-2,2-dimethyl-7-methoxy-3-phenyl-4-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-2*H*-1-benzopyran (Centchroman),

weiter Verbindungen vom 1,1,2-Triphenylbut-1-en-Typ, insbesondere das 3,3'-(2-Phenyl-1-buten-1-yliden)bis[phenol]-diacetat [J. Cancer Res. Clin. Oncol., (1986), 112, S. 119-124];

ferner kommen als steroidale Östrogenantagonisten beispielsweise infrage:
17α-Ethinyl-11α-methylestra-1,3,5(10)-trien-3,17β-diol und 16β-Ethylestra-1,3,5(10)-trien-3,17β-diol,
N-Butyl-11-(3,17β-dihydroxyestra-1,3,5(10)-trien-7α-yl)-*N*-methylundecansäureamid und 7α-[9-[(4,4,5,5,5-Pentafluorpentyl)sulfinyl]nonyl]estra-1,3,5(10)-trien-3,17β-diol.

Erfindungsgemäß bevorzugt sind in jedem Fall solche Östrogenantagonisten, die besonders stark und möglichst selektiv am Endometrium wirken (beispielsweise Tamoxifen, Nafoxidin, 7α-[9-[(4,4,5,5,5-Pentafluorpentyl)sulfinyl]nonyl]estra-1,3,5(10)-trien-3,17β-diol).
Die Schwellendosis für endometriumselektive Wirkung wird an ovarektomierten, estradiolsubstituierten Ratten ermittelt. Als Parameter dient die mitotische Aktivität (Proliferationsmarker: PCNA). Als Schwellendosis gilt diejeniege Menge des Östrogenantagonisten, bei der nur ein Effekt am Uterus, nämlich eine Hemmung der estrogeninduzierten Proliferation des Endometriums, beobachtet wird.

Als Antiöstrogene gemäß vorliegender Erfindung können auch Aromatasehemmer in Verbindung mit Progesteronantagonisten verwendet werden. Aromatasehemmer unterdrücken die Synthese der Östrogene aus deren Vorstufen. Beispiele für Aromatasehemmer sind Atamestan = 1-Methylandrosta-1,4-dien-3,17-dion (DE-A 33 22 285), Pentrozol = 5-[Cyclopentyliden(1*H*-imidazol-1-yl)methyl]-2-thiophencarbonitril (EP-A 0 411 735) oder 4-(5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridin-5-yl)benzonitril-monohydrochlorid (Cancer Res., 48, S. 834-838, 1988).
Die Verwendung von Östrogenantagonisten ist aber gegenüber derjenigen von Aromatasehemmern in jedem Fall bevorzugt, da die Östrogenantagonisten die Serum-

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Östrogenkonzentration nicht beeinflussen und somit eine Beeinträchtigung des Zyklus vermieden wird.

Eine AÖ-Dosiseinheit enthält 0.01-100 mg Tamoxifen oder eine biologisch äquivalente Menge einer anderen antiöstrogen wirksamen Verbindung.
Ihre Formulierung kann analog wie die der Progesteronantagonisten erfolgen.

Progesteronantagonistisch- und antiöstrogen wirksame Verbindungen können z. B. lokal, topisch, enteral oder parenteral appliziert werden.

Vorzugsweise kommen der Progesteronantagonist und das Antiöstrogen in einer gemeinsamen Dosierungseinheit zur Anwendung.

Die nachfolgenden Beispiele dienen der näheren Erläuterung der vorliegenden Erfindung:

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Beispiel 1

10,0 mg	11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on
140,5 mg	Laktose
69,5 mg	Maisstärke
2,5 mg	Polyvinylpyrrolidon
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
225,0 mg	Gesamtgewicht der Tablette

Beispiel 2

20,0 mg	Tamoxifen (Antiestrogen mit agonistischer Partialwirkung)
50,0 mg	11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on
105,0 mg	Laktose
40,0 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben angegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

Beispiel 3

5,0 mg	7α-[9-(4,4,5,5,5-Pentafluorpentylsulfinyl)nonyl]estra-1,3,5(10)-trien-3,17β-diol (reines Antiestrogen)
50,0 mg	11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on

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110,0 mg	Lactose
50,0 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben angegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

Beispiel 4

0,5 mg	11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on
0,2 mg	7α-[9-(4,4,5,5,5-Pentafluorpentylsulfinyl)-nonyl]-estra-1,3,5(10)-trien-3,17β-diol (reines Antiestrogen)
159,5 mg	Lactose
54,8 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben ngegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

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Beispiel 5

Zusammensetzung einer öligen Lösung:

100,0 mg	Tamoxifen
343,4 mg	Rizinusöl
608,6 mg	Benzylbenzoat
1052,0 mg	= 1 ml
	Die Lösung wird in eine Ampulle gefüllt

Beispiel 6

5,0 mg	11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(1-propinyl)estra-4,9-dien-3-on (RU-38486),
10,0 mg	(*Z*)-*N*,*N*-Dimethyl-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]ethanamin, (Tamoxifen; Antiestrogen mit agonistischer Partialwirkung)
140,0 mg	Laktose
60,5 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben angegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

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Pharmakologische Beobachtungen

Versuch 1:

Die Versuche wurden an intakten Meerschweinchen mit normalem Zyklus durchgeführt. Die Behandlung wurde am Tag 1 post coitum angefangen. Die Tiere wurden über 6 Tage mit Vehikel (Benzylbenzoat/Rizinusöl), bzw. dem Tamoxifen in einer Dosis von 0,3, 1, 3 mg/Tag/Tier oder der progesteronantagonistisch wirksamen Verbindung Onapriston (0.3, 1,0, 3,0 mg/Tag/Tier), jeweils alleine, oder mit einer Kombination beider Verbindungen behandelt. Die Substanzen wurden subkutan appliziert. Als Parameter dient die Zahl der Implantationstellen am Tag 12 post coitum.

Die Kombination von Schwellendosen beider Komponenten (AG 0,3, 1 mg/ AÖ ca. 0,3, 1 mg) führt zu einer signifikanten Zunahme der Wirksamkeit (100%ige Implantationshemmung bei 1 mg AG + 1 mg AÖ und 1 mg AG + 0,3 mg AÖ) nach sechstägiger Behandlung (Abb. 1). Die synergistische Wirkung beider Komponenten ist nach einer Behandlung über 8 Tage noch stärker ausgeprägt.

Versuch 2

Die Versuche wurden an intakten Meerschweinchen mit normalem Zyklus durchgeführt. Die Behandlung wurde an Tag 1 p.c. angefangen. Die Tiere (n=6/Gruppe) wurden über 6 Tage mit Vehikel (Benzylbenzoat/Rizinusöl), bzw Tamoxifen/Antigestagen in einer Dosis von 0,3, 1, 3 mg/kg/Tier oder der progesteronantagonistisch wirksamen Verbindung (*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estr-4-en-3-on jeweils alleine oder mit einer Kombination beider Verbindungen behandelt. Die Substanzen wurden s.c. appliziert. Als Parameter dient die Zahl der nichtgraviden Tiere an Tag 12.
Die Kombination von Schwellendosen (0,3 mg (*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estr-4-en-3-on (ZK 137.316) + 0,3 mg AÖ) führt zu einer signifikanten Zunahme der Wirksamkeit (ca. 80% Rezeptivitätshemmung,
Abb. 2)

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Versuch 3

Die Versuche wurden an intakten Meerschweinchen mit normalem Zyklus über einen Behandlungszeitraum von 2 Zyklen durchgeführt. Die Anpaarung fand im zweiten Zyklus statt.

Dosen von Onapriston: 0,1, 0,25, 0,5, 1,0 und 3,0 mg täglich s.c.

Dosen von Tamoxifen: 0,1, 0,25, 0,5, 1,0, 3,0 und 10,0 mg täglich s.c.

Die Kombination jeweils nur marginal wirksamer Einzeldosen (Onapriston 0,5 mg; Tamoxifen 0,5 mg) führt zu einer deutlichen Wirkungsverstärkung (Synergismus). Nur bei Verwendung einer Kombination im Sinne vorliegender Erfindung läßt sich eine vollständige Vermeidung von Schwangerschaften erzielen. In dem genannten Dosisbereich von Tamoxifen (0,1 - 10,0 mg/Tier) konnte keine vollständige Hemmung der Rezeptivität erreicht werden. Normale Schwangerschaften wurden bei 30% (10,0 mg) und 90% bis 100% (<1,0 mg) beobachtet. Auch nach der Behandlung mit hohen Onapriston-Dosen sind gelegentlich Schwangerschaften aufgetreten.

Nach einer Kombinationsbehandlung mit Onapriston und Tamoxifen (jeweils 1,0 mg) wird in allen Fällen eine vollständige Hemmung der Rezeptivität beobachtet. 100%ige Rezeptivitätshemmung bedeutet eine vollständige Vermeidung von Schwangerschaften.

Bei niedrigeren Dosen von Tamoxifen und Onapriston (<1,0 mg), die alleine keine bzw. eine marginale Wirkung aufweisen, lag die Rezeptivitätshemmrate bei 80% bis 100% aller Tiere.

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Patentansprüche

1. Verwendung mindestens einer Verbindung mit progesteronantagonistischer (PA) und mindestens einer Verbindung mit antiöstrogener (AÖ) Wirkung, jeweils in nicht-ovulationshemmender Dosierung in einer einzelnen Dosiseinheit, zur Herstellung von Arzneimitteln zur weiblichen Kontrazeption.

2. Verwendung mindestens eines kompetitiven Progesteronantagonisten und eines Antiöstrogens nach Anspruch 1 zur Herstellung eines Arzneimittels zur postkoitaler weiblichen Fertilitätskontrolle in einer einmalig zu verabreichenden Dosiseinheit.

3. Verwendung mindestens eines kompetitiven Progesteronantagonisten und eines Antiöstrogens nach Anspruch 1 zur Herstellung eines Arzneimittels zur bedarfsorientierten weiblichen Fertilitätskontrolle, welches unabhängig vom Zeitpunkt des Menstruationszyklus angewandt werden kann, in einer einmalig zu verabreichenden Dosiseinheit.

4. Verwendung nach einem der Anspruche 1-3, dadurch gekennzeichnet, daß der kompetitive Progesteronantagonist aus der Gruppe der folgenden Verbindungen ausgewählt ist:
11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on,
(*Z*)-11β-(4-Acetylphenyl)-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estra-4,9-dien-3-on,
(*Z*)-6'-(4-Cyanphenyl)-9,11α-dihydro-17β-hydroxy-17α-(3-hydroxy-1-propenyl)-4'*H*-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-on,
(*Z*)-9,11α-Dihydro-17β-hydroxy-17α-(3-hydroxy-1-propenyl)-6'-(3-pyridinyl)-4'*H*-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-on,
17α-Hydroxy-17β-(3-hydroxypropyl)-11β-[4-(1-methylethenyl)phenyl]-13α-estra-4,9-dien-3-on,
11β-[4-(3-Furanyl)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on
(*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estr-4-en-3-on,
(*E*)-11β-[4-[[(Acetyloxy)imino]methyl]phenyl]-17β-methoxy-17α-(methoxymethyl)estra-4,9-dien-3-on,

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(*E*)-11β-[4-[[[(Ethoxycarbonyl)oxy]imino]methyl]phenyl]-17β-methoxy-17α-(methoxymethyl)estra-4,9-dien-3-on,

5. Verwendung nach einem der Ansprüche 1-4, dadurch gekennzeichnet, daß die Verbindung mit antiöstrogener Wirkung ein Östrogenantagonist ist.

6. Verwendung nach Anspruch 5, dadurch gekennzeichnet, daß der Östrogenantagonist aus der Gruppe der folgenden Verbindungen ausgewählt ist:
(*Z*)-*N*,*N*-Dimethyl-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]ethanamin,
1-[2-[4-(3,4-Dihydro-6-methoxy-2-phenyl-1-naphthalinyl)phenoxy]ethyl]pyrrolidin-hydrochlorid,
[6-Hydroxy-2-(4-hydroxyphenyl)-3-benzothienyl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanon-hydrochlorid (Raloxifen),
N-Butyl-11-(3,17β-dihydroxyestra-1,3,5(10)-trien-7α-yl)-*N*-methylundecansäureamid,
7α-[9-[(4,4,5,5,5-Pentafluorpentyl)sulfinyl]nonyl]estra-1,3,5(10)-trien-3,17β-diol.

7. Verwendung von (*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estr-4-en-3-on als PA und (*Z*)-*N*,*N*-Dimethyl-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]ethanamin als AÖ nach einem der Ansprüche 1-3.

8. Verwendung nach einem der Ansprüche 1-3, dadurch gekennzeichnet, daß der kompetitive Progesteronantagonist und das Antiöstrogen in dem Arzneimittel zur Applikation in lokaler, topischer, enteraler oder parenteraler Weise hergerichtet ist.

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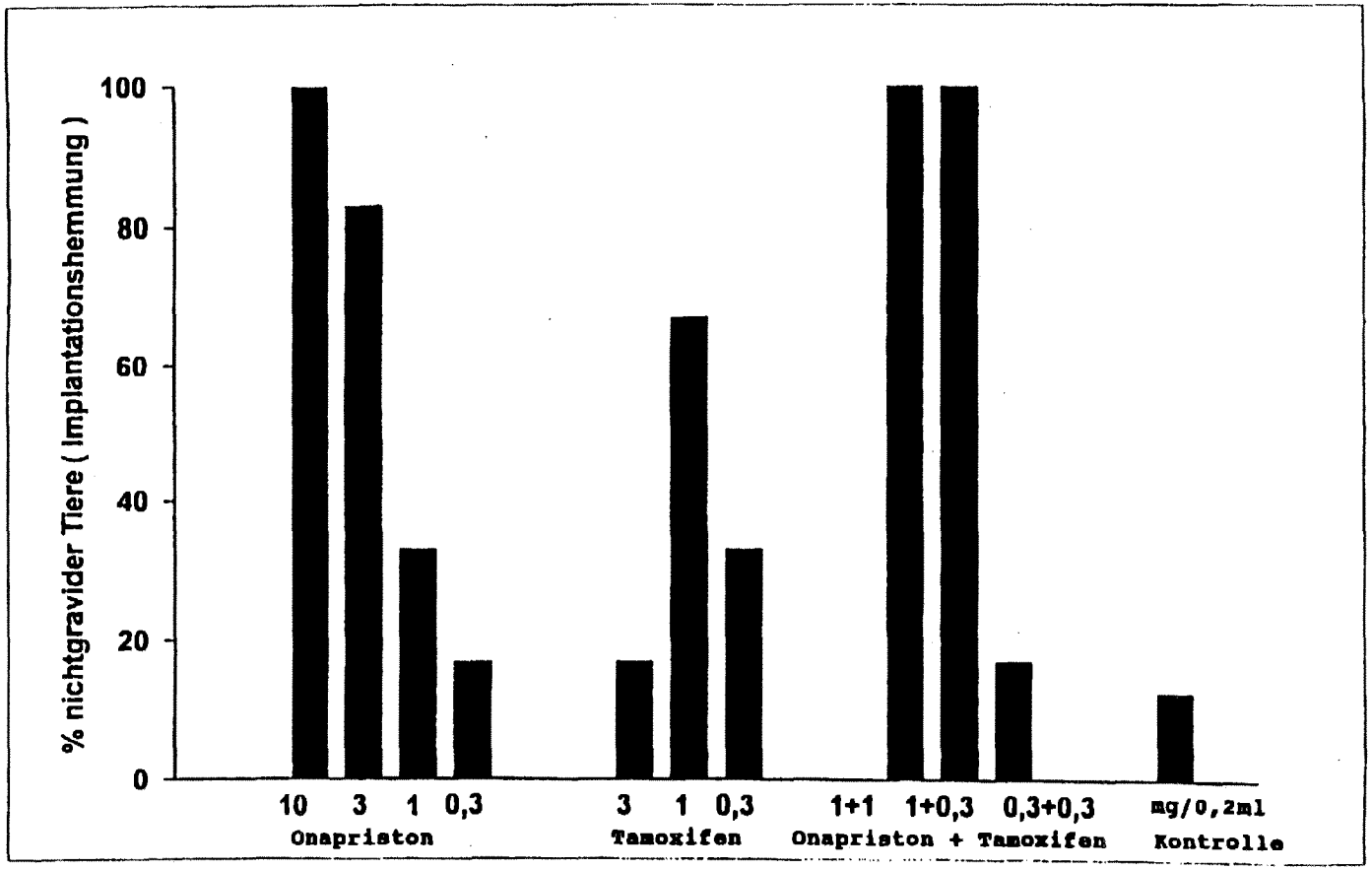
Rezeptivitätshemmung / Meerschweinchen nach postkoitaler Behandlung

Behandlung: d1 - d6 p.c. / Applikation: s.c. / Autopsie: d12 p.c. (n = 6 / Gruppe)



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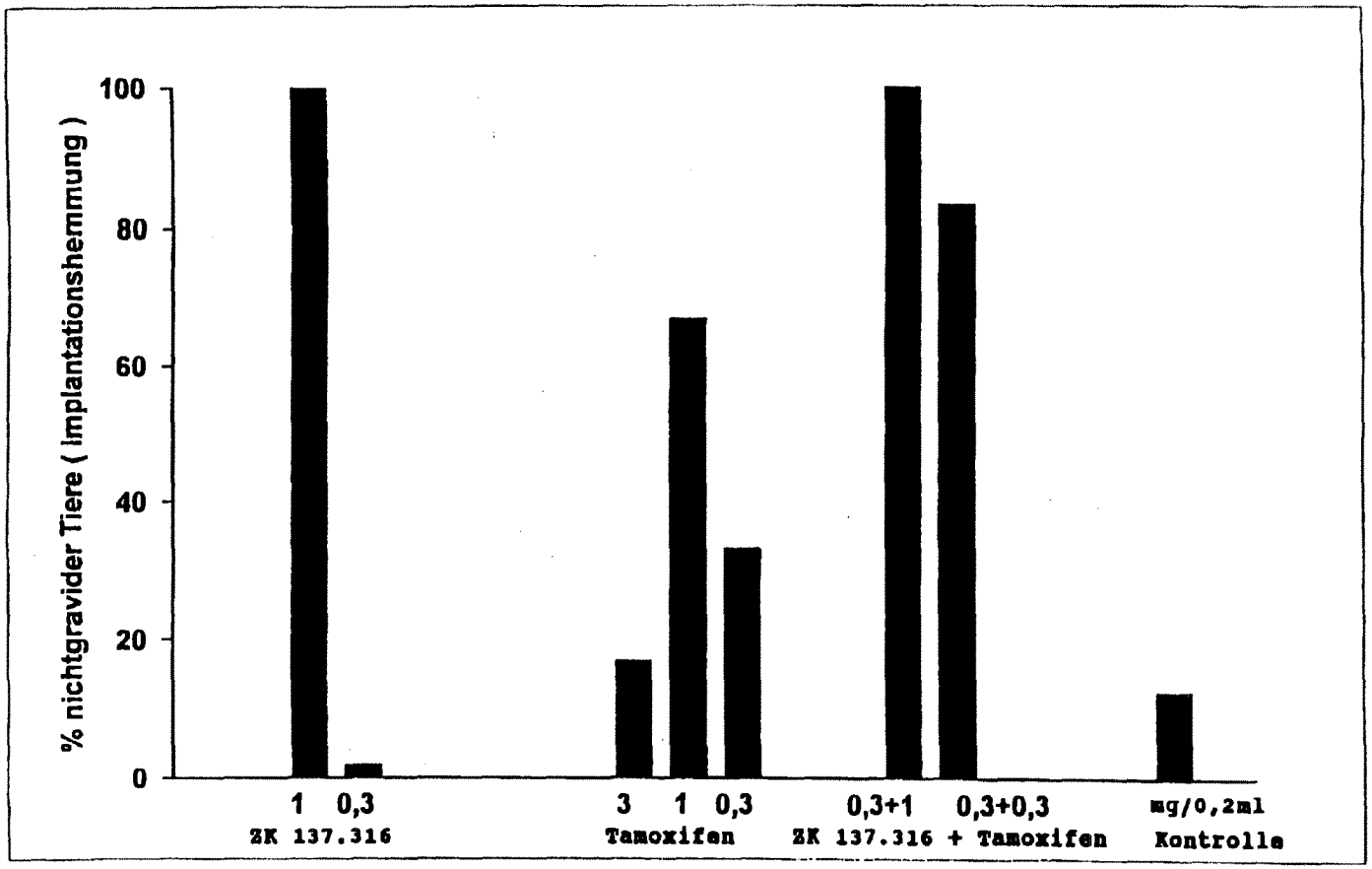
Rezeptivitätshemmung / Meerschweinchen nach postkoitaler Behandlung

Behandlung: d1 - d6 p.c. / Applikation: s.c. / Autopsie: d12 p.c. (n = 6 / Gruppe)



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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 95/05106

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565 //(A61K31/565,31:565),(A61K31/565,31:135)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 310 541 (SCHERING AG) 5 April 1989 see claims ---	1-8
A	EP,A,0 310 542 (SCHERING AG) 5 April 1989 see abstract -----	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 1996	29. 05. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 95/05106

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0310541	05-04-89	DE-A-	3733478	13-04-89
		AT-T-	106730	15-06-94
		AU-B-	2332188	20-04-89
		AU-B-	2332288	08-06-89
		CA-A-	1330039	07-06-94
		CA-A-	1329126	03-05-94
		DE-D-	3850026	06-07-95
		DE-A-	3876582	21-01-93
		EP-A-	0310542	05-04-89
		ES-T-	2053795	01-08-94
		ES-T-	2055745	01-09-94
		JP-A-	1106823	24-04-89
		JP-A-	1106822	24-04-89
		US-A-	4888331	19-12-89
EP-A-0310542	05-04-89	DE-A-	3733478	13-04-89
		AT-T-	106730	15-06-94
		AU-B-	2332188	20-04-89
		AU-B-	2332288	08-06-89
		CA-A-	1330039	07-06-94
		CA-A-	1329126	03-05-94
		DE-D-	3850026	06-07-95
		DE-A-	3876582	21-01-93
		EP-A,B	0310541	05-04-89
		ES-T-	2053795	01-08-94
		ES-T-	2055745	01-09-94
		JP-A-	1106823	24-04-89
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		US-A-	4888331	19-12-89

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INTERNATIONALER RECHERCHENBERICHT

Internales Aktenzeichen
PCT/EP 95/05106

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K31/565 //(A61K31/565,31:565),(A61K31/565,31:135)

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61K

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Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP,A,0 310 541 (SCHERING AG) 5.April 1989 siehe Ansprüche ---	1-8
A	EP,A,0 310 542 (SCHERING AG) 5.April 1989 siehe Zusammenfassung -----	1-8

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

☒ Siehe Anhang Patentfamilie

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Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
13.Mai 1996	29. 05. 96

Name und Postanschrift der Internationale Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Leherte, C

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INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlich. ..n, die zur selben Patentfamilie gehören

Inter nales Aktenzeichen
PCT/EP 95/05106

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
EP-A-0310541	05-04-89	DE-A-	3733478	13-04-89
		AT-T-	106730	15-06-94
		AU-B-	2332188	20-04-89
		AU-B-	2332288	08-06-89
		CA-A-	1330039	07-06-94
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		ES-T-	2053795	01-08-94
		ES-T-	2055745	01-09-94
		JP-A-	1106823	24-04-89
		JP-A-	1106822	24-04-89
		US-A-	4888331	19-12-89
EP-A-0310542	05-04-89	DE-A-	3733478	13-04-89
		AT-T-	106730	15-06-94
		AU-B-	2332188	20-04-89
		AU-B-	2332288	08-06-89
		CA-A-	1330039	07-06-94
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		EP-A,B	0310541	05-04-89
		ES-T-	2053795	01-08-94
		ES-T-	2055745	01-09-94
		JP-A-	1106823	24-04-89
		JP-A-	1106822	24-04-89
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(71) Applicant *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and
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(74) Agent: TAIT, Brian, Steele; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) **Title:** A SOLUTION FOR ORAL ADMINISTRATION CONTAINING ICI 182,780

(57) **Abstract**

The invention concerns a pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises ICI 182,780, a pharmaceutically-acceptable oil, a pharmaceutically-acceptable lipophilic surfactant, a pharmaceutically-acceptable hydrophilic surfactant, and a pharmaceutically-acceptable water-miscible solvent, and the use of the composition on oral administration to a warm-blooded animal to produce an antioestrogenic effect.

