IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

jc603 U.S. PTO
01/09/01

REQUEST FOR FILING APPLICATION
Under Rule 53(a), (b) & (f)
(No Filing Fee or Oath/Declaration)
(Do NOT use for Provisional or PCT Applications)
Use for Design or Utility Applications

PATENT APPLICATION

RULE 53(f) NO DECLARATION

Hon. Commissioner of Patents
Washington, DC 20231

Atty. Dkt. PM 275507 (M#) | PHM70635/US (Client Ref)

Date: January 9, 2001

Sir:

1. This is a Request for filing a new Patent Application(☐ Design ☒ Utility) entitled:

2. (Complete) Title: FORMULATION

without a filing fee or Oath/Declaration but for which is enclosed the following:

3. ☒ Abstract 1 page(s).

4. 22 Pages of Specification (only spec. and claims); 5. ☐ Specification in non-English language

6. 23 Numbered claim(s); and

7. ☒ Drawings: 1 sheet(s) ☐ 1 set informal; 8. ☒ formal of size: ☒A4 ☐11"

9. **DOMESTIC/INTERNATIONAL** priority is claimed under 35 USC 119(e)/120/365(c) based on the following provisional, nonprovisional and/or PCT international application(s):

Application No.	Filing Date	Application No.	Filing Date
(1)		(2)	
(3)		(4)	
(5)		(6)	

10. **FOREIGN** priority is claimed under 35 USC 119(a)-(d)/365(b) based on filing in Great Britain

Application No.	Filing Date	Application No.	Filing Date
(1) 0000313.7	January 10, 2000	(2) 0008837.7	April 12, 2000
(3)		(4)	
(5)		☐ See 3rd page for additional priorities	

11. 2 (No.) Certified copy (copies): ☒ attached; ☐ previously filed (date) _____ in U.S. Application No. / _____ filed on _____

12. ☐ This is a reissue of Patent No. _____

13. ☐ See top first page re prior Provisional, National, International application(s) (X box only if info is there and do not complete corresponding item 14 or 15.)

14. ☐ **Amend the specification** by inserting before the first line -- This is a ☐ Continuation-in-Part ☐ Divisional ☐ Continuation ☐ Substitute Application (MPEP 201.09) of:

14(a) ☐ National Appln. No. / _____ filed .-- (M#)

14(b) ☐ International Appln. No. PCT/ _____ filed _____ which designated the U.S., and that International Application ☐ was ☐ was not published under PCT Article 21(2) in English.--

15. ☐ **Amend the specification** by inserting before the first line: --This application claims the benefit of U.S. Provisional Application No. 60/ _____ , filed _____ .--

16. Extension to date: ☐ concurrently filed ☐ not needed ☐ previously filed

17. ☐ Small Entity Status is claimed (**pre**-filing confirmation **required**)

17(a) ☐ Attached: (No.) Small Entity Statement(s). (Since 9/8/00 Small Entity Statement not essential to make claim)

17(b) ☐ See **NONPUBLICATION REQUEST** under Rule 213(a) attached (PAT-258)

PAT-104 12/00

18. ☐ Prior application is assigned to

by Assignment recorded _____ Reel _____ Frame _____

19. ☐ **Attached:**

20. This application is made by the following named inventor(s) **(Double check instructions for accuracy.):**
(Listing of inventor(s) not a requirement, but list if known)

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21. NOTE: FOR ADDITIONAL INVENTORS, check box ☐
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NOTE: File in duplicate with 2 post card receipts (PAT-103) & attachments

APPLICATION UNDER UNITED STATES PATENT LAWS

Atty. Dkt. No. PM 275507/PHM 70635/US
(M#)

Invention: FORMULATION

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This is a:

- ☐ Provisional Application
- ☒ Regular Utility Application
- ☐ Continuing Application
  - ☒ The contents of the parent are incorporated by reference
- ☐ PCT National Phase Application
- ☐ Design Application
- ☐ Reissue Application
- ☐ Plant Application
- ☐ Substitute Specification
  Sub. Spec Filed _____
  in App. No. _____ / _____
- ☐ Marked up Specification re
  Sub. Spec. filed _____
  In App. No _____ / _____

SPECIFICATION

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

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

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.

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

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

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

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

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.

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.

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.

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

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

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.

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

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

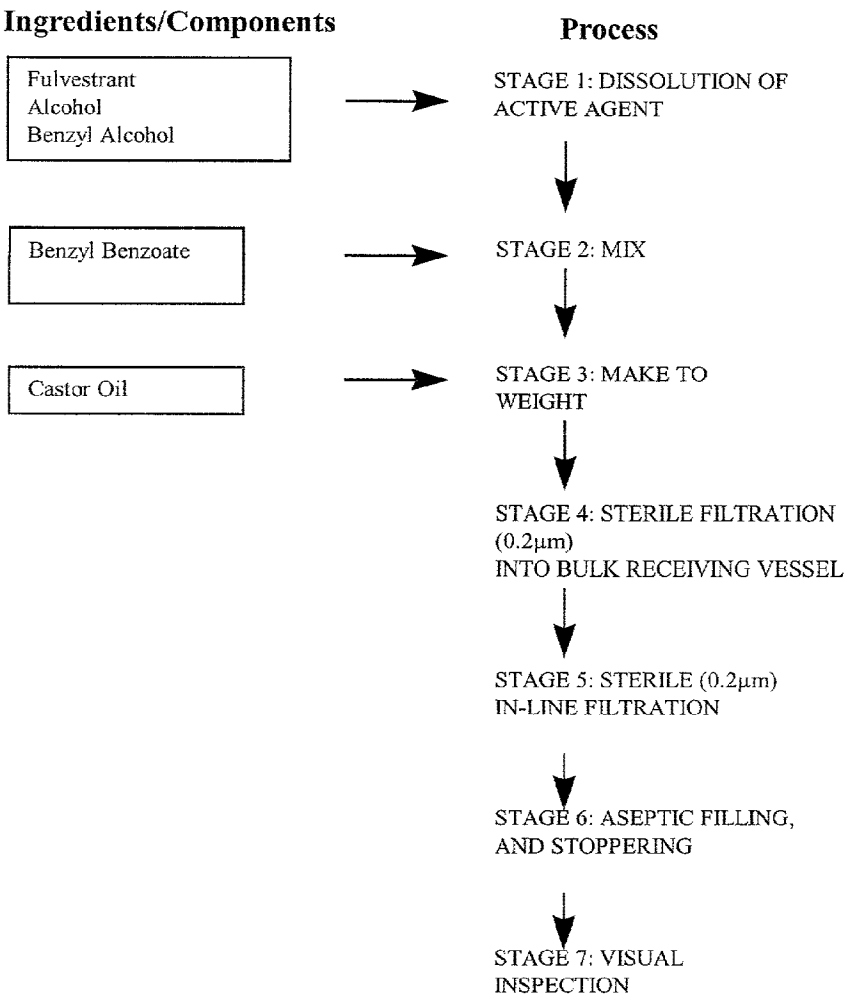
10% weight per volume of ethanol

15% weight per volume of benzyl benzoate

250mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

FLOW DIAGRAM OF MANUFACTURING



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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 .

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 $45mgml^{-1}$.

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.