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A SOLUTION FOR ORAL ADMINISTRATION CONTAINING ICI 182,780

The invention relates to a novel pharmaceutical composition, particularly to a pharmaceutical composition adapted for oral administration containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, and more particularly to a solution formulation containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol. The invention also relates to the use of the pharmaceutical composition of the invention for oral administration to a warm blooded animal to produce an antioestrogenic effect and to a method of producing an antioestrogenic effect by the oral administration of an effective amount of the pharmaceutical composition of the invention.

It is disclosed in European Patent Application No. 0 138 504 that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives of that invention. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration. For oral administration it is stated that a tablet or capsule containing the steroid derivative of the invention is particularly convenient. It is further stated therein that the tablet formulation can contain diluents, for example mannitol or maize starch, disintegrating agents, for example alginic acid, binding agents, for example methyl-cellulose, and lubricating agents, for example magnesium stearate. No pharmaceutically-acceptable diluent or carrier for a capsule formulation is specifically disclosed therein.

Subsequently the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol has been identified by the code number ICI 182.780 and that number shall be utilised for the compound hereinafter.

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It is further disclosed in Cancer Research, 1991, 51, 3867-3873 and J. Endocrinology, 1992, 135. 239-247 that the antioestrogenic effect of ICI 182,780 in immature rats, mature rats or monkeys can be assessed by the administration of a suspension of the compound in arachis oil. This formulation was dosed either orally or by subcutaneous injection. The studies in rats demonstrated that the potency of the compound when dosed in arachis oil suspension was at least ten fold poorer when administration was by the oral route than when administration was by the subcutaneous route suggesting that the oral bioavailability of the compound from that formulation was low. A prolonged antioestrogenic effect was demonstrated when a dispersion of the compound in arachis oil was administered subcutaneously.

It is further disclosed in, for example, Laboratory Animal Science, 1993, 43, 247-251 that ICI 182,780 may be formulated for administration by intramuscular injection in a castor oil-based depot formulation. That formulation when given to laboratory animals at a dose of 4 milligrams per kilogram was found to inhibit the effects of endogenous oestrogen for three to four weeks.

Furthermore it is disclosed in J. Endocrinology, 1992, 135, 239-247, J. Endocrinology, 1993, 138, 203-209 and Cancer Research, 1994, 54, 408 that ICI 182,780 may be provided for administration by daily intramuscular injection in a 'short-acting' liquid formulation comprising ICI 182,780 in a propylene glycol-based solution.

It is an object of the present invention to provide a solution formulation containing the hydrophobic drug ICI 182,780 which does not exhibit, or which exhibits to a lesser degree, the problem of low oral bioavailability.

Many pharmaceutical compositions have been disclosed which are stated to be suitable for the dosing of hydrophobic drugs. Many of these formulations contain an oil such as arachis oil in which the hydrophobic drug is dissolved or dispersed. However the lack of miscibility of the oil with the aqueous environment of the gastrointestinal tract can lead to variable rates of absorption of the drug. To try to overcome the problem, it is common practice for a surfactant to be added to the pharmaceutical composition, particularly a hydrophilic surfactant such as a surfactant with a hydrophilic-lipophilic balance (HLB) of greater than about 8 and less than about 30. Such a surfactant may

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produce an emulsion which, if the particle size is small, may lead to more complete absorption of the hydrophobic drug. However the use of hydrophilic surfactants may give a formulation of poor homogeneity as the surfactant may not be sufficiently miscible with the oil in which the hydrophobic drug is dissolved or dispersed. In a further refinement of such hydrophilic surfactant formulations, it is known that a lipophilic surfactant may be added to try to obtain the desired balance of hydrophilic and hydrophobic components to provide a stable emulsion when the formulation is added to an aqueous environment. The problem with this approach is that for each hydrophobic drug more than routine skill and knowledge is required to identify the exquisite balance of lipophilic and hydrophobic components which will provide a pharmaceutical composition of that hydrophobic drug which can be dosed orally to provide a reasonable oral bioavailability.

The many and various pharmaceutical compositions of the hydrophobic drug cyclosporin illustrate the complexities in this field of pharmaceutical research.

Thus, for example, it is disclosed in UK Patent Application No. 2 222 770 that cyclosporin may be formulated in a mixture of an oil such as a medium chain fatty acid triglyceride, a hydrophilic phase such as a mono- or di-alkyl ether of a polyoxyalkanediol, and a surfactant such as a hydrophilic or lipophilic surfactant or mixtures thereof.

Further it is disclosed in UK Patent Application No. 2 257 359 that cyclosporin may be formulated in a mixture of an oil such as a mixture of mono-, di- and tri-glycerides, a hydrophilic surfactant such as a surfactant having a HLB of at least 10, and the hydrophilic solvent 1,2-propylene glycol.

In addition it is disclosed in UK Patent Application No. 2 228 198 that cyclosporin may be formulated in a mixture of an oil such as a fatty acid triglyceride, a lipophilic surfactant such as a glycerol fatty acid partial ester, and a hydrophilic surfactant having a HLB of at least 10.

It has also been disclosed in PCT Patent Application WO 95/24893 that a hydrophobic drug may, for example, be formulated in a mixture of an oil such as a complete or partial ester of a medium chain or long chain fatty acid with a low molecular weight mono-, di- or polyhydric alcohol (for example a vegetable oil), a lipophilic surfactant such as a fatty acid or a mono- or di-glyceride of a fatty acid, and a hydrophilic surfactant having a HLB of greater than 10.

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While this prior art shows some promising results, it should be recognised that ICI 182,780 is not a cyclic peptide like cyclosporin. ICI 182,780 is also a compound of higher molecular weight (Mol. Wt. = 603) and lipophilicity (estimated log P = 8 approx.) than the many drugs listed in PCT Patent Application WO 95/24893. Accordingly a pharmaceutical composition of ICI 182,780 is not disclosed in this prior art, nor can such a formulation be directly or unambiguously identified from consideration of this prior art.

We have investigated the factors which influence the solubilisation of ICI 182,780 and the maintenance of the compound in an absorbable form when it is dosed orally. We have developed solvents and mixtures of solvents which effectively solubilise the compound and we have also identified those oils and surfactants which facilitate the presentation of the compound in a suitable emulsion form to allow the enhanced absorption of the compound. We have discovered that surprisingly the selection and combination of particular classes of ingredients from within the formulations of known hydrophobic drugs provides the desired increase in oral bioavailability.

According to the invention there is provided a pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent.

Suitable pharmaceutically-acceptable oils include, for example, medium or long chain (C6 to C22, preferably C12 to C20, more preferably C6 to C12) fatty acids and mono-, di- or tri-glycerides of such fatty acids and mixtures of said fatty acids and mono-, di- and tri-glycerides. Preferably the pharmaceutically-acceptable oil is a triglyceride of a C6 to C12 fatty acid or a diglyceride of a C14 to C20 fatty acid. Examples of preferred pharmaceutically-acceptable oils include vegetable oils such as soyabean oil, olive oil, arachis oil and coconut oil, fractionated vegetable oils such as fractionated coconut oil, and animal oils such as fish liver oil. Of these oils, fractionated coconut oil is more preferred.

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Suitable fractionated coconut oils include, for example, those made available commercially under the trade name "Miglyol" from Huls (UK) Ltd., Milton Keynes, UK such as:-

Miglyol 810 which comprises a mixture of caprylic and capric acid triglycerides having an approximate fatty acid composition of C6 : 2%; C8 : 68%; C10 : 28% and C12 : 2%;

Miglyol 812 which comprises a mixture of caprylic and capric acid triglycerides having an approximate fatty acid composition of C6 : 3%; C8 : 56%; C10 : 36% and C12 : 5%; and

Miglyol 818 which comprises a mixture of caprylic, capric and linoleic acid triglycerides having an approximate fatty acid composition of C6 : 3%; C8 : 53%; C10 : 33%; C12 : 4% and C18 : 5%.

Of these fractionated coconut oils, Miglyol 812 is preferred.

Suitable pharmaceutically-acceptable lipophilic surfactants include, for example, surfactants with a hydrophilic-lipophilic balance (HLB) of less than about 10, for example fatty acids such as capric, caprylic, oleic and linoleic acid, and mono- or di-glycerides (or mixtures of mono- and di-glycerides) of fatty acids such as capric, caprylic and oleic acid, for example the lipophilic surfactants made available under the trade name "Imwitor" from Huls (UK) Ltd. such as Imwitor 988, Imwitor 742 and Imwitor 308 and those made available under the trade name "Capmul" from Karlshamns, Karlshamn, Sweden such as Capmul MCM.

Of these lipophilic surfactants, mixtures of the mono- and/or di-glycerides of capric and caprylic acids such as Imwitor 988 and Imwitor 742, especially Imwitor 988, are preferred.

Suitable pharmaceutically-acceptable hydrophilic surfactants include, for example, surfactants with a HLB of greater than about 10, for example the condensation products of an alkylene oxide such as ethylene oxide with castor oil or with hydrogenated castor oil, for example the hydrophilic surfactants made available under the trade name "Cremophor" from BASF, Cheadle Hulme, Cheshire, England such as Cremophor RH40, those made available under the trade name "Etocas" from Croda Chemicals, North

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Humberside, England such as Etocas 40, and those made available under the trade name "Nikkol" from Nikko Chemicals Co. Ltd., Tokyo, Japan such as Nikkol HCO-60.

Of these hydrophilic surfactants, Cremophor RH40 is preferred.

Suitable pharmaceutically-acceptable water-miscible solvents include, for example, a (1-4C)alcohol such as ethanol and propanol, a poly-alcohol, for example, a monomeric poly-alcohol such as a (1-4C)alkylenepolyol, for example glycerol (propane-1,2,3-triol), or a (1-12C)glycol, for example ethylene glycol (ethane-1,2-diol), propylene glycol (propane-1,2-diol), diethylene glycol (3-oxapentane-1,5-diol), triethylene glycol (3,6-dioxaoctane-1,8-diol) and tetraethylene glycol (3,6,9-trioxaundecane-1,11-diol). Alternatively a suitable pharmaceutically-acceptable water-miscible solvent is, for example, a polymeric poly-alcohol such as polyethylene glycol (PEG), for example a PEG having an average molecular weight in the range 150 to 800 such as PEG 200, PEG 300, PEG 400 and PEG 600. Alternatively a suitable pharmaceutically-acceptable water-miscible solvent is, for example, an ether derivative of a pharmaceutically-acceptable poly-alcohol as defined hereinbefore, for example a mono-(1-4C)alkyl ether derivative such as a mono-methyl ether derivative or, for example a mono-cyclic ether derivative such as a furfurylmethyl, tetrahydrofurfurylmethyl or tetrahydropyranylmethyl ether derivative. Examples of such suitable etherified poly-alcohols include glycerol mono-methyl ether, ethylene glycol mono-methyl ether, propylene glycol mono-methyl ether, ethylene glycol mono-tetrahydrofurfurylmethyl ether, diethylene glycol mono-methyl ether, diethylene glycol mono-ethyl ether (ethyl digol), diethylene glycol mono-tetrahydrofurfurylmethyl ether (glycofurol), diethylene glycol mono-tetrahydropyranylmethyl ether, triethylene glycol mono-methyl ether, triethylene glycol mono-ethyl ether, triethylene glycol mono-tetrahydrofurfurylmethyl ether, tetraethylene glycol mono-methyl ether and tetraethylene glycol mono-tetrahydrofurfurylmethyl ether. A suitable pharmaceutically-acceptable water-miscible solvent includes a mixture of two or more of the above-mentioned suitable water-miscible solvents. Preferred pharmaceutically-acceptable water-miscible solvents include propylene glycol and ethyl digol. Preferably ethanol or propylene glycol, or a mixture of ethanol and propylene glycol is used.

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In a further advantage of the invention, it has been determined that, surprisingly, the combination of the above-mentioned ingredients of the pharmaceutical composition of the invention in the correct ratios improves the desired increase in oral bioavailability. In the table below, the advantageous relative ratios (as percentages of the weight of the formulation) are disclosed:-

Component	Generally	Preferred	More Preferred	Further Preferred
ICI 182,780	1-20%	2-18%	5-15%	8-12%
oil	1-20%	2-18%	5-15%	5-15%
hydrophilic surfactant	5-45%	10-40%	20-30%	20-30%
lipophilic surfactant	15-70%	25-60%	35-50%	35-50%
water-miscible solvent	1-30%	2-28%	5-25%	8-16%

The solution formulation of the invention may be presented in a form suitable for oral administration, for example a unit dosage form may be metered onto a spoon of suitable size and administered by mouth. Alternatively the solution formulation may be encapsulated by methods well known to those skilled in the arts of pharmaceutical science, for example by encapsulation within a shell comprising a gelatin or starch capsule such as a hard gelatin or starch capsule or a soft gelatin capsule [which may be formed from gelatin, an appropriate plasticiser (such as glycerin and sorbitol) and water].

The compositions of the invention may be obtained using conventional pharmaceutically-acceptable diluents well known in the art such as colouring, sweetening, flavouring and/or preservative agents. In the case of a soft gelatin capsule said diluents may be present in the liquid solution formulation encapsulated within the gelatin capsule or alternatively they may be present within the gelatin shell of the capsule. Capsule forms of the invention may be coated or uncoated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

The amount of active ingredient i.e. ICI 182,780, which is employed in a single dosage unit will necessarily vary depending on the host treated and the particular dosage

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form employed. For example a solution formulation which is administered on a spoon will generally have a volume in the range, for example, 0.5 ml to 10 ml and will contain the active ingredient at a concentration in the range, for example, 5 mg/ml to 150 mg/ml, preferably in the range, for example, 20 mg/ml to 100 mg/ml. Alternatively a soft gelatin capsule having an internal volume of, for example, 0.5 ml, 1 ml, 2 ml, 3 ml or 5 ml may be employed and will contain the active ingredient at a concentration in the range, for example, 5 mg/ml to 150 mg/ml, preferably in the range, for example, 15 mg/ml to 120 mg/ml, more preferably 100 mg/ml.

The size of the dose of ICI 182,780 will naturally vary according to the nature and severity of the disease state being treated, and the age of the animal or patient being treated. In general ICI 182,780 will be administered so that a daily dose in the range, for example, 0.1 to 10 mg/kg body weight is received given, if required, in divided doses. Preferably a daily dose in the range, for example, 0.1 to 2 mg/kg body weight will be administered.

As stated previously it was disclosed in J. Endocrinology, 1992, 135, 239-247 and 1993, 138, 203-209 that ICI 182,780 may be formulated for administration by intramuscular injection as a solution formulation comprising ICI 182,780 in a propylene glycol-based solution. There was no disclosure therein of the dosing of that solution formulation by the oral route. The only specific disclosures of the administration of ICI 182,780 by the oral route were made in the first of the above-mentioned papers in J. Endocrinology and in Cancer Research, 1991, 51, 3867-3873 wherein the formulation comprised a suspension of the compound in arachis oil.

Thus according to this aspect of the invention there is provided the use of a solution formulation comprising:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent;

in the manufacture of a medicament for oral administration to a warm-blooded animal to produce an antiocstrogenic effect.

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This aspect of the invention also includes a method of producing an antioestrogenic effect by the oral administration to a warm-blooded animal in need of such an effect of an effective amount of a solution formulation comprising:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent.

In these aspects of the invention the weight ratios of the ingredients of the solution formulation are as defined hereinbefore. In addition the single dosage unit of the liquid solution formulation and the daily dosage rate are as defined hereinbefore.

The invention will now be illustrated in the following Examples which involve tests of the aqueous dispersion profiles and oral bioavailabilities of ICI 182,780 contained within various pharmaceutical formulations. In general the test procedures used were those described below:-

Test of Aqueous Dispersion Profiles

The aqueous dispersion profiles of the solution formulations of the invention were assessed using the following conventional procedure which was conducted at ambient temperature. An aliquot (0.2 ml of the formulations containing 2 g of ICI 182,780 per 100 ml and 0.04 ml of the formulation containing 10 g of ICI 182,780 per 100 ml) of each test formulation was added to an aqueous sodium chloride solution (0.154 M, 10 ml) in a vial. The vial was sealed with a cap and the contents were mixed by the repeated inversion of the vial. The dispersion of the formulation and/or the precipitation of the active ingredient of the formulation was assessed visually.

Test of Oral Bioavailability

The oral bioavailability of ICI 182,780 in the dog from various formulations of the compound was determined using the following method. Each test formulation was dosed to a group of five male beagle dogs, each weighing approximately 18 kg. Unless

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otherwise stated the studies were carried out with the animals in a 'fasted' state, that is the animals were not fed later than 18 hours prior to the dosing of a test formulation and they were not fed until 5 or 6 hours after dosing. The formulation of Example 1 was dosed orally by gavage. Each of the other formulations was contained in a hard gelatin capsule (size 00) and dosed orally. In each case, water (approximately 150 ml) was dosed immediately thereafter by way of gavage. Blood samples were taken from an external jugular vein at various times up to 8 hours after dosing. The level of ICI 182,780 in each blood sample was determined using a conventional radioimmunoassay using an analogous procedure to that described in Cancer Research, 1994, 54, 408 {antibodies were obtained on administration to a group of sheep of a conjugate obtained by a mixed anhydride based coupling of 17β-(3-carboxypropionyloxy)-7α-[9-(4,4,5,5,5-pentafluoropentylthio)nonyl]-oestra-1,3,5(10)-triene-3-ol [obtained from 7α-[9-(4,4,5,5,5-pentafluoropentylthio)nonyl]oestra-1,3,5(10)-triene-3,17β-diol (Example 35 of European Patent Application No. 0 138 504) and succinic acid] and thyroglobulin}.

Using this methodology, the oral bioavailability of ICI 182,780 obtainable from each test formulation was assessed using the conventional parameters of maximum drug concentration [Cp (max)], the area under the graph of drug concentration versus time [AUC (0-8h)] and a percentage figure for the oral bioavailablity based on a comparison of the AUC results obtained for the test formulation and for a formulation which was dosed intramuscularly (IM) comprising:-

IM Formulation	% Weight in grams per ml
ICI 182,780	2.0
Ethanol	10.0
Water (Ph. Eur.)	8.0
poloxamer 407	1.0
propylene glycol (Ph. Eur.)	to 100%

The following calculation was carried out to determine the oral bioavailability:-

$$\% \text{ Oral Bioavailability} = \frac{\text{AUC (oral)} \times \text{Dose (IM)}}{\text{AUC (IM)} \times \text{Dose (oral)}} \times 100$$

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Comparative Example 1

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a precipitate which was noted to aggregate over a period of about 10 minutes.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	2.0	Dose	50 mg
ethanol	10.0	Cp (max)	13.3 ± 2.7 ng ml^{-1}
water	8.0	AUC (0 to 8 hours)	34.9 ± 6.3 ng h ml^{-1}
propylene glycol	to 100%	Bioavailability	1.1 %

Comparative Example 2

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a crude emulsion.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
ethanol	13.5	Cp (max)	14 ± 2 ng ml^{-1}
Imwitor 988	76.5	AUC (0 to 8 hours)	28 ± 5 ng h ml^{-1}
		Bioavailability	0.8 %

Comparative Example 3

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually.

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Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
propylene glycol	10.0	Cp (max)	20 ± 4 ng ml^{-1}
Imwitor 988	80.0	AUC (0 to 8 hours)	51 ± 10 ng h ml^{-1}
		Bioavailability	1.5 %

Example 1

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
Imwitor 988	40.0		
Cremophor RH40	26.8	Cp (max)	83 ± 19 ng ml^{-1}
Miglyol 812	13.2	AUC (0 to 8 hours)	194 ± 34 ng h ml^{-1}
ethanol	10.0	Bioavailability	5.5 %

Example 2

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

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Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
Imwitor 988	45.9		
Cremophor RH40	22.95	Cp (max)	78 ± 17 ng ml^{-1}
Miglyol 812	7.65	AUC (0 to 8 hours)	193 ± 35 ng h ml^{-1}
propylene glycol	13.5	Bioavailability	5.4 %

Example 3

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
Imwitor 742	40.0		
Cremophor RH40	26.8	Cp (max)	80 ± 14 ng ml^{-1}
Miglyol 812	13.2	AUC (0 to 8 hours)	195 ± 26 ng h ml^{-1}
ethanol	10.0	Bioavailability	5.6 %

Example 4

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

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Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
Imwitor 988	37.4		
Cremophor RH40	22.95	Cp (max)	83 ± 11 ng ml^{-1}
Miglyol 812	7.65	AUC (0 to 8 hours)	194 ± 24 ng h ml^{-1}
ethanol	7.0	Bioavailability	5.6 %
propylene glycol	15.0		

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CLAIMS

1. A pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent.

2. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable oil is a triglyceride of a C6 to C12 fatty acid or a diglyceride of a C14 to C20 fatty acid.

3. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable oil is fractionated coconut oil.

4. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable lipophilic surfactant is a mixture of mono- and di-glycerides of capric and caprylic acids.

5. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable hydrophilic surfactant is the condensation product of ethylene oxide with castor oil or with hydrogenated castor oil.

6. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable water-miscible solvent is ethanol, propylene glycol, diethylene glycol mono-ethyl ether or diethylene glycol mono-tetrahydrofurfurylmethyl ether, or a mixture thereof.

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7. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	2-18%
oil	2-18%
hydrophilic surfactant	10-40%
lipophilic surfactant	25-60%
water-miscible solvent	2-28%

8. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	5-15%
oil	5-15%
hydrophilic surfactant	20-30%
lipophilic surfactant	35-50%
water-miscible solvent	5-25%

9. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	8-12%
oil	5-15%
hydrophilic surfactant	20-30%
lipophilic surfactant	35-50%
water-miscible solvent	8-16%

10. The use of a pharmaceutical composition as claimed in any one of claims 1 to 9 in the manufacture of a medicament for oral administration to a warm-blooded animal to produce an antioestrogenic effect.

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11. A method of producing an antioestrogenic effect by the oral administration to a warm-blooded animal in need of such an effect of an effective amount of a solution formulation as claimed in any one of claims 1 to 9.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/03022

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565 A61K9/08 A61K47/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 24893 A (SCHERER LTD R P ;LACY JONATHAN ERNEST (GB); EMBLETON JONATHAN KENN) 21 September 1995 cited in the application * p.14,; p.17, l.24-p.19, l.4; p.24, l.13-18; p.28, l.9; claims 1-9 *	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 1997	26.03.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Uiber, P

Form PCT ISA/210 (second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ational Application No
PCT/GB 96/03022

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9524893 A	21-09-95	AU 1897495 A	03-10-95
		CA 2185347 A	21-09-95
		EP 0750495 A	02-01-97

Form PCT ISA 210 (patent family annex) (July 1992)

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EP 1 250 138
Patentee: AstraZeneca AB
Opponent: Gedeon Richter Ltd.
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A Case of Adenomyosis in a Pigtailed Monkey Diagnosed by Magnetic Resonance Imaging and Treated with the Novel Pure Antiestrogen, ICI 182,780

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The menstrual cycle occurs in Old World monkeys, apes, and humans. The pathologic occurrence of heterotopic uterine endometrial tissue is common in these species, particularly in captive nonhuman primates (1) and in humans. Adenomyosis is the occurrence of endometrium within the myometrium, while endometriosis is the occurrence of endometrium outside the uterus, for example, on the serosal surface of the myometrium or bowel, on the ovaries, or within the pelvic adipose tissue. The disorder in primates provides an excellent model of the human disease. Human endometriosis is commonly treated with endocrine agents such as danazol or goserelin, and adenomyosis can be expected to respond similarly. In macaques, also, endometriosis can be successfully treated with hormone analogue therapy (2). Early disease is, however, often asymptomatic, and early diagnosis is difficult, although now possible with magnetic resonance imaging (MRI) (3–8). Magnetic resonance imaging noninvasively yields quantitative, three-dimensional information about the soft tissues; it has consequently proved useful to quantitatively assess the response of benign uterine lesions to therapy (9–12). Herein we describe a case of adenomyosis in a pigtailed monkey *(Macaca nemestrina nemestrina)* diagnosed by MRI and treated with the pure estrogen antagonist, ICI 182,780.

This case was encountered in the course of a series of studies in monkeys of the efficacy and pharmacology of novel endocrine agents being developed to treat hormone-dependent cancers (13, 14). Magnetic resonance imaging was performed on 22 untreated asymptomatic mature females, using the multislice oblique MRI techniques described previously (15). The case we describe was in the only 1 of 22 monkeys discovered to have any obvious abnormality by MRI. The uterus occupied 26.3 cm^3 and was substantially enlarged, grossly distorted, and asymmetric (Figure 1), with patchy high-signal features in the myometrium.

This monkey was a mature (6.4 kg) female. It was sexually mature when imported from Indonesia directly to these laboratories. After 6 months' quarantine, it was housed thereafter with another female, in sight of other female and male pigtailed monkeys, at a minimum temperature of 24°C, in natural light supplemented with artificial light (7:00 a.m. to 4:00 p.m.) and fed a proprietary chow (Old World Monkey Diet, BP Nutrition Ltd., Northwich, Cheshire, U.K.) supplemented daily with fresh fruit and vegetables. It had regular menstrual cycles (detected by vaginal swabbing) during 5 years (mean length, 29 days, S.D. 4 days, n = 68), typical of the species. Hormone (estradiol and progesterone) profiles during complete menstrual cycles were determined at intervals, for which daily blood samples (2 ml) were drawn from the saphenous vein; these were also typical of the species (16). Neither swabbing nor venipuncture required removing the monkey from its cage. No uterine abnormality was noted during MRI performed 2.5 years earlier, when the uterine volume was 8.9 cm^3. The animal appeared to be well throughout and no outward signs of the developing uterine abnormality were detected.

A provisional diagnosis of adenomyosis was made. Notwithstanding the putative lesions, the animal was considered suitable for entry into an experimental protocol (13) designed to evaluate the efficacy in monkeys of a novel pure estrogen antagonist, ICI 182,780 (7α-[9-(4,4,5,5,5,-pentafluoro-pentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol), recently described by us (17). ICI 182,780 has high affinity for the estradiol receptor but, unlike nonsteroidal antiestrogens such as tamoxifen, has been shown to be devoid of partial agonist (estrogenic) activity. It may, therefore, offer some advantages in the treatment of breast cancer and uterine disorders such as endometriosis and adenomyosis. Six additional examinations were made during two nonconsecutive menstrual cycles. After the end of the second cycle, the monkey was treated with ICI 182,780. Two separate doses each of 4 mg/kg were given i.m. in a castor-oil-based depot formulation, on days 2 and 31 (day 1 defined as the day of onset of menstruation). This dose and formulation have previously been found to inhibit the effects of endogenous estrogen in normal animals for 3 to 4 weeks (13). Magnetic resonance imaging continued for 12 weeks, during and after treatment; in total, 17 MRI examinations were made.

The design of our method for uterine MRI and its precision are described in detail elsewhere (14, 15). Anesthesia for restraint during MRI was induced with ketamine (0.7

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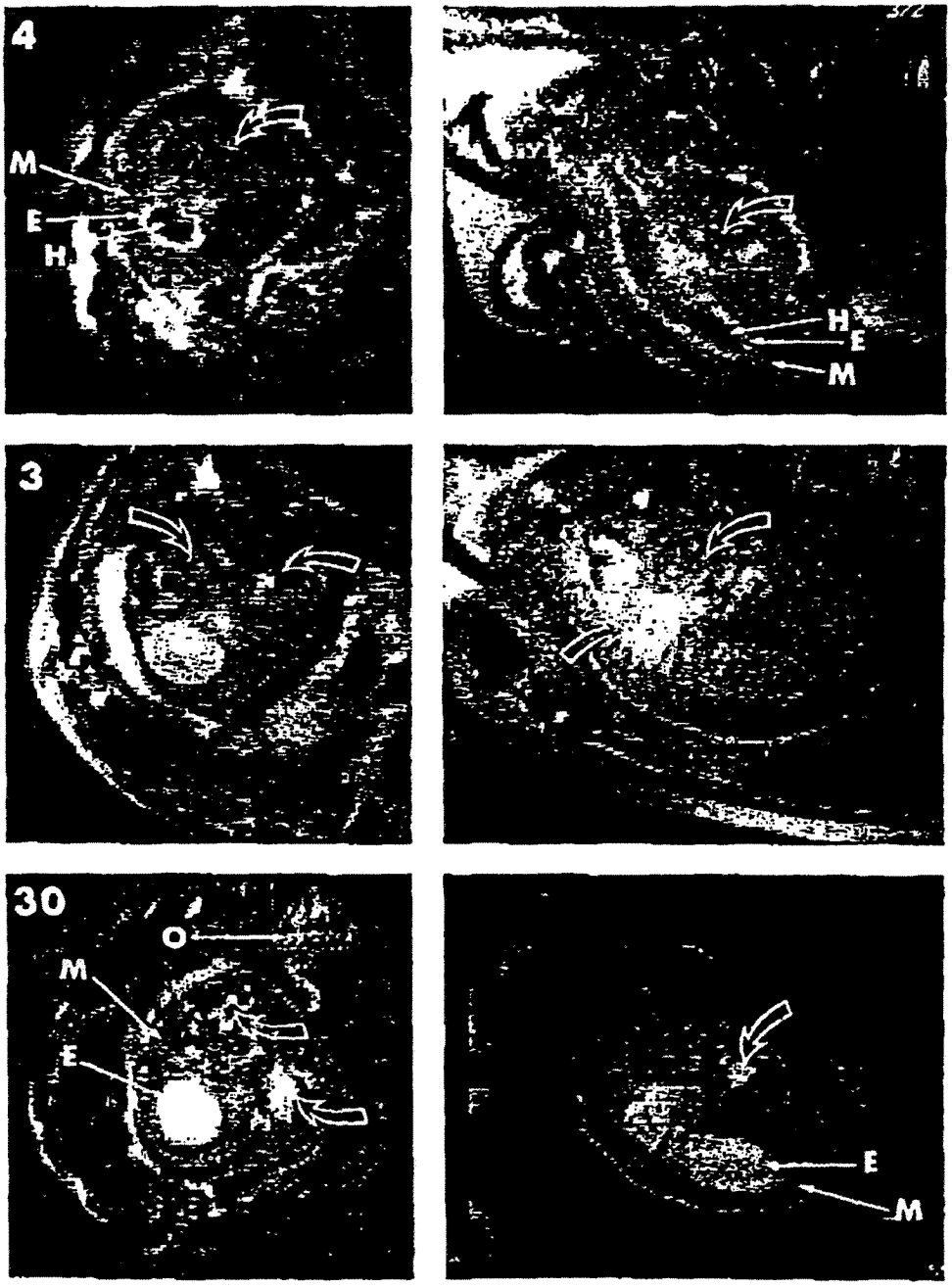

InnoPharma Exhibit 1046.0669

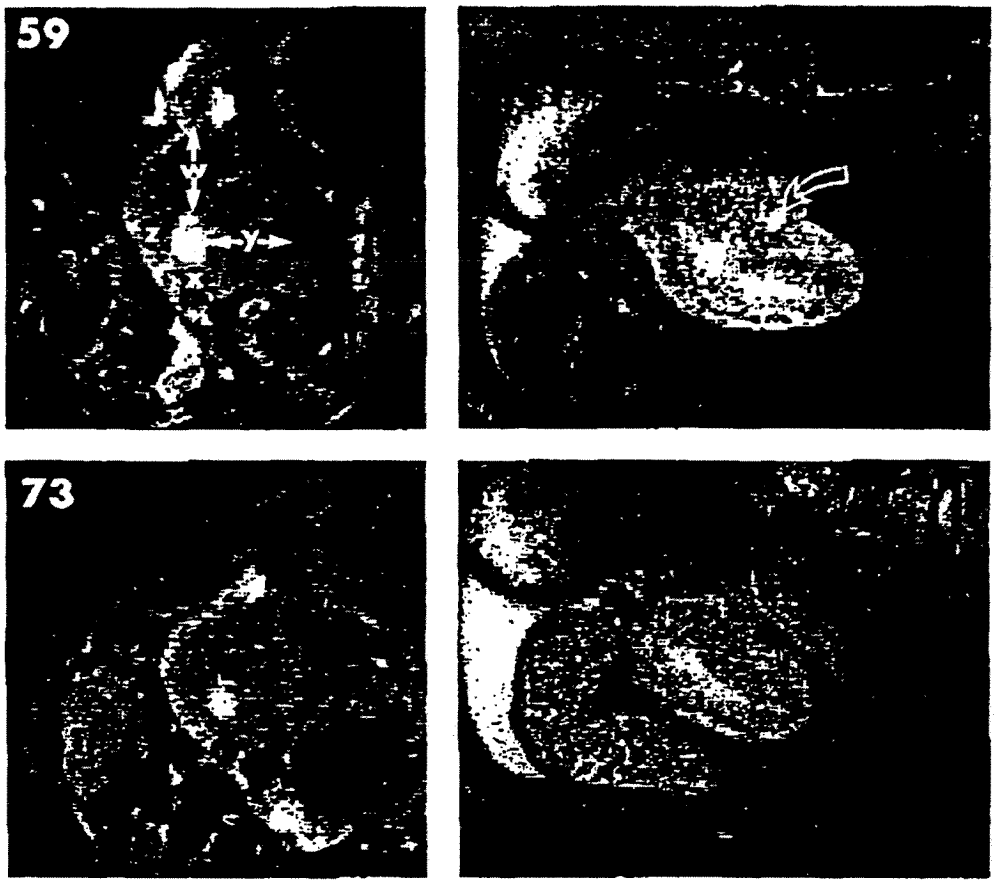

Figure 1. Magnetic resonance images before, during, and after therapy of adenomyosis in a pigtailed monkey. Each pair of images shows one of the eight oblique slices (left) and one of the eight sagittal slices (right). The sagittal images show a detail corresponding to 65 mm x 81 mm: top of the image is dorsal and left is caudal. High signal is also sometimes seen from the intervertebral discs (dorsal and cranial) and from the urinary bladder (caudal). The oblique images are transverse axial through corpus uteri and show a detail corresponding to 65 mm x 65 mm; left is ventral and caudal. Top pair (page 248), at diagnosis; second pair, at beginning of second untreated cycle; third pair, 28 days of first treatment; fourth pair (top), 28 days of second treatment showing lesion width measurement; bottom pair, 42 days after second treatment. The numbers in the figure refer to days after onset of menstruation. M, myometrium; E, endometrium; H, menstrual hemorrhage; O, ovary; open arrows, adenomyosis. The reported lesion width is the mean (for the two oblique midcorpal slices) of dimensions (w minus x) and (y minus z).

mg/kg i.m., Vetalar®, Parke-Davis, Eastleigh, Hampshire, U.K.) and maintained with halothane (Fluothane®, ICI Pharmaceuticals, Macclesfield, Cheshire, U.K.). We used a Biospec 400/2.3 instrument (Oxford Research Systems, Coventry, U.K.) incorporating a magnet with flux density 2.35 Tesla. The orientation of the uterus within the pelvis varies from day to day depending on the volume and disposition of the contents of the urinary bladder and distal portion of the intestines. Hence, it is advantageous for quantitative studies to use oblique MRI techniques that force the presentation of the uterus for image analysis to be similar from examination to examination. Sagittal sighting images were used to determine the spatial coordinates of the uterine cervix and fundus. From these coordinates, MRI parameters were calculated to allow the acquisition of eight contiguous oblique slice images whose thickness, position, and orientation were forced to depend on the vector connecting the fundus and cervix. Fat-suppressed spin-echo images were acquired with an echo time of 50 msec and repetition time of 3 seconds. Image resolution in plane was

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0.6 mm. This method has previously been shown to provide reproducible presentation of the uterus, independent of its size, location, and orientation in the pelvis (14). From each examination, three parameters were measured: endometrial volume (EV) obtained as described previously (14, 15) from area measurements of eight contiguous oblique slices; myometrial volume (MV) obtained similarly; and a measure of that part of the myometrial width attributable to the lesion (Figure 1).

During each untreated cycle, MV remained fairly constant; EV was high during menstruation. Ovulation occurred during both cycles, and EV increased rapidly during the subsequent luteal phase. The changes in EV were larger and more variable than observed previously in the population of healthy animals (14). The width of the lesion increased steadily during each cycle (Figure 2).

After the first dose of ICI 182,780, a similar pattern to the untreated cycles was noted, with EV and lesion width increasing in the luteal phase. However, in the 4 weeks after the second dose, EV, MV, and lesion width decreased by 87%, 57%, and 45%, respectively (Figures 1 and 2), and the lesion became much less conspicuous in MRI (Figure 1). Subsequently, some regrowth in measured lesion width was noted, but EV and MV declined further. Serum hormone measurements revealed that ovulation occurred slightly later and after higher preovulatory peak estradiol concentrations than in earlier untreated cycles (1460 pmol/l on day 22, compared with 500 to 540 pmol/l on days 17 to 20) and was followed by a normal luteal phase pattern of progesterone secretion (3.2 to 22.1 nmol/l) lasting 14 days. During 39 days after the second treatment, plasma estradiol concentrations fluctuated between 40 and 237 pmol/l, except for a peak of 1,117 pmol/l on cycle day 21; progesterone concentrations remained at basal values (0.32 to 1.92 nmol/l) throughout this period. Ovulation therefore did not occur.

Eighty days after treatment began, the monkey was euthanized by intravenous injection of sodium pentobarbitone (Euthatal®, May and Baker, Dagenham, Essex, U.K.) before it recovered consciousness after completing the last MRI procedure. No gross abnormalities were observed at necropsy. Histologic examination of the uterus disclosed multifocal endometrial tissue scattered throughout the myometrium (adenomyosis). In addition, small foci of endometriosis were present within adipose tissue adjacent to the ovaries and uterus.

A second retrospective examination of the magnetic resonance images revealed occasional small high-signal foci within the adipose tissue and on the serosal surface of the uterus, consistent with the endometriosis noted during histologic examination. However, under our MRI conditions, these were nonspecific and too small to be diagnostically useful or quantifiable. Although adenomyosis is not routinely treated in women (except perhaps incidentally during therapy for endometriosis or leiomyoma), the lesions are quite analogous to endometriosis and, hence, could be expected to respond to the same hormonal therapies (18). We conclude that asymptomatic adenomyosis in monkeys can be diagnosed by MRI, and that removing the endogenous estrogen drive by means of pure estrogen antagonist was, in this case, beneficial in reducing the size of the lesion.

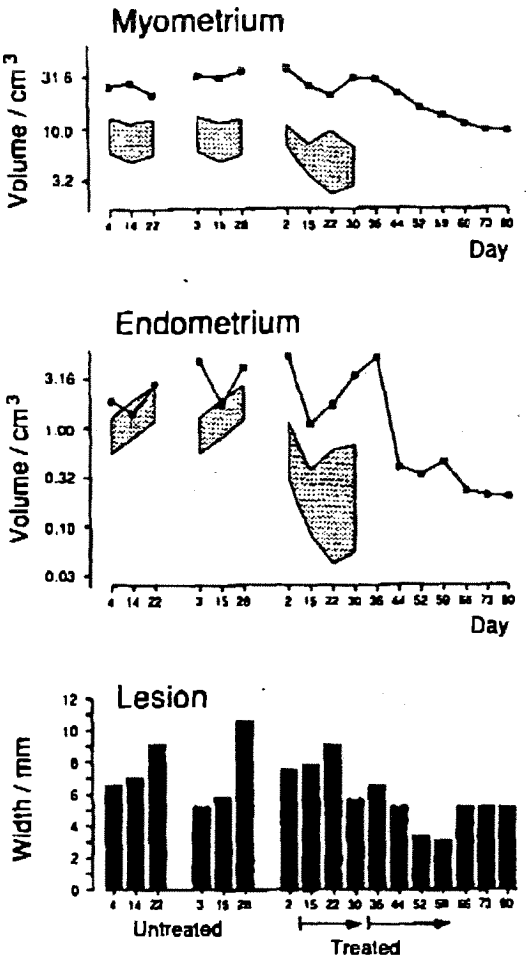

Figure 2. Response of myometrial volume, endometrial volume, and lesion width during two untreated cycles and two consecutive antiestrogen treatments. The stippled areas represent values for normal animals (mean ± 1 SD), untreated (n = 10) or treated with a single depot of ICI 182,780 (4 mg/kg, i.m., n = 6). Each volume was measured independently by two observers (J. C. W., S. A. B.) and the mean is shown. Each lesion width value is the mean for the same four locations in the corpus uteri, two of which are shown in Figure 1. Days are referred to the day of onset of the most recent menstruation.

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United States Patent [19]

Cavanak

[11] **4,388,307**

[45] **Jun. 14, 1983**

[54] **GALENICAL COMPOSITIONS**

[75] Inventor: **Thomas Cavanak**, Oberwil, Switzerland

[73] Assignee: **Sandoz Ltd.**, Basel, Switzerland

[21] Appl. No.: **347,276**

[22] Filed: **Feb. 9, 1982**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 208,181, Nov. 19, 1980, abandoned, which is a continuation-in-part of Ser. No. 82,487, Oct. 9, 1979, abandoned, which is a continuation of Ser. No. 16,950, Mar. 2, 1979, abandoned.

[30] **Foreign Application Priority Data**

Mar. 7, 1978 [CH] Switzerland 2461/78
Mar. 14, 1978 [CH] Switzerland 8634/78

[51] **Int. Cl.**³ **A61K 37/00; A61K 47/00**
[52] **U.S. Cl.** **424/177**; 424/365
[58] **Field of Search** 424/177, 365

[56] **References Cited**

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Primary Examiner—Delbert R. Phillips
Attorney, Agent, or Firm—Gerald D. Sharkin; Robert S. Honor; Walter F. Jewell

[57] **ABSTRACT**

The present invention provides a pharmaceutical composition comprising a pharmacologically active monocyclic peptide and a carrier comprising at least one of the following components:
(a) a non-ionic ester of a triglyceride and a polyalkylene polyol,
(b) a saturated fatty acid triglyceride, and
(c) a mono- or di-glyceride

having improved physical and absorption properties.

15 Claims, No Drawings

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GALENICAL COMPOSITIONS

This is a continuation-in-part of our co-pending application Ser. No. 208,181, filed Nov. 19th, 1980, now abandoned which in turn in a continuation-in-part of our application Ser. No. 82,487, filed Oct. 9th, 1979, now abandoned, which in turn was a continuation of our application Ser. No. 16,950, filed Mar. 2nd, 1979, now abandoned.

This invention relates to galenical compositions, particularly compositions containing a pharmacologically active mono-cyclic peptide.

Because of the hydrophobic and/or lipophilic character of such peptides, pharmaceutical formulations thereof with conventional solid or liquid pharmaceutical excipients tend to have disadvantages. For example the peptide may not be satisfactorily absorbed, the composition may not be well tolerated, the composition may not be sufficiently stable on storage, e.g. against crystallizing-out of the peptide, and/or the concentration of the peptide capable of being solubilized without crystallizing-out may be low, e.g. of the order of 3% or lower.

Problems of this nature arise not only with liquid formulations, but such solid forms such as solid "solutions", e.g. in the form of oral pellets, produced for example by melting a solid carrier, mixing in the active ingredients and allowing the mixture to solidify.

While there are many known proposals to alleviate or overcome problems of this type, it has been found after exhaustive trials that many of these proposals are inadequate in the area of the monocyclic peptides, in particular cyclosporins, with which the invention is concerned. It has, however, surprisingly been found that certain classes of glycerides used as carrier components do assist in alleviating these difficulties; in particular they, for example, may enable achievement of higher blood levels of active agent or avoid other problems such as instability.

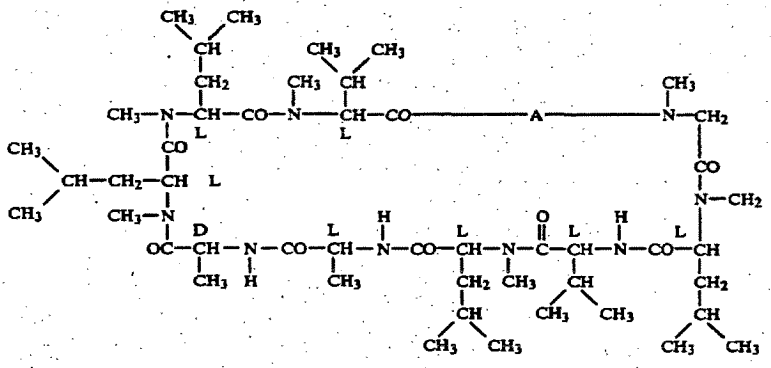
The present invention accordingly provides a pharmaceutical composition comprising a pharmacologically active mono-cyclic peptide and carrier comprising at least one of the following components:

(a) a trans esterification product of a natural or hydrogenated vegetable oil triglyceride and a polyalkylene polyol,

(b) a saturated fatty acid triglyceride, and

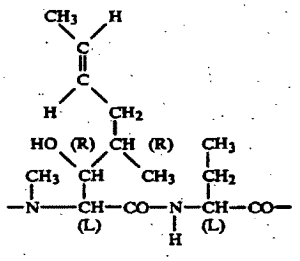
(c) a mono- or di-glyceride.

The compositions of the invention are particularly suitable for hydrophobic and/or lipophilic peptides which are insoluble or difficultly soluble in conventional pharmaceutical vehicles, in particular cyclosporins, including those having a basic ring structure as follows:

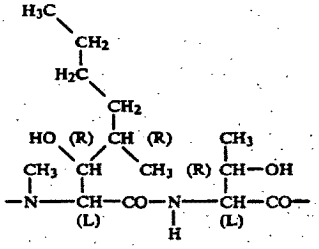


wherein A is a bivalent moiety containing two amino acids linked together.

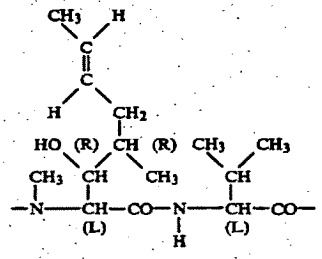
A may be for example:



(cyclosporin A)



(dihydro-cyclosporin C)



(cyclosporin D)

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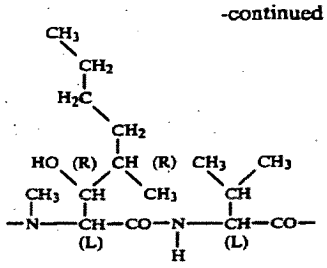


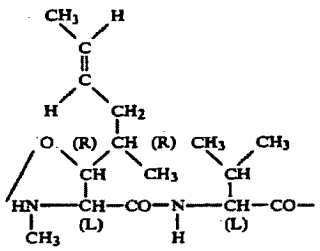
(dihydro-cyclosporin D), or

number=145–175 and a hydrophilic-lipophilic balance (H.L.B.)=4).

Component (b) may be obtained in conventional manner by esterifying a triglyceride with saturated fatty acids having a carbon chain length of 8 to 12 carbons. Generally these glycerides will have an iodine number of less than 2. Examples of the triglycerides with which this invention is concerned are the MIGLYOLS ® (Dynamit Nobel Witten/Rukr Germany), especially Miglyol 812, or Myritol 318 (Henkel Düsseldorf, Germany). The physical and chemical composition of Miglyols are shown in Table I.

TABLE I

	MIGLYOL 810	MIGLYOL 812	MIGLYOL 818	MIGLYOL 840
PHYSICAL CHARACTERISTICS				
Acid value	0.1 max	0.1 max.	0.2 max.	0.1 max.
Saponification value	340–360	325–345	315–320	320–340
Iodine value	1 max.	1 max.	10 max.	1 max.
Unsaponifiable matter (%)	0.3 max.	0.3 max.	0.2 max.	0.3 max.
Iodine colour value	2.0 max.	2.0 max.	3.1 max.	2.0 max.
Cloud point	0° C. max.	10° C. max.	10° C. max.	−10° C. max.
Moisture (%)	0.15 max.	0.15 max.	0.15 max.	0.15 max.
Density at 20° C.	0.94–0.96	0.94–0.96	0.93–0.95	0.92–0.94
Refraction at 20° C.	1.4490–1.4510	1.4480–1.4500	1.4490–1.4510	1.440–1.442
Viscosity at 20° C. (cps.)	27–30	28–32	30–33	9–12
DISTRIBUTION OF THE FATTY ACIDS IN THE GLYCERIDE				
Fatty Acids				
Hexanoic acid (C_6)	2% max.	3% max.	3% max.	3% max.
Octanoic acid (C_8)	65–75%	50–65%	45–60%	65–80%
Decanoic acid (C_{10})	25–35%	30–45%	25–40%	15–30%
Lauric acid (C_{12})	2% max.	5% max.	2–5%	3% max.
Linoleic acid (C_{18})	—	—	3–6%	—



(iso-cyclosporin D)

Cyclosporin A, dihydrocyclosporin C and isocyclosporin D are the preferred peptides. Cyclosporins e.g. as identified above are known compounds having known pharmacological activity, e.g. as described in U.S. Pat. Nos. 4,117,118 and 4,108,985 and in Belgian Pat. No. 866,810.

Component (a) may be prepared in conventional manner, e.g. as described in U.S. Pat. No. 3,288,824. The ester may be formed by transesterification of a triglyceride particularly a triglyceride from a vegetable oil, e.g. from kernel oil, almond oil, ground nut oil, olive oil and/or palm oil, with one molar part of a polyethylene glycol MW 200 to 800 and obtainable according to the process described in the U.S. Pat. No. 3,288,824 mentioned before, the contents of which are incorporated by reference. These esters may be obtained from Etablissement Gattefosse, Boulogne sur Seine, France, under the trade name LABRAFIL (see Fiedler, Lexikon der Hilfstoffe p. 320, 1971). The preferred ester is Labrafil M 1944 CS (a polyoxyethylated kernel oil) mixture having a density D^{20}=0.940–0.965, an acid number <2, an iodine number=60–90, a saponification

Component (c) is preferably one of the mono- or di-glycerides approved for pharmaceutical use, e.g. a mono- or di-(C_{16}–C_{20}) fatty acid glyceride, e.g. of stearic acid or especially of oleic acid. Preferably component (c) is glycerol mono-oleate (Monooleinum-Pharmacopoea Helvetica Sixth Edition).

Naturally when the components (a) and/or (c) present are solid, these should be chosen such that they can be melted at temperature at which the peptide is stable. Such components include, for example, glycerol monostearate or glycerol di-stearate, and Labrafil 2130.

The preferred total concentration of component (a) and/or component (b) and/or component (c) present in the pharmaceutical compositions according to the invention, as well as the weight ratio of individual components when two or more of these are present, will naturally depend, inter alia, on the particular component(s) used, and in particular on the solvent/solubilizing effect thereof, the particular mono-cyclic peptide used, the concentration of mono-cyclic peptide desired in the final composition and the solvent/solubilizing effect of any further pharmaceutical excipients present. In general the preferred weight ratio of component (a), (b) and/or (c) to peptide is 10 parts in total of the component (or components) to 0.2 to 10 parts of peptide, or more preferably 1 to 10 parts by weight of peptide, and conveniently from 1 to 7 parts by weight of peptide.

The pharmaceutical compositions of the invention may be made by mixing a pharmacologically active mono-cyclic peptide with the liquid carrier comprising component (a) and/or (b) and/or (c) as defined above. If the component (a) or (c) is solid, temperatures up to about 70° C. may be used, to produce a liquid melt in which the active agent may be dissolved in. The composition may be cooled and then, for example, ground.

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The pharmaceutical compositions may be formulated in conventional manner, if desired with further pharmaceutical excipients, into forms suitable for oral or parenteral administration. Preferably they are in liquid form.

Examples of preferred compositions are:

(a) Solutions for drinking, e.g. Example 1 hereinafter,

(b) Emulsions for drinking,

(c) Injection solutions, e.g. Examples 2 and 4 hereinafter,

(d) Solutions contained in capsules, e.g. Example 6 hereinafter,

(e) Pellets for oral administration.

The modes of administration are preferably intramuscular and subcutaneous administration or more preferably oral administration. In particular when component (b) is present, the pharmaceutical composition is preferably used for parenteral administration.

The pharmaceutical compositions according to the invention may be formulated with or without further exipients.

In particular solubilizing agents and solvents may be present in a concentration of up to 60% of the total composition, if desired, in order to attain a satisfactory concentration of peptide.

(i) Ethanol may be used as a further solubilizing agent/solvent. The ethanol content by weight may be for example 2 to 5% for parenteral compositions and 1 to 20% for oral compositions, calculated on the total composition.

(ii) For a parenteral composition, an alternative further solubilizing agent/solvent is a benzoic acid benzyl ester. This may be present at from 5 to 40% of by weight of the total composition.

(iii) A vegetable oil, such as olive oil or corn oil, may be present in both oral and parenteral compositions as Vehicle. The vegetable oil content by weight may be for example for 35 to 60%, calculated on the total composition.

(iv) For emulsions for drinking, preferably agent (a) and/or (c) as defined above is present as well as a lecithin such as soya lecithin. Such emulsions may contain from 20% to 80% by weight water and contain ethanol as a solubilizing agent/solvent.

(v) For oral pellets, it is preferred to use a solid or semi-solid component (a) or (c), especially component (c). Colloidal silicic acid, sugar, and microcrystalline cellulose are suitable excipients.

Compositions in accordance with the invention comprising a cyclosporin and a carrier comprising a component (a) together with (i) ethanol and (iii) a vegetable oil as set forth above are especially advantageous in that they provide solutions characterised by a high degree of stability. In particular they exhibit markedly improved stability compared with equivalent compositions in which one or other of the components (i) or (iii) are omitted, particularly when higher concentrations of cyclosporin (e.g. of the order of 10% and even up to 20% by weight based on the total weight of the composition) are present. Thus on storage over longer periods of time, compositions formulated with a carrier comprising (a) and (i) only exhibit cyclosporin precipitation at lower temperatures, e.g. at temperatures of ca. 5° C., such as are commonly employed for storage of pharmaceuticals, e.g. in hospitals, while compositions formulated with a carrier comprising (a) and (iii) only, exhibit cyclosporin precipitation at both lower and elevated temperatures, e.g. at temperatures of from 5° up to 50° C. In contrast, for compositions formulated with a carrier comprising all three ingredients, no precipitation of the cyclosporin is observed on storage over longer periods of time, both at lower and elevated temperatures, e.g. at temperatures of from 5° to 50° C., even when higher concentrations of cyclosporin, e.g. as aforesaid, are present. The compositions of the invention thus have the advantage of a greatly improved shelf-life with reduced temperature criticality. Unlike compositions in which one of the ingredients (i) and (iii) is omitted, they can be transported and kept in reserve at both lower and elevated temperatures, for periods in excess of several months for later use as, and when, required.

Compositions comprising a three component system (a)+(i)+(iii) also have the advantage of providing a self-emulsifying system in the presence of water, without immediate precipitation of the active ingredient. This is of importance in respect to the bio-availability of the active agent, since precipitation in e.g. the aqueous medium of the stomach or on intra-muscular injection leads to severely impaired resorption. The occurrence of problems in relation to cyclosporin bio-availability employing hitherto known formulations has been recognised and discussed e.g. in Calne et al., "IRCS Medical Science; Drug Metabolism and Toxicology; Immunology and Allergy; Kidneys and Urinary System; Pharmacology; Surgery and Transplantation" 5, 595, (1977).

The properties of the compositions according to the invention may be determined in conventional manner. The stability of solutions particularly against crystallization-out of the active agent may be determined using known tests. Tolerability of injection forms may be determined by observing the extent of bleeding and inflammations after injection, e.g. into thighs of rabbits and rhesus monkeys, and the time taken for these to heal, as well as by using other usual tolerability tests.

The absorption of the pharmacologically active peptide, e.g. rapid onset of a satisfactory concentration of the peptide in the blood, and a high total absorption of the peptide over 24 hours, is indicated in standard tests.

In one test a pharmaceutical composition according to the invention is administered to rabbits, rats, dogs or rhesus monkeys orally, intramuscularly or subcutaneously, at a dose of from 2 to 600 mg/kg animal body weight of active peptide. Blood serum samples and urine samples are taken at regular intervals thereafter, e.g. every hour, and are analysed for the concentration of peptide therein in conventional manner.

For example the pharmacological activity in a sample may be ascertained in conventional manner according to known tests. In the case of cyclosporin A the effect of the peptide present in inhibiting lymphocyte proliferation may be ascertained. Thus the blood serum is collected at regular intervals after administration, and is added at a concentration of from 0.3 to 10% to a mouse in vitro spleen cell suspension in which lymphocyte proliferation is induced by Concavalin A over a 72 hour culture period. ^{3}-H-thymidine is then added and the thymidine incorporation after 24 hours is measured to indicate the lymphocyte proliferation.

If desired, the peptide may be administered in radioactive form. For example in the case of the cyclosporins, in one experiment 100 mg of ^{3}H-labelled cyclosporin A (prepared by cultivation of the known strain *Tolypocladium inflatum* Gams NRRL 8044 in the presence of methionine marked with tritium in the SCH_3 group thereof) contained in a pharmaceutical composition according to the invention in the form of a drinking

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solution, or in a capsule, is administered perorally, or in the form of an injection solution is administered intramuscularly, to male beagle dogs. Blood samples are obtained from each dog every 15 minutes after administration up to 1 hour after administration and thereafter every hour thereafter up to 8 hours after administration. The urine is collected also. Determination of the ratio-activity in the blood and in the urine indicates the peptide absorption.

The amount of peptide to be administered in the pharmaceutical compositions according to the invention will naturally depend upon the mode of administration, the effect desired and the condition to be treated.

In general the amount of peptide to be administered in a pharmaceutical composition according to invention will be of the same order to that administered by the same route in other pharmaceutical compositions.

In the case of the cyclosporins, the amounts to be administered for a therapeutically effective amount are well-known. When using compositions according to the invention a daily dose of from about 3 mg/kg to about 50 mg/kg is indicated in order to treat chronic inflammations or to provoke an immunosuppressive effect.

The following examples illustrate the invention. All temperatures are in degrees Centigrade.

EXAMPLE 1

Drink Solutions

(1a) 200 mg of cyclosporin A are dissolved on stirring in 1 ml of a mixture of Labrafil M 1944 CS and absolute ethanol (parts by weight 40:15) at 25°. 0.4 ml of olive oil or corn oil are added. The resultant mixture is filtered and filled into a small vial. The final solution contains for every 10 parts by weight of Labrafil; ca. 3 parts by weight of cyclosporin A, 3 parts by weight of ethanol and 5 parts by weight of olive oil or corn oil.

(1b) The composition of example (1a) may be produced on a large scale as follows:

150.00 kg Labrafil M 1944 CS are stirred for 5 minutes with 50.00 kg absolute ethanol. 50.00 kg cyclosporin A are then added to the mixture with stirring over a period of ca. 40 minutes until the cyclosporin A is completely dissolved. Ca. 212.00 kg olive oil are then added with stirring for ca. 10 minutes to give a total end weight of 462.50 kg. The obtained solution is filtered and filled into 50 ml containers which are then sealed, to give a total volume per container of 51.5 ml. As with any liquid composition comprising olive oil as an ingredient, the means of filtration employed is important.

If filtration is insufficient, and impurities, such as higher fatty acid ester components, present in the olive oil are not fully removed, these will separate out in the course of 1 to 2 months, producing a light ground sediment. While this is not critical to utility and does not reflect on the stability of the composition, i.e. on the stability of the active ingredient in the solution, for commercial purposes such sedimentation is preferably to be avoided. Suitably filtration for examples 1a and 1b is carried out by pre-filtration using a Seitz Supra 1000 (cellulose-Kieselguhr) layer filter or a Millipore Lifeguard CP 20 (fiber flass) filter, followed by filtration through a 7 μm polypropylene filtration cartridge, e.g. such as a Pall HDC BE cartridge.

For the purposes of administration composition 1a or 1b is advantageously mixed with a chocolate flavouring agent, e.g. as follows:

15 g Caotina (a chocolate flavouring agent available from the company Wander) are stirred into 50 ml of milk and the desired dosage of cyclosporin A drink-solution (7–12 ml of composition 1c) are added. The mixture is ingested immediately.

(1c) The following composition is obtained analogously to example (1a):

	Component	Content	
	Cyclosporin A	100.00 mg	
(a)	Labrafil M 1944 CS	300.00 mg	
(i)	100% Ethanol	100.00 mg	
(iii)	Olive oil	ca. 425.00 mg	to give an end volume of 1.00 ml.

The compositions 1a–1c above exhibit the advantages of a combination of carriers (a), (i) and (iii) as hereinbefore described.

EXAMPLE 2

Parenteral Forms for I.M. and S.C. Administration

100 mg of cyclosporin A are dissolved on stirring in a mixture of 40 mg ethanol and 0.5 ml Miglyol 812 at 25° C. The mixture is finally made up to 1 ml with Miglyol 812 and filled under sterile conditions into an ampoule. The final solution contains for every 10 parts by weight of Miglyol 812, 1 part by weight of cyclosporin A.

EXAMPLE 3

Parenteral Forms for I.M. and S.C. Administration

100 mg of cyclosporin A are dissolved on stirring in a mixture of 40 mg ethanol, 100 mg Labrafil M 1944 CS and 200 mg Miglyol 812 at 25°. The resulting mixture is made up to 1 ml with olive oil and filled under sterile conditions into an ampoule.

The final solution contains for every 10 parts by weight of Miglyol 812, 5 parts by weight each of cyclosporin A and Labrafil and 25 parts by weight of olive oil.

EXAMPLE 4

Parenteral Form for I.M. and S.C. Administration

200 mg of cyclosporin A are dissolved in a mixture of 400 mg benzoic acid benzyl ester and 0.3 ml Miglyol 812 at 25°. The resultant mixture is made up to 1 ml with Miglyol 812 and filled under sterile conditions into an ampoule.

The final solution contains for every 10 parts by weight of Miglyol 812, 6 parts by weight of cyclosporin A.

EXAMPLE 5

Parenteral Form for I.M. and S.C. Administration

200 mg of cyclosporin A are dissolved on stirring in a mixture of 50 mg ethanol, 300 mg Labrafil M 1944 CS and 0.3 ml Miglyol 812 at 25°. The resultant solution is made up to 1 ml with Miglyol 812 and filled under sterile conditions into an ampoule.

The final solution contains for every 10 parts by weight of Miglyol 812, 7 parts by weight of Labrafil and 5 parts by weight of cyclosporin A.

EXAMPLE 6

Capsules for Oral Administration

200 mg of cyclosporin A are dissolved on stirring in a mixture of 600 mg Glycerol mono-oleate and 30 mg ethanol at 30°. The final solution is encapsulated in a soft gelatine capsule.

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What we claim is:

1. A liquid pharmaceutical composition comprising a pharmaceutically effective amount of a cyclosporin and a carrier comprising the following components:

(a) a trans-esterification product of a natural vegetable oil triglyceride and a polyalkylene polyol;

(b) a vegetable oil; and

(c) ethanol; whrein the ratio of component (a) to cyclosporin is 10:0.2 to 10 parts by weight; the amount of component (b) is 35 to 60% by weight based on the total weight of the composition, and the amount of component (c) is 1 to 20% by weight based on the total weight of the composition.

2. Composition according to claim 1, wherein the cyclosporin is cyclosporin A.

3. Composition according to claim 1, wherein the cyclosporin is dihydrocyclosporin C.

4. Composition according to claim 1, wherein the cyclosporin is cyclosporin D.

5. Composition according to claim 1, wherein the cyclosporin is dihydrocyclosporin D.

6. Composition according to claim 1, wherein component (a) is a trans-esterification product of two molar parts of a natural vegetable oil triglyceride and one molar part of a polyethylene glycol of MW 200 to 800.

7. Composition according to claim 6, wherein the natural vegetable oil is kernel oil.

8. Composition according to claim 7, wherein component (a) is a polyoxyethylated kernel oil mixture, having a density of $D^{20}=0.940–0.965$, an acid number <2, an iodine number=60–90, a saponification number=145–175 and a hydrophilic-lipophilic balance (H.L.B.)=4.

9. Composition according to claim 1, wherein component (b) is olive oil or corn oil.

10. Composition according to claim 9, wherein component (b) is olive oil.

11. Composition according to claim 1, wherein the ratio of component (a) to cyclosporin is 10:1 to 10 parts by weight.

12. Composition according to claim 11, wherein the ratio is 10:1 to 7 parts by weight.

13. Composition according to claim 1, wherein components (b) and (c) together are present in an amount of up to 60% by weight based on the total weight of the composition.

14. Composition according to claim 1, formulated as solution for oral administration.

15. A liquid pharmaceutical composition comprising a pharmaceutically effective amount of a cyclosporin and a carrier comprising the following components:

(a) a trans-esterification product of a hydrogenated vegetable oil triglyceride and a polyalkylene polyol;

(b) a vegetable oil; and

(c) ethanol;

wherein the ratio of component (a) to cyclosporin is 10:0.2 to 10 parts by weight; the amount of component (b) is 35 to 60% by weight based on the total weight of the composition, and the amount of component (c) is 1 to 20% by weight based on the total weight of the composition.

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(54) **Antigestagen- und antiöstrogenwirksame Verbindungen zur Behandlung hormonabhängiger Tumoren.**

(57) Mittel, enthaltend mindestens eine antigestagen- und mindestens eine antiöstrogenwirksame Verbindung, sind zur Behandlung hormonabhängiger Tumoren geeignet.

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Beschreibung

Antigestagen- und antiöstrogenwirksame Verbindungen zur Behandlung hormonabhängiger Tumoren

Die Erfindung betrifft Mittel zur Behandlung hormonabhängiger Tumoren, enthaltend mindestens eine Verbindung mit antigestagener (AG) und mindestens eine Verbindung mit antiöstrogener (AÖ) Wirkung sowie die Verwendung einer Kombination von AG mit AÖ für die angegebene Indikation.

Antiöstrogenwirksame Verbindungen sind zur Behandlung von Krankheiten geeignet, die durch Östrogene bedingt oder von Östrogenen abhängig sind, beispielsweise zur Behandlung von östrogenabhängigen Tumoren, wie Mammakarzinom, Prostatahyperplasie oder Meningeom.

So wird zum Beispiel das Antiöstrogen Tamoxifen zur palliativen Behandlung des nichtoperablen Mammakarzinoms sowie zur adjuvanten Therapie nach Primärbehandlung des Mammakarzinoms angewandt. Mit Tamoxifen wird die Krankheit jedoch nicht geheilt. Für die Sekundärtherapie werden Gestagene oder Aromatasehemmer verwendet. In der Praemenopause führen Ovariektomie, Tamoxifen oder LHRH-Analoga (LHRH = Luteinizing hormon releasing hormons) zu vergleichbaren Ansprechraten (Lit. H.T. Mouridsen and R. Paridaens, Eur. J. Cancer Clin. Oncol., 24, S. 99 - 105, 1988).

In neuerer Zeit wird auch die Verwendung von Antigestagenen im Bereich der Tumortherapie, insbesondere für die Indikation Mammacarcinom diskutiert. Eine erste Phase-II-Studie mit 17β-Hydroxy-11β-(4-dimethylaminophenyl)-17α-(prop-1-inyl)-estra-4,9-dien-3-on an postmenopausalen bzw. ovariektomierten Endokrintherapieresistenten Patientinnen mit metastasierendem Mammacarcinom wird von Maudelonde et al. in Hormonal Manipulation of Cancer, Eds. J.G.M. Klijn, R. Paridaens und J.A. Folkens in Raven Press, S. 55 (1987) berichtet.

Der Erfindung liegt die Aufgabe zugrunde, Arzneimittel für die Behandlung hormonabhängiger Tumoren bereitzustellen, die eine hohe, möglichst höhere Wirksamkeit im Vergleich zu den bekannten Mitteln haben.

Diese Aufgabe wird durch die Erfindung gelöst.

Es wurde gefunden, daß in der Kombination von AG und AÖ die Wirksamkeit der Einzelkomponenten beträchtlich verstärkt wird. Die erfindungsgemäße Kombination beruht auf der Erkenntnis, daß das Wachstum hormonabhängiger Tumoren gleichzeitig von Östrogenen und Gestagenen abhängig ist. So konnten in einem Großteil der Mammacarcinome sowohl Östrogen- als auch Progesteronrezeptoren nachgewiesen werden. Durch die Kombination von AG und AÖ auf Rezeptorebene im Tumor wird nicht nur eine Ovarblockade, sondern auch eine Blockade der aus anderen Geweben entstehenden betreffenden Hormone bewirkt. Eine Kombination von AG und AÖ eignet sich daher zur Therapie sowohl des prä- wie des postmenopausalen Mammacarcinoms.

Das Gewichtsverhältnis beider Komponenten kann dabei in weiten Grenzen variiert werden. So können sowohl gleiche Mengen AG und AÖ als auch ein Überschuß eines der beiden Komponente eingesetzt werden. AG und AÖ werden gemeinsam, getrennt, gleichzeitig und/oder zeitlich abgestuft (sequential), in einem Gewichtsverhältnis von im wesentlichen 1:50 bis 50:1, vorzugsweise 1:30 bis 30:1, und insbesondere 1:15 bis 15:1 verwendet.

Vorzugsweise können AG und AÖ kombiniert in einer Dosiseinheit appliziert werden.

Als Antigestagene kommen alle Verbindungen infrage, die eine starke Affinität zum Gestagenrezeptor (Progesteronrezeptor) besitzen und dabei keine eigene gestagene Aktivität zeigen. Als kompetitive Progesteronantagonisten kommen beispielsweise folgende Steroide infrage:
11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-on (RU-38486),
11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-18-methyl-17α-propinyl-4,9(10)-estradien-3-on und
11β-[(4-N,N-Dimethylamino)-phenyl]-17aβ-hydroxy-17aα-propinyl-D-homo-4,9(10),16-estratrien-3-on (alle EP-A 0 057 115);
ferner
11β-p-Methoxyphenyl-17β-hydroxy-17α-ethinyl-4,9(10)-estradien-3-on (Steroids 37 (1981) 361-382) und
11β-(4-Dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on (EP-A 0129 499)

Die Antigestagene werden gemäß vorliegender Erfindung in Mengen von 10 mg bis 200 mg eingesetzt; im allgemeinen wird man mit 50 bis 100 mg 11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9(10)-gonadien-3-on pro Tag oder einer biologisch äquivalenten Menge eines anderen Antigestagens auskommen.

Als antiöstrogen wirkende Verbindungen kommen Antiöstrogene und Aromatasehemmer infrage. Antiöstrogene und Aromatasehemmer gemäß vorliegender Erfindung können sowohl von Steroiden abgeleitet oder nicht-steroidale Verbindungen sein. Unter antiöstrogen wirkenden Verbindungen gemäß vorliegender Erfindung sollen aber nur solche Verbindungen verstanden werden, die möglichst selektiv wirken, d.h. die im wesentlichen nur die Wirkung von Östrogen hemmen und/oder deren Konzentration senken. Die Antiöstrogene wirken als kompetitive Östrogenantagonisten, indem sie Östrogen vom Rezeptor verdrängen, während Aromatasehemmer die Biosynthese des Östrogens unterdrücken. Verbindungen vom Typ des Aminoglutethimids, 3-alkylierte 3-(4-Aminophenyl)-piperidin-2,6-dione und andere, die außer dem Östrogenspiegel auch auf andere Sexualhormonserumkonzentrationen erniedrigend wirken, sind gemäß vorliegender Erfindung als antiöstrogen wirksame Verbindungen nicht geeignet.

Als Antiöstrogene kommen alle gebräuchlichen Antiöstrogene in Betracht, die vorstehend genannte Bedingung erfüllen. Sie können etwa in gleichen Mengen eingesetzt werden wie die bereits im Handel

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befindlichen Antiöstrogene, das heißt die tägliche Dosis beträgt etwa 5 - 100 mg für Tamoxifen oder biologisch äquivalente Mengen eines anderen Antiöstrogens. Als nicht-steroidale Antiöstrogene seien beispielsweise genannt:
Tamoxifen = (Z)-2-[p-(1,2-Diphenyl-1-butenyl)-phenoxy]-N,N-dimethyläthylamin,
Nafoxidin = 1-2-[4-(6-Methoxy-2-phenyl-3,4-dihydro-1-naphthyl)-phenoxy]-äthyl-pyrrolidin, hydrochlorid,
Mer 25 = 1-[p(2-Diäthylaminoäthoxy)-phenyl]-2-(p-methoxyphenyl)-1-phenyläthanol und
Verbindungen vom 1,1,2-Triphenylbut-1-en-Typ, insbesondere das 1,1-Bis(3'-acetoxyphenyl)-2-phenyl-but-1-en (J. Cancer Res. Clin. Oncol., (1986), 112, S. 119 - 124).

Ferner kommen als steroidale Antiöstrogene infrage:
11α-Methoxy-17α-äthinyl-1,3,5(10)-östratrien-3,17β-diol,
16β-Äthylestradiol und
11-(3,17β-Dihydroxy-1,3,5(10)-estratrien-7α-yl)-undecansäure-(N-butyl-N-methyl)-amid (EP-A 0138 504).

Als Aromatasehemmer sind alle Verbindungen geeignet, die die Bildung von Östrogenen aus ihren Vorstufen hemmen, wie beispielsweise das in der deutschen Offenlegungsschrift 33 22 285 beschriebene
1-Methyl-androsta-1,4-dien-3,17-dion,
das in Journal of Clinical Endocrinology and Metabolism. 49, 672 (1979) beschriebene
Testolacton (17a-Oxa-D-homoandrost-1,4-dien-3,17-dion),
die in "Endocrinology" 1973, Vol. 92, No. 3, Seite 874 beschriebenen
Verbindungen
Androsta-4,6-dien-3,17-dion,
Androsta-4,6-dien-17β-ol-3-on-acetat,
Androsta-1,4,6-trien-3,17-dion
4-Androsten-19-chlor-3,17-dion,
4-Androsten-3,6,17-trion,
die in der deutschen Offenlegungsschrift 31 24 780 beschriebenen
19-alkynylierten Steroide,
die in der deutschen Offenlegungsschrift 31 24 719 beschriebenen
10-(1,2-Propadienyl)-steroide,
die in der europäischen Patentanmeldung, Veröffentlichungsnummer 100 566 beschriebenen
19-Thio-androstanderivate,
das in "Endocrinology" 1977, Vol. 100, No. 6, Seite 1684 und der US-Patentschrift 4,235,893 beschriebene
4-Androsten-4-ol-3,17-dion und dessen Ester,
die in der deutschen Offenlegungsschrift 35 39 244 beschriebenen
1-Methyl-15α-alkyl-androsta-1,4-dien-3,17-dione,
die in der deutschen Offenlegungsschrift 36 44 358 beschriebenen
10β-Alkinyl-4,9(11)-östradien-derivate
und das in der europäischen Patentanmeldung 0250262 beschriebene
1,2β-Methylen-6-methylen-4-androsten-3,17-dion.

Als nicht-steroidaler Aromatasehemmer sei beispielsweise das [4-(5,6,7,8-Tetrahydroimidazo[1,5α]-pyridin-5-yl)benzonitril-monohydrochlorid] erwähnt (Cancer Res., 48, S. 834-838, 1988).

Die Dosierung liegt bei 1 - 1000 mg 1-Methyl-androsta-1,4-dien-3,17-dion pro Tag oder biologisch äquivalenten Dosen von anderen Aromatasehemmern.

Antigestagen- und antiöstrogenwirksame Verbindungen können zum Beispiel lokal, topisch, subcutan, enteral oder parenteral appliziert werden.

Für die enterale Applikation kommen insbesondere Tabletten, Dragees, Kapseln, Pillen, Suspensionen oder Lösungen infrage, die in üblicher Weise mit den in der Galenik üblichen Zusätzen und Trägersubstanzen hergestellt werden können. Für die lokale oder topische Anwendung kommen beispielsweise Vaginalzäpfchen oder transdermale Systeme wie Hautpflaster infrage.

Die bevorzugte subcutane Injektion wird mit einer öligen Lösung der betreffenden Komponente (n) vorgenommen.

Eine AG-Dosiseinheit enthält etwa 10 - 200 mg 11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9(10)gonadien-3-on oder eine biologisch äquivalente Menge eines anderen Antigestagens.

Eine AÖ-Dosiseinheit enthält 1 - 100 mg Tamoxifen oder 10 - 200 mg 1-Methyl-androsta-1,4-dien-3,17-dion oder eine biologisch äquivalente Menge einer anderen antiöstrogen wirksamen Verbindung.

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Beispiel 1

10,0 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
140,5 mg	Laktose
69,5 mg	Maisstärke
2,5 mg	Polyvinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
225,0 mg	Gesamtgewicht der Tablette

Beispiel 2

50,0 mg	1-Methyl-androsta-1,4-dien-3,17-dion
115,0 mg	Laktose
50,0 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette

Beispiel 3

25,0 mg	1-Methyl-androsta-1,4-dien-3,17-dion
25,0 mg	11B-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17B-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
115,0 mg	Laktose
50,0 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben angegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

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Beispiel 4

10,0 mg	Tamoxifen
10,0 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
135,0 mg	Laktose
60,0 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben angegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

Die folgenden Beispiele 5 bis 12 beziehen sich auf die Zusammensetzungen öliger Lösungen. Die hergestellten Lösungen werden in Ampullen abgefüllt.

Beispiel 5

100,0 mg	Tamoxifen
343,4 mg	Rizinusöl
608,6 mg	Benzylbenzoat
1052,0 mg	= 1 ml

Beispiel 6

55,0 mg	1-Methyl-androsta-1,4-dien-3,17-dion
55,0 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
343,4 mg	Rizinusöl
608,6 mg	Benzylbenzoat
1062,0 mg	= 1 ml

Die erfindungsgemäßen Wirkstoffe können auch mit jeweils der Hälfte der oben angegebenen Zusätze getrennt in zwei Kammern abgefüllt werden.

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Beispiel 7

10 mg	11-(3,17β-Dihydroxy-1,3,5(10)estratrien-7α-yl)-undecansäure-(N-butyl-N-methyl)-amid
0,9 ml	Rizinusöl
0,1 ml	Benzylbenzoat
1,0 ml	

Beispiel 8

10 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
0,9 ml	Rizinusöl
0,1 ml	Benzylbenzoat
1,0 ml	

Beispiel 9

10 mg	1,1-Bis(3'-acetoxyphenyl)-2-phenyl-but-1-en
0,9 ml	Olivenöl
1,0 ml	

Beispiel 10

10 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1(Z)-enyl)-4,9-estradien-3-on
0,9 ml	Olivenöl
1,0 ml	

Beispiel 11

60 mg	11-(3,17β-Dihydroxy-1,3,5(10)estratien-7α-yl)-undecansäure-(N-butyl-N-methyl)-amid
10 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on
0,9 ml	Rizinusöl
0,1 ml	Benzylbenzoat
1,0 ml	

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Beispiel 12

60 mg	1,1-Bis(3'-acetoxyphenyl)-2-phenyl-but-1-en
10 mg	11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1(Z)-enyl)-4,9-estradien-3-on
1,0 ml	Olivenöl
1,0 ml	

Ergebnisse

Die Ergebnisse der Untersuchungen am hormonabhängigen, östrogen- und progesteronrezeptor-positiven MXT(+)-Mammacarcinom der Maus (Watson C., Medina D., Clark J.H., Cancer Res. 1977, 37, S. 3344-3348) sind den Tabellen 1 und 2 sowie der Abbildung 1 zu entnehmen.

Als MXT-Tumor wurde die XT-Linie M 3.2. verwendet, die freundlicherweise von Dr. A. E. Bogden, EG + G Bogden Laboratories, Worcester, MA, USA als gefrorene Probe zur Verfügung gestellt wurde. Nach Auftauen wurden Stücke mit einem Volumen von ungefähr 2 mm^3 subcutan in intakte, weibliche 8-10 Wochen alte BDF1-Mäuse (Charles River Wiga, BRD) implantiert.

Nachdem der Tumor einen Durchmesser von ungefähr 1 cm erreicht hatte, wurde er weiter auf BDF1-Mäuse übertragen, wie später beschrieben werden wird. Tumoren wurden von verschiedenen Generationen der Übertragungen genommen, eingefroren und in flüssigen Stickstoff aufbewahrt.

Für die Durchführung eines Versuches wurden Tumorstücke einer gefrorenen Probe in 3-5 Mäuse implantiert. Im nächsten Versuchsabschnitt wird die Hormonabhängigkeit der Tumoren durch Implantation in intakte und ovariektomierte Mäuse getestet (J. Med. Chem., 1985, 28, S. 1880-1885).

Wenn in den ovariektomierten Mäusen nach 6 Wochen eine Inhibierung des Tumorwachstums von mehr als 90 % im Vergleich zu den intakten Kontrolltieren auftritt, so können diese Tumoren für weitere Untersuchungen verwendet werden. Zwei bis drei Tumoren wurden von ein bis zwei als Spender dienenden Tieren entnommen und in MEM 199-Medium (MEM = Minimum Essential Medium) in Stücke von ungefähr 2 mm Durchmesser geschnitten. Diese Stücke werden - wie oben beschrieben - subcutan in BDF1-Mäuse (2 Tumoren / Maus) implantiert.

a) Therapie etablierter Tumoren

20 Tage nach Implantation der Tumoren werden die Mäuse nach Tumoren abgetastet. Nur Mäuse mit zwei ertastbaren Tumoren werden verwendet. Diese Tiere werden willkürlich in Gruppen von 9 bis 10 Tieren eingeteilt. Am nächsten Tag wird mit der 2 oder 3 Wochen dauernden Behandlung begonnen. Die Testsubstanzen werden 6 mal wöchentlich s.c. injiziert. Die Tumorflächen werden durch Messen mit einem Greifzirkel 1- oder 2mal wöchentlich gemessen. Als Tumorfläche gilt das Produkt aus dem längsten und dem dazu senkrechten Durchmesser. Am Ende der Behandlung werden die Tiere gewogen und getötet. Die Tumoren, Ovarien, Uteri und Vaginae wurden entfernt und deren Feuchtgewichte bestimmt (J. Med. Chem., loc. cit.).

b) Prophylaxe-Modell

Nach Implantation der Tumoren wurden die Tiere willkürlich in Gruppen von 9 - 10 Tieren eingeteilt. Am nächsten Tag wird mit der Behandlung begonnen. Die Testsubstanzen werden täglich subcutan als ölige Lösungen (10 %ige Benzylbenzoat-Lösung) injiziert, oder es wird eine Ovariektomie durchgeführt. Nach 6wöchiger Behandlung wird mit den Tieren wie oben weiterverfahren.

aa) Therapie etablierter Tumoren

Antiöstrogenwirksame Verbindungen

Eine 6 mal wöchentlich s.c. applizierte Dosis von 30 mg/kg Körpergewicht 11-(3,17β-Dihydroxy-1,3,5(10)estratrien-7α-yl)- undecansäure-(N-butyl-N-methyl)-amid (=AÖ-A) führte bei der Therapie etablierter Tumoren zu einer Wachstumshemmung von 33 % bezogen auf die Tumorfläche.

Antigestagene

Mit dem Antigestagen 11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-on (=AG-B) wurde bei s.c.-Applikation von 6 mal wöchentlich 5 mg/kg Körpergewicht eine Wachstumshemmung von 52 % bezogen auf die Tumorfläche beobachtet.

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AG/AÖ-Kombination

Die Kombination der beiden Verbindungen AÖ-A und AG-B in den oben angegebenen Dosen verursacht eine Hemmung von 72 %, bezogen auf die Tumorfläche. Der Effekt der Kombination ist signifikant besser ($p < 0,05$) als die jeweiligen Monotherapien und ist sogar der Ovariektomie, wenn auch nicht signifikant, überlegen.

Werden zur Beurteilung der Wachstumshemmung der Tumoren nicht die Tumorflächen, sondern die Tumorgewichte herangezogen, gelangt man zu vergleichbaren Ergebnissen, wie sich aus Tabelle 1 ergibt.

bb) Prophylaktische Therapie von Tumoren (Tabelle 2)

Im Prophylaxe-Modell des MXT(+)-Tumors, bei dem die Therapie sofort nach der Implantation des Tumors begonnen und für 6 Wochen fortgesetzt wird, hat das Antiöstrogen 1,1-Bis-(3'-acetoxyphenyl)-2-phenyl-but-1-en (=AÖ-C) keinen signifikanten Antitumoreffekt (Dosis = 8 mg/kg)

Das Antigestagen 11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1(Z)-enyl)-4,9-estradien-3-on (= AG-D) hemmt in diesem Modell das Tumorwachstum, und zwar um 68 %. Die Kombination der beiden vorstehend genannten Komponenten AÖ-C und AG-D führt ebenfalls zu einer deutlichen Verstärkung der Antitumorwirkung im Vergleich zu der antigestagen Komponente allein.

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TABELLE 1 MXT(+)-MAMMACARCINOM DER MAUS (THERAPIE ETABLIERTER TUMOREN)

	Tumorfläche (mm^2)	% T/C	Tumorgewicht (mg)	% T/C
Kontrolle	251 ± 134	100	2199 ± 1185	100
Ovariektomie	113 ± 61	45	941 ± 368*	43
AÖ-A, 30 mg/kg	168 ± 41	67	1579 ± 389	72
AG-B, 5 mg/kg	120 ± 62	48	976 ± 513*	44
AÖ-A, 30 mg/kg + AG-B, 5 mg/kg	71 ± 23	28	487 ± 153*	22

* $p<0,05$ (U-Test) gegen Kontrolle

Dosierung: 6 x wöchentlich s.c. in Rizinusöl/Benzylbenzoat

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TABELLE 2

EINFLUß VON AG-D ALLEIN UND IN KOMBINATION MIT AÖ-C MIT MXT M 3.2 MAMMATUMOR-MODELL

Substanz	Dosis (a) (mg/kg)	Tumorgewicht (b) (% T/C)
1. AG-D	1,0	32*
AG-D + AÖ-C	1,0 + 8,0	8*
2. AG-D	1,0	47*
AG-D + AÖ-C	1,0 + 16,0	21*

(a) Dosis : 3 x wöchentlich s.c. in Olivenöl
(b) Werte nach 6 Wochen Therapie

% T/C Therapiegruppe/Kontrolle x 100

* $p < 0,01$ (U-Test nach Wilcoxon)

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Patentansprüche

1) Mittel, enthaltend mindestens eine Verbindung mit antigestagener (AG) und mindestens eine Verbindung mit antiöstrogener (AÖ) Wirkung zur Behandlung hormonabhängiger Tumoren.

2) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß AG und AÖ in einem Gewichtsverhältnis von 1:50 bis 50:1 stehen.

3) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß AG und AÖ in getrennten Dosiseinheiten vorliegen.

4) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß AG und AÖ in einer gemeinsamen Dosiseinheit vorliegen.

5) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AG-Dosis einheit 10 bis 200 mg 11β-[(4-N,N-Dimethylamino)-phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9(10)-gonadien-3-on oder eine biologisch äquivalente Menge einer anderen antigestagen wirksamen Verbindung enthält.

6) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AG-Dosiseinheit 10 bis 200 mg 11β-[(4,N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-(3-hydroxy-prop-1(Z)-enyl) -4,9-estradien-3-on enthält.

7) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AÖ-Dosiseinheit 1 - 100 mg Tamoxifen oder eine biologisch äquivalente Menge einer anderen antiöstrogen wirksamen Verbindung enthält.

8) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AÖ-Dosiseinheit 10 - 200 mg 1-Methyl-androsta-1,4-dien-3,17 oder eine biologisch äquivalente Menge einer anderen antiöstrogen wirksamen Verbindung enthält.

9) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AÖ-Dosiseinheit 10 - 200 mg 11-(3,17β-Dihydroxy-1,3,5(10)-estratrien-7α-yl)-undecansäure-(N-butyl-N-methyl)-amid enthält.

10) Mittel nach Anspruch 1, dadurch gekennzeichnet, daß eine AÖ-Dosiseinheit 10 - 200 mg 1,1-Bis(3'-acetoxyphenyl)-2-phenyl-but-1-en-enthält.

11) Verwendung einer Kombination einer antigestagen - mit einer antiöstrogenwirksamen Verbindung für die Behandlung hormonabhängiger Tumoren.

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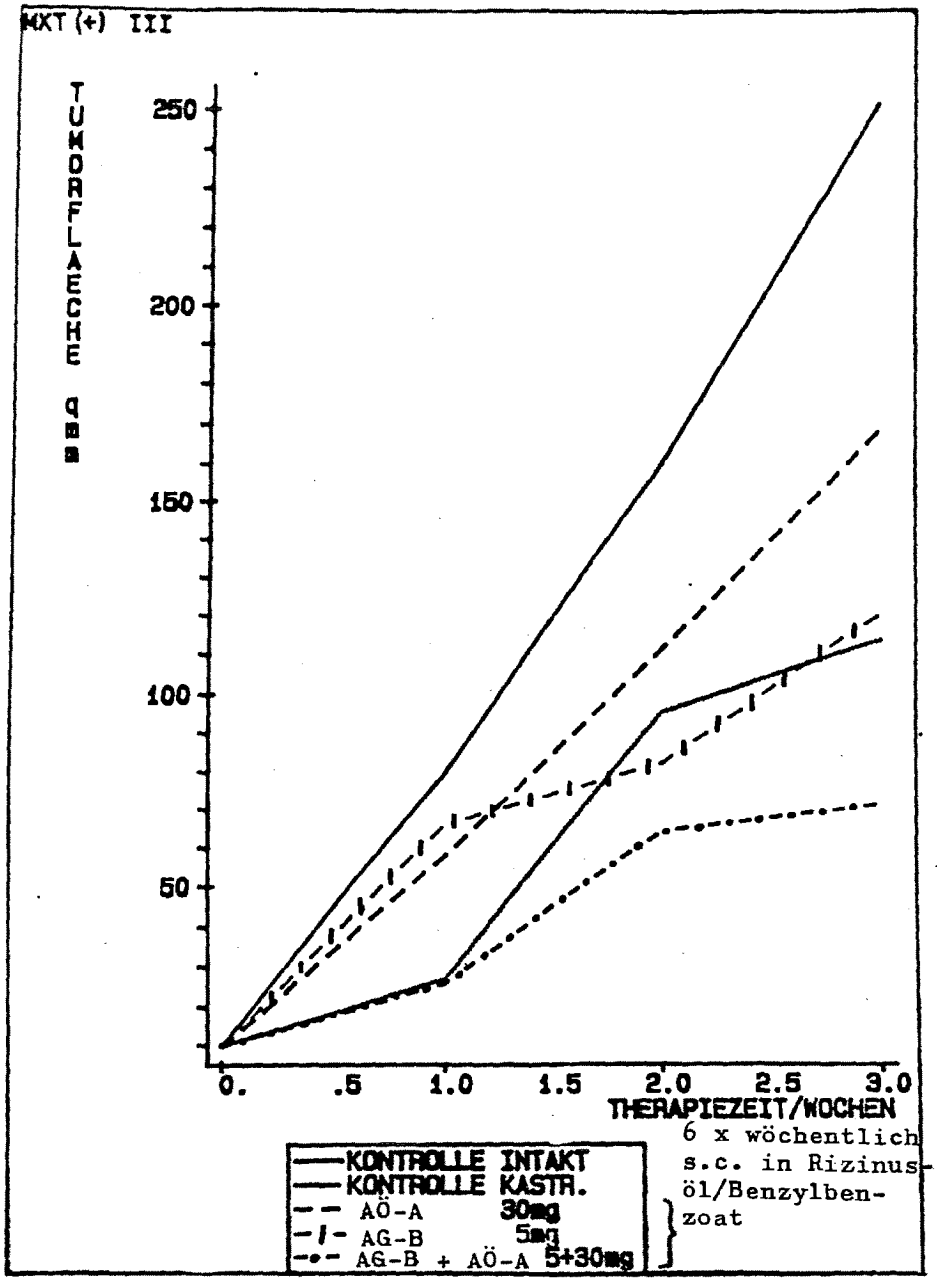

Abb. 1

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Europäisches Patentamt

EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung

EP 88 73 0222

EINSCHLÄGIGE DOKUMENTE

Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.4)
D,A	EP-A-0 138 504 (IMPERIAL CHEMICAL INDUSTRIES PLC) * Seite 13, Zeile 12 - Seite 14, Zeile 5; Seite 74, Zeilen 2-8; Ansprüche 6,7 *	1-11	A 61 K 31/565// (A 61 K 31/565 A 61 K 31:135)
D,A	DE-A-3 322 285 (SCHERING AG)	1-11	
D,A	EP-A-0 129 499 (SCHERING AG)	1-11	

RECHERCHIERTE SACHGEBIETE (Int. Cl.4)

A 61 K

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt

Recherchenort	Abschlußdatum der Recherche	Prüfer
DEN HAAG	21-12-1988	BRINKMANN C.

KATEGORIE DER GENANNTEN DOKUMENTE

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
O : nichtschriftliche Offenbarung
P : Zwischenliteratur

T : der Erfindung zugrunde liegende Theorien oder Grundsätze
E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
D : in der Anmeldung angeführtes Dokument
L : aus andern Gründen angeführtes Dokument

& : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

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Patentee: AstraZeneca AB
Opponent: Gedeon Richter Ltd.
Our Ref.: M 2363 EP/OPP

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definite bearing on the usefulness of any column packing prepared. The performances of the seven supports mentioned previously were examined under the same operating conditions. The supports that can be used for lightly loaded packings are: glass beads, Gas Chrom-P, and Chromosorb W-HMDS. The other four supports cannot be used for lightly loaded column packing since their interaction with the antihistamines causes excessive peak tailing.

The hydrogen flame detector used in conjunction with the 0.010-in. stainless capillary column would not respond to compounds with boiling points above 330°. This limitation prevented evaluation of this column for the analysis of these antihistamines.

The 100-ft. 0.065-in. copper open tubular column was coated with XF-1150 and evaluated using the above group of antihistamines. The Sr^{90} ionization detector was used with a column flow of 36 ml./minute. The retention times obtained were comparable to the 6-ft.-XF-1150 packed column, but the peak base widths were considerably wider. Because of this increase in base width, the 0.065-in. column was less efficient than the 6-ft. packed column.

A 250-ft. 0.065-in. column wound on a $1^1/_4$-in. diameter mandrel has been reported to be more efficient than a packed column (15). There are two possible reasons why efficiency was less than previously reported: (*a*) the column was shorter (100 ft.), and (*b*) the winding configuration was markedly different. The column was wound on a $1^1/_4 \times {}^1/_4$-in. bar which resulted in a definite flattening of the tube around the edge of the bar.

CONCLUSIONS

The antihistamines investigated, except for meclizine, can be separated, identified, and concentration estimated using the Carbowax 20M, PDEAS, and XF-1150 columns described. The PDEAS column is the most efficient of the three for the analysis of antihistamines.

The usefulness of the 0.010-in. capillary and the 0.065-in. open tubular columns cannot be properly evaluated until the mentioned limitations are removed.

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Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones

By C. RIFFKIN, R. HUBER, and C. H. KEYSSER

Steroid hormones may be administered parenterally in high concentrations as oil solutions. In this form they exhibit a prolonged action and reduce the number of injections required. To accommodate the demand for increasingly greater concentrations of hormones in solution, castor oil in combination with other suitable oil-miscible solvents, has been found to fulfill a need. The development of several formulations together with the results of animal testing, as well as clinical trials in humans, attest to the acceptability of this oil for the purposes intended.

FIXED OILS are included in the "United States Pharmacopeia XVI" as nonaqueous vehicles for injection and are characterized as being of vegetable origin, essentially odorless, and without suggestion of rancidity. They must also comply with certain measurable physical limits specified for the saponification, acid, and iodine values.

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The authors are indebted to the Chemical Control Laboratories for their assistance with the assays; to Dr. N. Coy and H. Roberts of the Physical and Analytical Section, for their development of special assays; to G. Lockwood of the Pharmacology Section for the animal muscle irritation tests; and especially to Dr. B. C. Reifenstein, Jr., of the medical staff, for the information concerning the clinical trials.

After subcutaneous injection, Deanesly and Parkes (1) observed the persistence of olive oil and castor oil in animal tissue. Comparing other oils Brown, *et al.* (2), reported that sesame and corn oils were superior to cottonseed and peanut oils because they were less irritating, less antigenic, more quickly released from tissue, and possessed superior physical properties.

More recently the use of steroid hormone medication has expanded considerably. Due to limited water solubility, hormones have been administered as aqueous suspensions or solutions in oil. It has been claimed that the latter provided the slow release preferred in cyclical

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TABLE I.—ANALYSIS OF COMMERCIAL OILS AND COMPARISON TO U.S.P. XVI SPECIFICATIONS

Oil	Lot No.	ml. 0.02 *N* NaOH Equiv. to Free Fatty Acid in 10-Gm. Sample	Sapon. Value	Iodine Value
Castor Oil	U.S.P. specs.	35.0[a]	179–185	83–88
	23946	14.0	183.3	84.8
	25589	4.6	179.8	87.0
	23463	7.9	182.7	84.5
	33742	9.2	180.4	84.2
Sesame Oil	U.S.P. specs.	3.0	188–195	103–116
	23549A	0.5	189.6	106.9
	26953	1.4	194.0	111.8
	33646	0.75	189.6	104.7
	29981	0.45	191.7	108.2
Cottonseed Oil	U.S.P. specs.	2.0	190–198	109–116
	49684	...	195.9	111.8
	44441	...	196.3	113.1
Corn Oil	U.S.P. specs.	2.0	187–193	102–128
	52148	1.0	194.5	119.1
	36716	1.2	191.4	124.4
	33436	1.2	189.3	125.0
	33715	1.0	189.3	123.0
Peanut Oil	U.S.P. specs.	2.0	185–195	84–100
	22160	1.2	192.0	94.4
	20993	1.4	191.7	93.2
	33622	0.8	193.1	87.8
	26147	1.2	190.4	93.9

[a] The U.S.P. specifies that the titration of free fatty acids in oral grade castor oil shall not exceed 7 ml. of 0.1 *N* NaOH which is equal to 35.0 ml. of 0.02 *N* NaOH.

TABLE II.—SOLUBILITY OF STEROIDS IN U.S.P. OILS AT 25°

Steroid	mg./ml. Castor Oil	mg./ml. Sesame Oil	mg./ml. Peanut Oil
17-Hydroxyprogesterone caproate	55.6	23.4	27.9
Testosterone	38.6	5.4	8.1
Estradiol valerate	60.6	16.1	18.8
Progesterone	52.0	22.9	23.5

therapy (3). Using withdrawal bleeding in human females as the criterion, Master, *et al.* (4), compared the duration of action of an aqueous suspension of progesterone with an oil solution, and confirmed the superiority of the latter. The prolongation of activity was generally related to storage in the fatty depots of the body (5).

In 1952 Junkmann (6) determined that a testosterone ester dissolved in sesame oil prolonged the androgenic effects in castrated rats. Davis and Wied (7) demonstrated that prolonged activity was also obtained in humans when oil solutions of a progesterone derivative were injected. There was still a limiting factor, however, in that only a relatively small amount of hormone could be dissolved in the traditional oils. To increase the solvent power of the oil it was necessary to add compatible and nonirritating cosolvents. Such additions consisted of benzyl benzoate, benzyl alcohol, ethyl lactate, ethyl oleate, etc. The U.S.P. recognized the need for such "other vehicles," with the restrictions that they must be safe in the volume of injection administered, and that they should not interfere with the therapeutic efficacy of the preparation or its testing.

Demand for increased hormone concentrations per dose, furthered the search for an acceptable oil with greater solubilizing power *per se*. Boschann (8) in 1954, observed that 17-hydroxyprogesterone caproate in a castor oil–ethyl lactate vehicle was well tolerated. In addition, private communications from clinicians in West Germany[1] reported good tolerance to Proluton-Depot containing a castor oil–benzyl benzoate vehicle. Since then other hormones have been used as solutions in ricinoleic acid esters, as well as in castor oil (9–11). Accordingly, an investigation was undertaken into the suitability of castor oil as a vehicle for parenteral administration of steroid hormones.

METHODS AND RESULTS

Representative samples of U.S.P. oils obtained from commercial sources were tested in accordance with the official method for free fatty acid content, saponification, and iodine values. The results are listed in Table I along with the U.S.P. XVI specifications for these oils.

Solubility of selected steroids in various oils was determined in the following manner. An excess of steroid was stirred for 4 hours at room temperature (25°) in the test oil, after which the undissolved solids were removed by filtration, and the clear solution assayed for steroid content. Table II shows the results obtained.

An attempt was made to reduce the free fatty acids in castor oil by treatment with alumina and anhy-

[1] Dr. Napp, Universitats-Krankenhaus, Hamburg; Dr. Pots, Humboldt-Universitat-Charite Frauenklinik, Berlin; Dr. Prill, Universitats-Frauenklinik, Wurzburg; and Dr. Rauscher, Universitats-Frauenklinik, Vienna.

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TABLE III.—ABSORPTION OF OIL FROM ANIMAL MUSCLE[a]

Days after Injection	Oil	ml. 0.02 N NaOH Equiv.	Residual Oil in Muscle (estd.)
1–3	Castor oil (aged)	50	1 day —50% 3 days—20%
1–3	Castor oil U.S.P.	13	1 day —30% 3 days—10%
1–3	Sesame oil U.S.P.	1.4	1 day —30% 3 days—30%
7–60	All oils	...	Declining 10 to 2%

[a] 1 ml. injected into back muscle of rabbit.

drous sodium sulfate. Three grams of dried, powdered, amorphous aluminum oxide (Merck No. 1097) and 6 Gm. of anhydrous sodium sulfate, reagent grade, were suspended in 120 ml. of oil and heated at 80° under a blanket of nitrogen for 1.5 hours. After allowing the oil to cool to room temperature, the solids were filtered off and the acids titrated in the usual manner. A significant reduction in free fatty acid was not obtained.

The absorption characteristics of oils with varying fatty acid content were examined and compared on a biological basis. Aged castor oil with a high free fatty acid content was compared to fresh U.S.P. castor oil with a low acid content and U.S.P. sesame oil by injecting 1 ml. of oil into the back muscles of rabbits, approximately 2 in. from the iliac crest. A rotational pattern of injection was used and the oil samples were stained to aid visibility in the tissues. The animals were sacrificed and the muscles excised and examined grossly. The results were averaged and appear in Table III.

The test disclosed that oil migrated or was carried to the fascia, and very small amounts remained for 60 days. Localized degeneration produced by the high acid value castor oil was essentially healed in 7 days, and the low acid value castor oil appeared to be no more irritating than sesame oil.[2]

In a specific test for irritation 0.25 ml. of the above oil samples were also injected into the *vastus lateralis* muscles of rabbits. After 2 days the animals were sacrificed and the injected muscles examined grossly for evidence of irritation. It was found that the castor oil containing a high level of free fatty acid produced a lesion size measuring approximately 121 mm.[2]. The lesion itself was characterized mainly by degeneration of local tissue without necrosis. Castor oil with low free fatty acid and sesame oil, on the other hand, produced no measurable lesion at the injection site.

Combinations of benzyl alcohol and benzyl benzoate with both castor oil and sesame oil were also injected into the *vastus lateralis* muscles of rabbits and Table IV lists the lesion sizes produced.

Solutions which were formulated for clinical trials in humans were prepared by dissolving the steroid hormones in appropriate vehicles at 60° under nitrogen. The solutions were then filtered through a coarse sintered-glass filter with the aid of nitrogen pressure, filled into vials, and sterilized by autoclaving for 2 hours at 121° (15 lb. steam pressure). The products were then submitted for assay, safety, and animal muscle irritation testing prior to release for clinical investigation.

[2] Due to the apparent increase in free fatty acids with aging, subsequent work utilized fresh oils which required for neutralization less than 3 ml. of 0.1 N NaOH (15 ml. of 0.2 N NaOH) per 10 Gm. of sample.

DISCUSSION

Throughout the investigation it was desirable to have a reference oil to serve as a basis for comparison. Since sesame oil is universally accepted as a parenteral oil vehicle, it was chosen as the "standard" vegetable oil to be compared to castor oil, with and without other cosolvents. The physical, chemical, and biological properties of sesame oil are well documented and require no comments here.

Chemically, castor oil consists of the triglycerides of ricinoleic acid, together with small quantities of glycerides of other acids. The quantitative composition is given by Eckey (12) as follows: ricinoleic acid 87%, oleic acid 7.4%, linoleic acid 3.1%, dihydroxyricinoleic acid 0.6%, and miscellaneous acids 2.4%. Two grades are commonly recognized in this country—U.S. No. 1 which is cold pressed oil, and U.S. No. 3 which is oil extracted from the pressed cake. Only the former is used for medicinal purposes.

The high viscosity of castor oil compared to other vegetable oils is undoubtedly related to hydrogen bonding and it is probably the hydroxy groups which contribute to the greater polarity and superior solvent power of the oil. As indicated in Table I, the saponification and iodine values of commercial castor oil appear to be slightly lower than the U.S.P. XVI limits for oils used for injection. On the other hand, the content of free fatty acids even in fresh oil, varies considerably and exceeds the traditional limits for injectable oils. The significance of this is somewhat obscure, although "Remington's Practice of Pharmacy, 12th edition," page 387, states "a low free fatty acid content is essential since it indicates a fresh and pure product and not one that is likely to have become old and heavily contaminated with bacterial products."

Despite better solubility of steroids in castor oil, other cosolvents were necessary to dissolve the

TABLE IV.—LOCAL IRRITATION PRODUCED IN RABBIT MUSCLE BY INJECTION OF VARIOUS OIL VEHICLES[a]

Identification	Composition	Lesion size, mm.[2]
SHY-47-2	Sesame oil 98% Benzyl alcohol 2%	61
SHY-47-4	Castor oil 98% Benzyl alcohol 2%	Too small to measure
SHY-47-3	Sesame oil 95% Benzyl alcohol 5%	506
SHY-47-5	Castor oil 95% Benzyl alcohol 5%	106
SHY-14-2	Sesame oil 65% Benzyl benzoate 35%	291
SHY-14-5	Castor oil 65% Benzyl benzoate 35%	184
SHY-47-6	Sesame oil 63% Benzyl benzoate 35% Benzyl alcohol 2%	207
SHY-47-7	Castor oil 63% Benzyl benzoate 35% Benzyl alcohol 2%	262
SHY-14-3	Sesame oil 50% Benzyl benzoate 50%	291
SHY-14-6	Castor oil 50% Benzyl benzoate 50%	158

[a] A 0.25-ml. quantity of the oil vehicle was injected into the *vastus lateralis* muscle of the rabbit. Two days later the muscle was excised and the lesion size measured in mm.[2].

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increasingly higher concentrations required by therapeutic regimens. Often these materials contributed additional advantages. For example, the addition of benzyl alcohol or benzyl benzoate to castor oil resulted in a lower and more favorable viscosity, making it easier to inject. Also, benzyl alcohol was an effective preservative and local anesthetic.

The nature of the irritative response depended on the particular hormone, its concentration in the formulations, and/or the composition of the vehicle. Although rabbit muscles are more sensitive than human muscles, they were selected primarily because local changes in the muscle were observed easily. It was not always possible, however, to correlate muscle irritation in animals to that of humans.

A numerical assignment to lesion size was used solely as a convenience for grading response. The numbers alone do not adequately describe the nature of the response, however. More completely it is characterized by the amount of hemorrhage and edema and the incidence, degree, and extent of local degeneration produced by the injection. A slight, reversible irritative response may cover a large area and a severe irreversible one may be comparatively small. A decrease in the size of the degenerated area indicates a reversible condition. The presence of necrosis, which is the most damaging situation, means that the cellular structure was destroyed and repair must take place. The debris must be removed and the original cellular mass in the area replaced with fibrous connective tissue. The extent of this fibrosis or formation of scar tissue gives an index of the amount of irreversible damage. Fortunately necrosis was not encountered, indicating the lack of permanent muscle damage. Since these changes take time, final assessment of the effects of an injection in the muscle frequently required observation for 7 days or longer.

It is unfortunate that pain cannot be measured by any known method of animal testing. The animal usually does not respond unless the painful stimulus is marked. Furthermore, the pain caused by injection into human muscle is not usually proportionate to the irritation produced either in animal muscle or in human muscle. Realizing that these limitations are inherent in animal test methods, it remained for final acceptability to be determined in man.

When it was discovered that 17-hydroxyprogesterone caproate possessed high progestational activity, potencies of the order of 65 mg./ml. were used. By increasing the dose, additional prolongation of action was obtained, and eventually concentrations of the order of 250 mg./ml. were required. Such a solution in sesame oil produced acceptable animal muscle tolerance, but the pain and local reaction in humans was so great as to prohibit the adoption of the formulation as a commercial product (see Table V, Lot Pr. 142-53/15-10).[8] Solutions were also prepared using castor oil as the vehicle, and Table V lists the formulations tested and the results obtained. Information obtained from the clinical trials (14–21) attested to the acceptability and safety of the adopted formulations.

Inherent in the development of an acceptable formulation of 17-hydroxyprogesterone caproate was the required development of a suitable assay method. This was accomplished by Roberts and Florey (13) using paper-strip chromatography.

Since estrogens are more potent than progestogens and require less per dose, an acceptable formulation of estradiol valerate was easier to prepare. Besides use in estrogen therapy, estradiol valerate has found utility in the treatment of carcinoma, and for that purpose high dosages were required. Concentrations were increased from 10 to 40 mg./ml. and

[8] Reactions in excess of 5–6% were considered unacceptable.

TABLE V.—EVALUATION OF 250 mg./ml. 17-HYDROXYPROGESTERONE CAPROATE SOLUTIONS IN VARIOUS OIL VEHICLES

Vehicle Composition	Animal Muscle Lesion Size, mm.[a]	Lot Number and Remarks on Clinical Testing
Sesame oil 50% Benzyl benzoate 50%	1049	Pr.142-53/15-7—238 injections, 20.6% reactions, rejected
Castor oil 58% Benzyl benzoate 40% Benzyl alcohol 2%	691	Pr.142-53/15-8—270 injections, 23.2% reactions, rejected
Sesame oil 60% Benzyl benzoate 35% Benzyl alcohol 5%	697	Pr.142-53/15-10—189 injections, 10.7% reactions, rejected
Castor oil 54% Benzyl benzoate 46%	258	Pr.142-53/15-11—503 injections, 4.2% reactions, accepted
Castor oil 52% Benzyl benzoate 46% Benzyl alcohol 2%	633	Pr.142-53/15-13—924 injections, 1.3% reactions, accepted

[a] Injection of 0.25 ml. into *vastus lateralis* muscle of rabbits and lesion size determined 2 days after injection.

TABLE VI.—EVALUATION OF ESTRADIOL VALERATE IN VARIOUS OIL VEHICLES

Composition	Animal Muscle Lesion Size, mm.[a]	Lot Number and Remarks
20 mg./ml. in Castor oil 78%, Benzyl benzoate 20%, Benzyl alcohol 2%	197	Es.31-53/15-B—Commercially available
30 mg./ml. in Sesame oil 60%, Benzyl benzoate 40%	306	DEK-98-2—Not tested clinically; dosage increased to 40 mg./ml.
30 mg./ml. in Castor oil 80%, Benzyl benzoate 20%	194	Es.31-53-V—Not tested clinically; dosage increased to 40 mg./ml.
40 mg./ml. in Sesame oil 65%, Benzyl benzoate 30%, Benzyl alcohol 5%	803	SHX-94-4—Too irritating; not tested clinically
40 mg./ml. in Sesame oil 58%, Benzyl benzoate 40%, Benzyl alcohol 2%	496	Es.31-53-8—201 injections, 23.2% reactions, rejected
40 mg./ml. in Castor oil 58%, Benzyl benzoate 40%, Benzyl alcohol 2%	250	Es.31-53-A—826 injections, 2.67% reactions (all mild), accepted

[a] Injection of 0.25 ml. into *vastus lateralis* muscle of rabbits and lesion size determined 2 days after injection.

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again formulations containing castor oil in the vehicle proved to be less irritating than similar preparations containing sesame oil. Physically and chemically both oil solutions were stable. Based on acceptable preliminary data, formulations such as those listed in Table VI were prepared and tested. Acceptability in humans was confirmed by clinicians and described in the literature (22, 23) and in case reports.[4]

SUMMARY

1. The development and testing of parenteral steroid hormone formulations has been described, using castor oil as a vehicle.

2. After ascertaining stability and animal muscle irritation, selected formulations were evaluated in humans. They exhibited a prolonged action, were effective and well tolerated.

3. Examples of commercially available products are the estrogen, estradiol valerate[5] at 20 mg./mL. and 40 mg./mL., and the progestogen, 17-hydroxyprogesterone caproate[6] at 250 mg./mL.

[4] Case reports: estradiol valerate, 20 mg./mL., in castor oil 78%, benzyl benzoate 20%, benzyl alcohol 2%—90 injections in 46 patients. Two mild local reactions. Estradiol valerate 40 mg./mL. in castor oil 58%, benzyl benzoate 40%, benzyl alcohol 2%—51 patients. Number of injections not completely tabulated. One report is in press.

[5] Marketed as Delestrogen by E. R. Squibb & Sons, New York, N. Y.

[6] Marketed as Delalutin by E. R. Squibb & Sons, New York, N. Y.

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Isolation of Marrubiin, a Sterol, and a Sesquiterpene from *Marrubium vulgare*

By HAROLD J. NICHOLAS*

A simple column chromatographic method for isolating the bicyclic diterpene marrubiin from acetone and ethanol extracts of *Marrubium vulgare* L. is described. An unsaturated sterol of the stigmastanol series, present in esterified form, and a sesquiterpene ($C_{15}H_{22}O_2$) have been isolated from the extracts.

IN PREPARATION for radioactive tracer work on the biosynthesis of marrubiin it was necessary to examine extracts of the plant for associated terpenoid substances. A convenient column chromatographic method was therefore devised for separating relatively pure marrubiin from crude acetone extracts. Two new terpenoid substances were detected in the extracts.

EXPERIMENTAL

Materials and Methods.—Ground *M. vulgare* L. was obtained from the Wunderlich-Diez Corp., Hasbrouck Heights, N. J.[1] This material was exhaustively extracted with hot acetone or hot ethanol. Either solution on removal of solvent by distillation (the last stages *in vacuo*) yielded black, viscous material which was used for further examination. Melting points were determined on a Fisher-Johns melting point apparatus. Optical rotations (in $CHCl_3$) and C—H analyses were determined by Drs. G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England. An infrared spectrum of the unidentified diterpene was determined on a Perkin-Elmer spectrophotometer by the KBr disk method.[2] An infrared spectrum of the sterol was determined in chloroform solution in a 0.1-mm. sealed cell, compensated with $CHCl_3$, on a Beckman IR-4 recording infrared spectrophotometer,[3] and by the KBr disk method. The

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The author is indebted to Fuad Jarjoura and Sharon Moriarity for their technical assistance.
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[1] This firm has given assurance that the material investigated was *M. vulgare* or white horehound, not *Ballota hirsuta* (black horehound).

[2] We are indebted to the Department of Pathology, University of Kansas, for this determination.

[3] Determined by Sadtler Research Laboratories, Philadelphia, Pa.

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Opposition against EP Patent 1 250 138
Patentee: AstraZeneca AB
Opposition by: Gedeon Richter Ltd.
Our Ref.: M2363 EP/OPP

Munich, July 19, 2006
PT/DH/ISS/MSC

Facts and arguments

1. The subject matter of EP 1 250 138 B1

EP 1 250 138 B1 (in the following "the opposed patent") relates to sustained release pharmaceutical formulations for administration by injection containing the steroidal antioestrogen fulvestrant. In particular, the patent relates to fulvestrant solutions in a ricinoleate vehicle which further comprises an alcohol and a non-aqueous ester.

A suitable feature analysis of Claim 1 of the opposed patent is as follows:

(1.1) A pharmaceutical formulation, comprising
(1.2) fulvestrant in
(1.3) a ricinoleate vehicle;
(1.4) a pharmaceutically acceptable non-aqueous ester solvent, and
(1.5) a pharmaceutically acceptable alcohol
wherein the formulation is adapted for
(1.6) intra-muscular administration and
(1.7) attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

To start with, above feature 1.7 does not represent a technical feature which is able to effectively distinguish the claimed subject matter from any prior art teaching. Rather, feature 1.7 has to be regarded as a mere result to be achieved (desideratum).

Claim 2 is formulated as an independent claim, however, most of its features are more or less identical to those of claim 1. Notably, the wording of claim 2 slightly deviates from the wording

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of claim 1 (e.g. claim 2 mentions "intra-muscular injection", whereas claim 1 refers to "intra-muscular administration" which however describes the same technical result since a intra-muscular administration can only be achieved by an injection). In essence, claim 2 specifies the features of claim 1 as follows:

- the alcohol of above feature (1.5) is specified in claim 2 to be 30% or less weight per volume of formulation;
- the ester component of above feature (1.4) is specified to be present as at least 1% weight per volume of formulation (it is also mentioned that the ester 1.4 is miscible with the ricinoleate vehicle 1.3 which is also disclosed in claim 1).

Claim 3 relates to claims 1 or 2 and mentions that the blood plasma fulvestrant concentration of above feature (1.7) is at least $2.5ngml^{-1}$.

Claim 4 is again independent. It is more or less identical to claim 2, however, the above "desideratum" feature (1.7) is not contained. Instead, it is said that the formulation exhibits at least $45mgml^{-1}$ fulvestrant.

Claims 5 to 17 are dependent claims which define preferred amounts of alcohol (claims 5 to 8) and ester (claims 9 to 17).

Claims 18 to 30 relate to preferred embodiments of the alleged invention. Although some of these claims (e.g. claims 18 and 19) are formulated in an independent manner, they comprise all features as mentioned in a previous independent claim (e.g. claim 4) and should therefore be regarded as dependent claims. All claims 18 to 29 relate to specific examples of alcohols, esters and the ricinoleate vehicle and to their relative amounts within the formulation. Claims 27 to 29 relates to specific amounts and concentrations of the active ingredient fulvestrant and to specific volumes of the formulation.

Claim 31 is a dependent claim which relates to the use of the formulation in medical therapy.

Dependent Claim 32 is a "Swiss-type claim" which relates to the treatment of benign or malignant disease of the breast or reproductive tract.

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Dependent Claim 33 relates to a syringe containing the claimed formulation.

2. The cited prior art

D1: EP 0 346 014 A1
D2: WO 96/19997
D3: WO 97/21440
D4: Waterton et al., Laboratory Animal Science, vol. 43, no. 3, 1993, p. 247-251
D5: US 4,388,307
D6: EP 0 310 542 A1
D7: Riffkin et al.: J. Pharm. Sci. (1964), 53(8), 891-895

Documents D1 to D4 have already been cited in the International Search Report. Document D7 has been mentioned in the opposed patent on page 5, last two entries of table 1.

3. Opposition under Art. 100(a) EPC, Lack of Patentability

3.1. Lack of Novelty of Claim 1

Document D1 belongs to the patent family of US 5,183,814 which is admitted as prior art in paragraph [0014], page 6, line 1 of the opposed patent. Patentee, however, points out to an alleged complication in as far the US patent counterpart to D1 uses a "high alcohol concentration". It should be noted at the outset that claim 1 does not exclude any high alcohol concentration at all.

Example 3 of Document D1 (see page 9 of D1) discloses the following features (lines 37 to 40 on page 9): An oil based injection formulation (feature 1.1) of fulvestrant (1.2) which further comprises benzyl alcohol (1.5) and castor oil (1.3). The described formulation is administered by intramuscular injection (1.6). Thus, all features except for 1.4 and 1.7 are already met by this example of D1.

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On page 7, lines 24/25 of D1, the oily solutions described in D1 are referred to as depot formulations which provide a selective antioestrogenic effect for a period of e.g. 1 to 6 weeks. Consequently, also feature 1.7 is fulfilled.

On the other hand, besides the fact that feature 1.7 is defined by a wish of a result to be achieved (see previously page 1 of this brief), the own specification on page 11 line 38 in section [0048] and Figure 1 show the claimed effect only for 5 days rather than "at least 2 weeks".

On page 5, line 16 of D1, esters or partial esters derived from fatty acids and hexitol anhydrides (e.g. sorbitan monooleate) are mentioned as suitable emulsifying agents for pharmaceutical formulations (pharmaceutically acceptable) on the basis of castor oil (page 5, line 13 of D1). In the paragraph starting in line 20 of page 5, inter alia "oily suspensions" are described, wherein it is made reference to dispering-, wetting- and suspending agents "as mentioned above". This means that also the mentioned esters or partial esters derived from fatty acids and hexitol anhydrides from page 5 , line 16 may be contained in the oily formulations as disclosed in D1. Since it is clear for a skilled person with common technical knowledge that these esters will likewise act as solvents (the skilled person knows that there is hardly any ester that will not exhibit solvent features) also feature 1.4 of claim 1 is fulfilled.

Besides, such fatty acid esters from D1 are structurally closely related to ethyl oleate, isopropyl myristate or isopropyl palmitate, which are mentioned as specific and particularly preferred examples (see paragraph [0029], page 7, lines 49/50 of the opposed patent) for the ester components according to the opposed patent.

Since all features of claim 1 are anticipated by D1, clam 1 lacks novelty.

3.2. *Lack of Inventive Step of Claim 1*

If disregarding the novelty-destroying character of D1, e.g. by saying (just arguendo) that D1 discloses all features except for 1.4, D1 can be considered the closest prior art to the

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subject matter of claim 1. This is so, because D1 has the maximum amount of features in common with the claimed subject matter and relates to oily pharmaceutical formulations of the particular active ingredient fulvestrant. The only distinguishing feature between this closest prior art and the subject matter of claim 1 would then be argued to represent the claimed presence of a pharmaceutically acceptable non-aqueous ester solvent (feature 1.4), which is allegedly missing (in fact it is not!) in D1.

According to the opposed patent (please be referred to paragraph [0014], page 6, lines 4/5), D1 is also considered as the closest prior art. The technical effect of the use of an ester component is the allowance for reducing the alcohol concentration in the known, alcohol containing oily fulvestrant formulation. The high alcohol concentration within the formulations of D1 is said to (allegedly) "complicate" the manufacture at a commercial scale (paragraph [0014], page 6, lines 2 to 4 of the opposed patent). Therefore, the problem underlying the opposed patent is seen as the prevention of the precipitation of the active ingredient fulvestrant when lowering the alcohol concentration, which in turn seems to be a goal which should be achieved in order to prevent manufacturing complication.

Before this background, it was therefore the objective problem underlying the alleged invention to provide an oily injection formulation of fulvestrant on the basis of a ricinoleate vehicle which has a reduced alcohol content.

a) Combination of D1 and D5

When looking for a solution to this objective technical problem, the person skilled in the art would have consulted technical literature generally relating to the galenics of oily injectable formulations of lipophilic pharmaceutical compounds. Thereupon, he/she would have consulted e.g. D5 which relates to galenic compositions (which is already reflected in the title of D5: "galenic compositions") of hydrophobic/lipophilic agents (see col. 1, lines 31/32 of D5), in this particular case cyclosporins.

Apart from vegetable oil (D5, col 5, line 34) which forms the basis for the described vehicles, an alcohol (col. 5, line 25) and/or esters (see col. 5, line 31/32 as well as

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components a) to c) mentioned in col. 3 and 4 of D5) are disclosed in D5 as being suitable solubilizing agents.

Thus, the skilled person would have learned from D5 that esters from this document are generally suitable as solubilizing agents in oily solutions, also in combination with alcohols. As a consequence, D5 provides an incentive for the skilled person to try the use of an ester compound in an oily solution in which the alcohol content is to be decreased.

It should be stressed that present claim 1 of the opposed patent does not include any effective limitation with regard to the chemical nature of the ester, apart from the definition "non-aqueous". This kind of "definition" for the ester component does of course not distinguish the claimed esters from those mentioned in D5 (e.g. the components referred to in D7 as "component a) to c)", i.e. fatty acid esters of glycerids).

Thus, from a combination of D1 with D5, the claimed subject matter lacks inventive step.

b) Combination of D1 and D2/D6

A skilled person seeking a solution for the objective technical problem might likewise have considered the technical field of oily injectable compositions with respect to specific antioestrogenic agents. In doing so, he/she would have learned from Examples 5 of both D2 and D6 (the examples 5 in both documents are identical), that a lipophilic antioestrogenic agent (in this particular case: tamoxifen) may be formulated as a solution in castor oil (= "Rizinusöl") and an ester compound (benzyl benzoate, i.e one of the preferred esters according to the opposed patent). Moreover, D6 also exemplifies (see example 8 of D6) an oily solution in castor oil/ benzyl benzoate of an antioestrogenic steroid (please note that also fulvestrant in fact is an antioestrogenic steroid).

Thus, since the use of an ester compound as a solubilizing agent for an antioestrogenic steroid in castor oil is disclosed in both D2 and D6, the skilled person would have tried out such an ester as a solubilizer when being faced with the above-mentioned objective technical problem relating to the antioestrogenic steroid fulvestrant.

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This is even more so, as D2 and D6 teach that an ester is a promising solubilizing agent for castor oil, wherein the latter also constitutes the basis of the underlying vehicle ("ricinoleate vehicle").

In the pursuit of solving the underlying problem, the skilled person would have tried to substitute some of the alcohol (which concentration is to be reduced according to the objective problem) contained in the formulation according to the closest prior at by such an ester solubilizer and would have directly arrived at the subject matter of claim 1.

In other words, claim 1 lacks inventive step over a combination of D1 with D2 or D6.

c) Combination of D1 and D7

Moreover, a person skilled in the art looking for a solution to the underlying problem would have consulted D7. This document generally relates to castor oil vehicle systems for prolonged action of the injected active ingredient (which form the basis of the claimed oily solutions). In particular, D7 relates to pharmaceutical formulations of steroid hormones, i.e. the same chemical class of active ingredients as fulvestrant.

It is reported in the last paragraph of the left column on page 892 of D7, that in order "to increase the solvent power of the oil it was necessary to add compatible and non-irritating cosolvents. Such additions consisted of benzyl benzoate, benzyl alcohol, ethyl acetate, ethyl oleate, etc.".

In other words, D7 recommends both the use of alcohols and esters in order to increase the solubility of the steroid in the castor oil system.

Consequently, in the right column of page 894 of D7, various oily formulations are exemplified which comprise a steroid, castor oil, benzyl alcohol and benzyl benzoate (see the last two entries of table V and the first and last entry of table VI on page 894 of D5).

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Hence, from document D7 it is clearly evident that "ternary" systems of castor oil/alcohol/ester were well-known and fully established in the pharmaceutical field, in particular in the field of steroids, in order to provide injectable, oily sustained release formulations.

Before the background of the closest prior art d1, which teaches a fulvestrant solution in castor oil/alcohol, the skilled person would, and not only could, certainly have tried the well-established ternary vehicle systems known from e.g. D7 and would have used an ester compound in addition to the binary oil/alcohol system known from D1 in order to replace some of the alcohol (whose concentration he/she intended to decrease in accordance with the objective technical problem). By doing so, the skilled person would have directly and inevitably arrived at the claimed solution.

In other words, claim 1 lacks inventive step over a combination of D1 with D5.

d) Remarks

In this regard, it is the firm believe of the opponent that the allegedly surprising finding of the patentee as referred to in paragraph [0019], page 6 of the opposed patent is nothing more than a non-patentable discovery which is not sufficient to confer patentability to a clearly obvious combination. In the cited paragraph it is said that the introduction of a non-aqueous ester solvent "surprisingly eases the solubilisation of fulvestrant".

This would be due to the fact that the solubility of the active ingredient fulvestrant is significantly lower than the solubility of fulvestrant in an alcohol and even castor oil. Accordingly, it would be surprising that the ternary system including the ester would provide better solubility compared with the binary system known e.g. from the closest prior art D1 (in this regard, it is referred to the specific values given in table 2 on page 6 of the opposed patent). We respectfully submit that such a discovery is by no means sufficient to render the clearly obvious subject matter of claim 1 inventive over e.g. the above-discussed combination of D1 and D7.

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Moreover, it is clear for a skilled person that the allegedly surprising finding as reported in above-cited paragraph [0019] of the opposed patent only applies for very specific oils, alcohols and esters mentioned in table 2 of the opposed patent. These few examples can by no means justify the extraordinary breadth of claim 1 in which in particular the definition of the alcohol and the ester component is practically not limited at all. In particular, the claimed subject matter in its broad scope is not limited to a ternary system where the solubility of fulvestrant in the employed ester component is from the outset lower than its solubility in the ricinoleate vehicle.

3.3. Lack of Inventive Step of Claim 2

No inventive merit can be seen in the features distinguishing the subject matter described in claim 2 from that of claim 1. An amount of 30% or less weight of the alcohol component is already known to the skilled person from D7, which teaches in the Examples a vehicle comprising 2 to 5% alcohol. The same holds true for the feature of at least 1% weight of the ester component which is also already known from D7 (D7 teaches in the Examples between 40 and 46% of benzyl benzoate).

Claim 2 lacks inventive step.

3.4. Lack of Inventive Step of Claim 3

As feature 1.7 of claim 1 of the opposed patent has to be considered as a mere desideratum, which is hence not suitable to distinguish the claimed subject matter from any prior art teaching, the same holds true for the specific "feature" of claim 3: It refers to a specific blood plasma fulvestrant concentration ($2.5 ngml^{-1}$) that should be attained for at least two weeks.

However, for the case that the Examining Division should consider the teaching of claim 3 as a valid technical feature of the claimed formulation, it is submitted that the adaptation of the obvious combination of D1 and D7 as to arrive at the claimed specific blood plasma

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concentration would have certainly been within the ordinary skill and routine experimentation of a person skilled in the art. On the other hand, should the feature of claim 3 be considered by the Opposition Division to provide inventive merit, then the claimed invention would be in fact not sufficiently disclosed. This is due to the fact that the opposed patent does not provide any suitable teaching or indication for the skilled person, how the particularly preferred therapeutically significant blood plasma level of fulvestrant as defined in claim 3 could be achieved.

Thus, claim 3 either lacks inventive step or the opposed patent lacks sufficient disclosure.

3.5. Lack of Inventive Step of Claims 5 to 19

All these claims relate to specific amounts of alcohol and/or ester component within the claimed pharmaceutical formulation, wherein the chemical nature of the alcohol and ester is not particularly restricted. All these values are either directly derivable from document D7 with regard to the specific alcohol/ester as disclosed therein or would be obvious for a person skilled in the art from his/her general technical knowledge and by applying routine experiments.

3.6. Lack of Inventive Step of Claim 20

The claim is characterized by the use of a mixture of ethanol and benzyl alcohol as the pharmaceutically acceptable alcohol component. Both specific alcohols are well-known in the pharmaceutical filed, in particular as solubilizing agents. Moreover, mixtures of solubilizing agents are also within the general technical knowledge of the skilled person.

In particular, the use of benzyl alcohol is disclosed in D1 and D7. Ethanol is exemplified in D5 as a suitable solubilizing agent. No inventive merit can be seen in the simultaneous use of these both specific alcohols. The claim lacks inventive step.

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3.7. Lack of Inventive Step of Claims 21 and 22

Both claims are related to specific preferred examples of the ester component contained in the claimed ternary vehicle system. However, at least the use of benzyl benzoate in an oily vehicle system on the basis of castor oil is clearly obvious from D7, since benzyl benzoate is employed in all described examples.

Furthermore, ethyl oleate is mentioned in the last paragraph of the left column on page 892 of D7 as a possible alternative solubilizing agent. Accordingly, it would have also been obvious for the skilled person to generally use fatty acid esters of lower alkanols as a solubilizer. Consequently, also the use of isopropyl myristate and isopropyl palmitate, as also alternatively mentioned in claim 21 of the opposed patent, would have been obvious for a person skilled in the art.

In other words, none of these both claims involve inventive step.

3.8. Lack of Inventive Step of Claims 23 to 26

These claims relate to the specific use of benzyl benzoate as the ester component and the relative amounts of this ester compound and the additional alcohol component within the formulation. All features of these claims are within the routine skill of the person skilled in the art and, thus, do not confer inventiveness to the claimed subject matter.

3.9. Lack of Inventive Step of Claims 27 to 29

The specific values referred to in these claims (i.e. the total volume of the formulation, concentration of fulvestrant, total amount of fulvestrant) represent unexceptionally the results of mere routine experiments of a person skilled in the art. Hence, the claimed subject matter does not involve inventive step.

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3.10. Lack of Inventive Step of Claim 30

For claim 30, the very same lack of inventive step arguments apply as already put forward for claims 20, 21/22 and 5 to 19.

3.11. Lack of Inventive Step of Claims 31 to 33

These claims do not contain any subject matter which was not already known or self-evident for the skilled person with respect to the known active pharmaceutical agent fulvestrant. Its use in therapy, in particular to treat the specific indications as mentioned in claim 32, as well as the possibility to administer the respective injectable solutions by means of a syringe are clearly not surprising for a skilled person. The claim clearly lacks inventive step.

4. Conclusion and Requests

As is evident from above, the subject matter of claims 1 to 33 do not satisfy the requirements of patentability. Thus, it is requested that the opposed patent be revoked in toto on the basis of Art. 100(a) EPC. In the unlikely event that the Opposition Division cannot comply with our request without further ado, we request oral proceedings in accordance with Art. 116 EPC.

Dr. Paul Tauchner
European Patent Attorney

Enclosure:
Documents D1 through D7

InnoPharma Exhibit 1046.0708

Fourth IDS

Attachment III

InnoPharma Exhibit 1046.0709

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Reference	Application No./Patent No.
Z70635-2X EP	05016921.8 - 2112
Applicant/Proprietor	
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Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the European search report (R. 61 EPC) or the partial European search report/ declaration of no search (R. 63 EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☐ additional set(s) of copies of such documents is (are) enclosed as well.

The following have been approved:

☑ Abstract ☑ Title

☐ The Abstract was modified and the definitive text is attached to this communication.

The following figure will be published together with the abstract: NONE

Refund of the search fee

If applicable under Article 9 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

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European Patent Office

SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 05 01 6921

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	EP 0 346 014 A (IMPERIAL CHEMICAL INDUSTRIES) 13 December 1989 (1989-12-13) * page 9; example 3 *	1-33	INV. A61K31/565 A61P35/00 A61K47/14 A61K47/44
Y	RIFFKIN C ET AL: "CASTOR OIL AS A VEHICLE FOR PARENTERAL ADMINISTRATION OF STEROID HORMONES." JOURNAL OF PHARMACEUTICAL SCIENCES AUG 1964, vol. 53, August 1964 (1964-08), pages 891-895, XP009094139 ISSN: 0022-3549 * page 892, column 1, last paragraph * * tables 5,6 *	1-33	
A	WO 96/19997 A (SCHERING) 4 July 1996 (1996-07-04) * claims 1,5,6,8 * * page 16; example 5 *	1-33	
A	WO 97/21440 A (ZENECA) 19 June 1997 (1997-06-19) * claims 1,6 * * examples 1,3,4 *	1-33	TECHNICAL FIELDS SEARCHED (IPC) A61K
A	JOHN C. WATERTON; ET AL.: "A Case of Adenomyosis in a Pigtailed Monkey Diagnosed by Magnetic Resonance Imaging and treated with the Novel Pure Antiestrogen, ICI 182,780" LABORATORY ANIMAL SCIENCE, vol. 43, no. 3, 1993, pages 247-251, XP000998289 * page 247, column 2, paragraph 2 *	1-33	
A	EP 0 310 542 A (SCHERING AG [DE]) 5 April 1989 (1989-04-05) * claim 8 *	1-33	

-/--

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

Place of search	Date of completion of the search	Examiner
Munich	4 January 2008	Sindel, Ulrike

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C04)

InnoPharma Exhibit 1046.0711

European Patent Office

SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 05 01 6921

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	US 4 388 307 A (CAVANAK THOMAS [CH]) 14 June 1983 (1983-06-14) * examples 2-5 * * column 5, line 5 - line 37 *	1-33	

TECHNICAL FIELDS SEARCHED (IPC)

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

Place of search	Date of completion of the search	Examiner
Munich	4 January 2008	Sindel, Ulrike

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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L : document cited for other reasons

& : member of the same patent family, corresponding document

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 05 01 6921

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

04-01-2008

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0346014 A	13-12-1989	AT 109351 T	15-08-1994
		AU 622184 B2	02-04-1992
		AU 3592389 A	07-12-1989
		CA 1337591 C	21-11-1995
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		DK 273489 A	07-12-1989
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		NZ 298769 A	29-09-2000
		PL 320786 A1	27-10-1997
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		ZA 9610426 A	23-06-1997

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

InnoPharma Exhibit 1046.0713

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 05 01 6921

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

04-01-2008

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0310542 A	05-04-1989	NONE	
US 4388307 A	14-06-1983	AR 223667 A1	15-09-1981
		AT 375828 B	10-09-1984
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EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

InnoPharma Exhibit 1046.0714

The examination is being carried out on the **following application documents**:

Description, Pages

1-19 as originally filed

Claims, Numbers

1-33 as originally filed

Drawings, Sheets

1/1 as originally filed

1 The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: EP-A-0 346 014 (IMPERIAL CHEMICAL INDUSTRIES) 13 December 1989

D2: RIFFKIN C ET AL: "CASTOR OIL AS A VEHICLE FOR PARENTERAL ADMINISTRATION OF STEROID HORMONES." JOURNAL OF PHARMACEUTICAL SCIENCES AUG 1964, vol. 53, August 1964 (1964-08), pages 891-895, XP009094139 ISSN: 0022-3549

D3: WO 96/19997 A (SCHERING) 4 July 1996 (1996-07-04)

D4: WO 97/21440 A (ZENECA) 19 June 1997 (1997-06-19)

D5: JOHN C. WATERTON; ET AL.: "A Case of Adenomyosis in a Pigtailed Monkey Diagnosed by Magnetic Resonance Imaging and treated with the Novel Pure Antiestrogen, ICI 182,780" LABORATORY ANIMAL SCIENCE, vol. 43, no. 3, 1993, pages 247-251, XP000998289

D6: EP-A-0 310 542 (SCHERING AG [DE]) 5 April 1989 (1989-04-05)

D7: US-A-4 388 307 (CAVANAK THOMAS [CH]) 14 June 1983 (1983-06-14)

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D1 discloses a formulation for intramuscular injection containing the antiestrogenic agent fulvestrant and benzyl alcohol in castor oil (which is an ricinoleate). 1 ml of the composition comprises 50 mg fulvestrant and 400 mg benzyl alcohol in castor oil (see example 3). The injected formulation provides a depot with antiestrogenic effect for a period of one to six weeks (see page 7, lines 20-25).

D2 describes vehicles for the parenteral administration of steroid hormones. Vegetable oils like castor oil are used as vehicles in admixture with benzyl alcohol and benzyl benzoate (see tables 5-6). Benzyl alcohol and benzyl benzoate are used as cosolvents to increase the solvent power of the oil (see page 892, first column, last paragraph).

D3 describes a liquid formulation comprising tamoxifen as antiestrogenic agent and the non-aqueous ester solvent benzyl benzoate in castor oil (see example 5). Other antiestrogenic compounds like fulvestrant may also be used in this formulation (see page 12, third paragraph and page 13, paragraphs 2-3).

D4 describes a solution formulation of fulvestrant for oral administration. The formulation comprises Imwitor 742 (mono- and/or diglycerides of capric and caprylic acids), Cremophor RH40 (macrogol glycerolhydroxystearate), Miglyol 812 and ethanol (see examples).

D5 discloses the application of a castor-oil based depot formulation of ICI 182,780 (= fulvestrant) to pigtailed monkeys (see page 247, 2nd column, 2nd paragraph). The ingredients of the composition are not disclosed.

D6 describes a liquid formulation comprising an antiestrogenic steroid and the non-aqueous ester solvent benzyl benzoate in castor oil (see example 8). Fulvestrant is not listed as antiestrogenic agent.

D7 describes parenteral formulations of cyclosporine comprising 2-5% ethanol, benzyl benzoate as solubilizer and vegetable oil (see examples 2-5).

2 Novelty

The subject-matter of claims 1-33 is new in the sense of Article 54(1) and (2) EPC in view of the present prior art.

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None of the cited prior art discloses a depot formulation for intramuscular administration comprising fulvestrant in a ricinoleate vehicle, a non-aqueous ester solvent and alcohol.

3 Inventive step

The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1-33 does not involve an inventive step in the sense of Article 56 EPC.

D1 which is the closest prior art differs from the present application in that it does not disclose a formulation comprising additionally a non-aqueous ester solvent.

The problem to be solved is the provision of an oily depot injection formulation of fulvestrant which has lower alcohol concentration than the formulation in D1 but also prevents the precipitation of fulvestrant (see page 6, 1st paragraph of present application).
The solution provided is the addition of a non-aqueous ester solvent.

D2 describes the use of benzyl alcohol and benzyl benzoate as cosolvents in oily parenteral formulations of steroid hormones (see page 892, first column, last paragraph). Benzyl alcohol is comprised in amounts of 2-5%, the content of benzyl benzoate varies from 20 to 50% in vehicles like castor oil (see tables 5-6).

Since fulvestrant is also a steroid, the person skilled in the art was motivated with reasonable expectation of success to combine the teaching of D1 and D2 and to add benzyl benzoate to the formulation of D1 with simultaneous reduction of the alcohol compound.
Hence, in the absence of a surprising effect, the subject-matter of present claims does not involve an inventive step.

Furthermore, in the description there is no evidence by means of experimental results showing that the problem of the application has been solved with the subject-matter of present claims 1-33. Figure 1 gives blood plasma concentrations of fulvestrant only till day 5 after intramuscular administration. There is no evidence given that a depot

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for at least 2 weeks is achieved.

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Electronic Patent Application Fee Transmittal

Application Number:	10872784
Filing Date:	22-Jun-2004
Title of Invention:	Formulation
First Named Inventor/Applicant Name:	John R. Evans
Filer:	Donald J. Bird
Attorney Docket Number:	056291-5004-01

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1050	1050

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**1230**

Electronic Acknowledgement Receipt

EFS ID:	3819294
Application Number:	10872784
International Application Number:	
Confirmation Number:	2093
Title of Invention:	Formulation
First Named Inventor/Applicant Name:	John R. Evans
Customer Number:	09629
Filer:	Donald J. Bird
Filer Authorized By:	
Attorney Docket Number:	056291-5004-01
Receipt Date:	21-AUG-2008
Filing Date:	22-JUN-2004
Time Stamp:	17:08:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1230
RAM confirmation Number	2294
Deposit Account	500310
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amendment_and_Response.pdf	2501960 5353e639ed436b72339b618a495f8868438 2dd7a	yes	32
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment - After Non-Final Rejection		1	3	
	Claims		4	5	
	Applicant Arguments/Remarks Made in an Amendment		6	32	
Warnings:					
Information:					
2	Rule 130, 131 or 132 Affidavits	Declaration.pdf	25548191 1d1c68b3d1e722bd369771e557828b4fe3c 4533c	no	289
Warnings:					
Information:					
3	Foreign Reference	EP0310542_with_translation.pdf	1478653 921c7221bef33b060a464f74e3ccffde6e578 bde	no	27
Warnings:					
Information:					
4	NPL Documents	Gupta_1999.pdf	6862544 b05509588bdefbce6efb9011cfb9824fb90a 142e	no	85
Warnings:					
Information:					
5	NPL Documents	Lopatin_1972.pdf	1194880 ddd1992fa8ddc7aa0a28b4ae99e368ceffba 4809	no	10
Warnings:					
Information:					
6	NPL Documents	Nema_1997.pdf	731965 2d6844c41eac4a3162ad5903d019f7c4a9e 72c9e	no	6
Warnings:					
Information:					
7	NPL Documents	PhysiciansDeskReference.pdf	2279394 a740e8ba23f1a96b36930f96a1d98e81b14f 997e	no	9

Warnings:					
Information:					
8	NPL Documents	Powell_1998.pdf	1395534 7ff711769a2c18ac3bcc320826f52d7855016cbe	no	18
Warnings:					
Information:					
9	NPL Documents	Strickley_Part_I_2000.pdf	2383996 b5c5d0d1c2757df340cc6bb8794ee3e8c9f3ba55	no	26
Warnings:					
Information:					
10	NPL Documents	Strickley_Part_II_2000.pdf	2075882 637d54367fbaa1b6240f90612167389ba2c5084c	no	28
Warnings:					
Information:					
11	NPL Documents	Strickley_Part_III_2000.pdf	1498354 b25b6d28294a8be30c50eaad8bb96fc2680bcc69	no	18
Warnings:					
Information:					
12	NPL Documents	Wang_1980.pdf	818271 c2ac9999e0bdf0cabe41058542349be55731e1ee	no	11
Warnings:					
Information:					
13	Information Disclosure Statement Letter	056291-5004-01-IDS.pdf	22453940 514ed1f6eb049e5031c8232d143527957c16c067	no	221
Warnings:					
Information:					
14	Fee Worksheet (PTO-06)	fee-info.pdf	31629 1ba738ed7780daa8ce6c99d773b061632bddca44	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	71255193	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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9629 7590 10/06/2008

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/06/2008

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/872,784	06/22/2004	John R. Evans	056291-5004-01	2093

TITLE OF INVENTION: FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	01/06/2009

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

9629 7590 10/06/2008

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WASHINGTON, DC 20004

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/872,784	06/22/2004	John R. Evans	056291-5004-01	2093

TITLE OF INVENTION: FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	01/06/2009

EXAMINER	ART UNIT	CLASS-SUBCLASS
HUI, SAN MING R	1617	514-177000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

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❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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InnoPharma Exhibit 1046.0726

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/872,784	06/22/2004	John R. Evans	056291-5004-01	2093

9629 7590 10/06/2008

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/06/2008

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 873 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 873 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

InnoPharma Exhibit 1046.0727

Notice of Allowability	Application No.	Applicant(s)	
	10/872,784	EVANS ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.

2. ☒ The allowed claim(s) is/are *35-46*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☒ Certified copies of the priority documents have been received in Application No. *09/756,291* .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 8/21/08
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/San-ming Hui/
Primary Examiner, Art Unit 1617

InnoPharma Exhibit 1046.0728

DETAILED ACTION

Applicant's amendments filed August 21, 2008 have been entered.

Claims 1-34 are cancelled. Claims 35-46 are added.

Claims 35-46 are pending.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: the unexpected solubility and the bioavailability of using the specific solvent mixture as recited have been demonstrated. Therefore, the herein claimed method employing such fulvestrant composition will obviate the outstanding rejection under 35 USC 103(a).

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Claims 35-46 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon - Fri from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1617

/San-ming Hui/
Primary Examiner, Art Unit 1617

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
10872784	EVANS ET AL.
Examiner	**Art Unit**
San-ming Hui	1617

ORIGINAL		INTERNATIONAL CLASSIFICATION														
CLASS	SUBCLASS	CLAIMED									NON-CLAIMED					
514	177	A	6	1	K	31 / 56 (2006.01.01)										

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	178				

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	35														
2	36														
3	37														
4	38														
5	39														
6	40														
7	41														
8	42														
9	43														
10	44														
11	45														
12	46														

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 12	
/San-ming Hui/ Primary Examiner.Art Unit 1617 (Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

InnoPharma Exhibit 1046.0731

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10872784	EVANS ET AL.
	Examiner	**Art Unit**
	San-ming Hui	1617

SEARCHED			
Class	**Subclass**	**Date**	**Examiner**

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
EAST: fulvestrant, breeast cancer,	3-3-08	SH

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**

InnoPharma Exhibit 1046.0732

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	"6774122".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:13
L2	803	514/177.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:15
L3	1088	514/178.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L4	1678233	castor oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L5	61027	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L6	117	fulvestrant and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L7	879	oil and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L8	10104	(benzyl adj benzoate) or (phenylmethyl adj benzoate)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L9	1500625	solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16

InnoPharma Exhibit 1046.0733

L10	4885	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L11	4	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (testosterone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L12	10	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L13	1010	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) and (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L14	61027	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L15	3048	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L16	1864	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L17	1035	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L18	2	((((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent) same steroid	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16

InnoPharma Exhibit 1046.0734

L19	1188	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L20	1188	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L21	61027	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L22	117	fulvestrant and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L23	879	oil and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L24	2	"4659516".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L25	5	"346014".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L26	10104	(benzyl adj benzoate) or (phenylmethyl adj benzoate)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L27	1500625	solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L28	4885	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16

InnoPharma Exhibit 1046.0735

L29	3	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (estrogen or estradiol or estrone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L30	4	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (testosterone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L31	10	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L32	1010	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) and (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L33	61027	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L34	3048	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L35	1864	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L36	1035	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L37	2	((((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent) same steroid	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16

InnoPharma Exhibit 1046.0736

L38	1188	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L39	57041	breast adj cancer	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L40	752	breast adj cancer and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L41	136	breast adj cancer same fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16
L42	466	cancer same fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2008/09/30 15:16

9/30/08 3:46:30 PM
C:\Documents and Settings\SHui\My Documents\EAST\Workspaces\10-872784fulvestrant.wsp

InnoPharma Exhibit 1046.0737

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Attorney Docket No. **056291-5004-01**	Application No. **10/872,784**
	Applicants: **John EVANS *et al.***	
PTO Form 1449 August 21, 2008	Filing Date: **June 22, 2004**	Group Art Unit: **1617**

U.S. PATENT DOCUMENTS

Initial		Document No.	Date	Name	Class	Sub-Class	Filing Date
	1.	US 3,164,520	January 5, 1965	Huber			
	2.	US 4,212,863	July 15, 1980	Cornelius			
	3.	US 4,388,307	June 14, 1983	Cavanak			

FOREIGN PATENT DOCUMENTS

		Document No.	Date	Country	Class	Sub-Class	Translation
	4.	EP 0310542A1	April 5, 1989	EPO			Yes

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

	5.	P.K. Gupta and G.A. Brazeau (eds). *Injectable Drug Development:Techniques to Reduce Pain and Irritation.* Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999)
	6.	P.V. Lopatin, V. P. Safonov, T. P. Litvinova and L. M. Yakimenko. Use of nonaqueous solvents to prepare injection solutions. *Pharm. Chem. J.* ***6***:724-733 (1972)
	7.	S. Nema, R.J. Washkuhn, and R.J. Brendel. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* **51**:166-71 (1997)
	8.	*Physicians' Desk Reference (27th edition).* 1277-1278, 1350-1354, 1391-1392 Medical Economics Company, Oradell, NJ (1973)
	9.	M. F. Powell, T. Nguyen, and L. Baloian. Compendium of excipients for parenteral formulations. *PDA J. Pharm. Sci. Technol.* **52**:238–311 [pages 238-255 provided] (1998)
	10.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) -Part I. *PDA J. Pharm. Sci. Technol.* **53**:324–349 (1999)
	11.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part II *PDA J. Pharm. Sci. Technol.* **54**:69–96 (2000)
	12.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part III. *PDA J. Pharm. Sci. Technol.* **54**:152–169 (2000)
	13.	Y.C. J. Wang and R. R. Kowal. Review of excipients and pH's for parenteral products used in the United States. *J. Parenteral Drug Assoc.* **34**:452–462 (1980).

Examiner /San Ming Hui/	Date Considered 09/30/2008

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

DB1/62070418.1 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.H./

InnoPharma Exhibit 1046.0738

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

9629 7590 10/06/2008

MORGAN, LEWIS & BOCKIUS LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/872,784	06/22/2004	John R. Evans	056291-5004-01	2093

TITLE OF INVENTION:

FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$1810	01/06/2009

EXAMINER	ART UNIT	CLASS-SUBCLASS
HUI, SAN MING R	1617	514-17700

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Morgan, Lewis & Bockius LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: AstraZeneca AB

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Sodertalje, Sweden

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:

☑ Issue Fee
☑ Publication Fee (No small entity discount permitted)
☑ Advance Order - # of Copies three (3)

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☑ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 50-0310 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date October 15, 2008

Typed or printed name Donald J. Bird Registration No. 25,323

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

InnoPharma Exhibit 1046.0739

Electronic Patent Application Fee Transmittal

Application Number:	10872784
Filing Date:	22-Jun-2004
Title of Invention:	FORMULATION
First Named Inventor/Applicant Name:	John R. Evans
Filer:	Donald J. Bird
Attorney Docket Number:	056291-5004-01

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1510	1510
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Printed copy of patent - no color	8001	3	3	9
		Total in USD ($)		**1819**

Electronic Acknowledgement Receipt

EFS ID:	4120331
Application Number:	10872784
International Application Number:	
Confirmation Number:	2093
Title of Invention:	FORMULATION
First Named Inventor/Applicant Name:	John R. Evans
Customer Number:	09629
Filer:	Donald J. Bird
Filer Authorized By:	
Attorney Docket Number:	056291-5004-01
Receipt Date:	15-OCT-2008
Filing Date:	22-JUN-2004
Time Stamp:	17:11:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1819
RAM confirmation Number	2624
Deposit Account	500310
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IssueFee.pdf	170840 6d5f4eb5d0c3932bcb3ebd08aabf53dd809ad354	no	1
Warnings:					
Information:					
2	Fee Worksheet (PTO-06)	fee-info.pdf	33376 ba41aec09f5e7b79d92b651e444c5c56b889b6d5	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	204216		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/872,784	11/25/2008	7456160	056291-5004-01	2093

9629 7590 11/05/2008

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 873 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

John R. Evans, Macclesfield, UNITED KINGDOM;
Rosalind U. Grundy, Macclesfield, UNITED KINGDOM;

InnoPharma Exhibit 1046.0744

AO 120 (Rev. 3/04)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Delaware on the following X Patents or ☐ Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
10cv18	1/7/2010	DISTRICT OF DELAWARE

PLAINTIFF	DEFENDANT
AstraZeneca Pharmaceuticals LP, et al	Teva Parenteral Medicines, Inc., et al

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,774,122 B2	8/10/2004	AstraZeneca AB
2	7,456,160 B2	11/25/2008	AstraZeneca AB
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
PETER T. DALLEO, CLERK OF COURT		11/8/2010

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

InnoPharma Exhibit 1046.0745

AO 120 (Rev. 3/04)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Delaware on the following X Patents or ☐ Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
10cv18	1/7/2010	DISTRICT OF DELAWARE

PLAINTIFF	DEFENDANT
AstraZeneca Pharmaceuticals LP, et al	Teva Parenteral Medicines, Inc., et al

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,774,122 B2	8/10/2004	AstraZeneca AB
2	7,456,160 B2	11/25/2008	AstraZeneca AB
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Stipulation of Dismissal filed and So Ordered 6/15/2011.

CLERK	(BY) DEPUTY CLERK	DATE
PETER T. DALLEO, CLERK OF COURT		~~1/8/2010~~ 6/16/2011

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:14–cv–03547–FLW–LHG	6/3/2014	TRENTON, NJ

PLAINTIFF	DEFENDANT
ASTRAZENECA PHARMACEUTICALS LP	SANDOZ INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 6,774,122 B2	August 10, 2004	AstraZeneca AB
2 US 7,456,160 B2	November 25, 2008	AstraZeneca AB
3 US 8,329,680 B2	December 11, 2012	AstraZeneca AB
4 US 8,466,139 B2	June 18, 2013	AstraZeneca AB
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Marlene Kalbach	6/3/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Northern District of Illinois on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
14-cv-7358	9/22/2014	Northern District of Illinois

PLAINTIFF	DEFENDANT
AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, AstraZeneca AB	Sagent Pharmaceuticals, Inc.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,774,122	8/10/2004	AstraZeneca AB
2	7,456,160	11/25/2008	AstraZeneca AB
3	8,329,680	12/11/2012	AstraZeneca AB
4	8,466,139	6/18/2013	AstraZeneca AB
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Thomas G. Bruton	Melissa Rivera	9/23/14

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:15–cv–00615–RMB–KMW	1/29/2015	CAMDEN, NJ
PLAINTIFF ASTRAZENECA PHARMACEUTICALS LP		DEFENDANT GLENMARK PHARMACEUTICALS LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 6,774,122	8/10/2004	AstraZeneca AB
2 7,456,160	11/25/2008	AstraZeneca AB
3 8,329,680	12/11/2012	AstraZeneca AB
4 8,466,139	6/18/2013	AstraZeneca AB
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Nicholas Zotti	1/29/2015

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:15–cv–07009–RMB–KMW	9/21/2015	CAMDEN, NJ
PLAINTIFF ASTRAZENECA PHARMACEUTICALS LP		DEFENDANT MYLAN PHARMACEUTICALS INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 6,774,122 B2	Aug. 10, 2004	AstraZeneca AB,
2 US 7,456,160 B2	Nov. 25, 2008	AstraZeneca AB,
3 US 8,329,680 B2	Dec. 11, 2012	AstraZeneca AB
4 US 8,466,139 B2	Jun. 18, 2013	AstraZeneca AB
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In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ JAIME KASSELMAN	9/21/2015

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AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:15–cv–06990–NLH–AMD	9/22/2015	CAMDEN, NJ

PLAINTIFF	DEFENDANT
HORIZON PHARMA IRELAND LIMITED	AMNEAL PHARMACEUTICALS LLC

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 9,132,110 B2	9/15/2015	HZNP LIMITED
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Brian D. Kemner	9/22/2015

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:15–cv–06039–RMB–KMW	8/7/2015	CAMDEN, NJ

PLAINTIFF	DEFENDANT
ASTRAZENECA PHARMACEUTICALS LP	AGILA SPECIALTIES, INC

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 6,774,122 B2	08/10/2004	ASTRAZENECA AB
2 7,456,160 B2	11/25/2008	ASTRAZENECA AB
3 8,329,680 B2	12/11/2012	ASTRAZENECA AB
4 8,466,139 B2	06/18/2013	AstraZeneca AB
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ JAIME KASSELMAN	8/7/2015

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Northern District of Texas, Dallas Division on the following

☑ Trademarks or ☐ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:15-cv-2607-M	8/7/2015	Northern District of Texas, Dallas Division

PLAINTIFF	DEFENDANT
Pathway Senior Living LLC	Pathways Senior Living LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	3,432,946	5/20/2008	Pathway Senior Living LLC
2			
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Karen Mitchell	s/A. Lowe	8/10/2015

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

InnoPharma Exhibit 1046.0753

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:15–cv–06075–PGS–DEA	8/6/2015	TRENTON, NJ

PLAINTIFF	DEFENDANT
MERCK SHARP & DOHME CORP.	ACTAVIS LABORATORIES FL, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 5,661,151	8/26/1997	Schering Corporation
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Karen McGonigle	8/6/2015

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:16–cv–01962–RMB–KMW	4/7/2016	CAMDEN, NJ

PLAINTIFF	DEFENDANT
ASTRAZENECA PHARMACEUTICALS LP	INNOPHARMA LICENSING LLC

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 6,774,122 B2	Aug. 10, 2004	AstraZeneca AB,
2 US 7,456,160 B2	Nov. 25, 2008	AstraZeneca AB,
3 US 8,329,680 B2	Dec. 11, 2012	AstraZeneca AB,
4 US 8,466,139 B2	Jun. 18, 2013	AstraZeneca AB
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In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Ryan Merrigan	4/7/2016

Copy 1––Upon initiation of action, mail this copy to Director Copy 3––Upon termination of action, mail this copy to Director
Copy 2––Upon filing document adding patent(s), mail this copy to Director Copy 4––Case file copy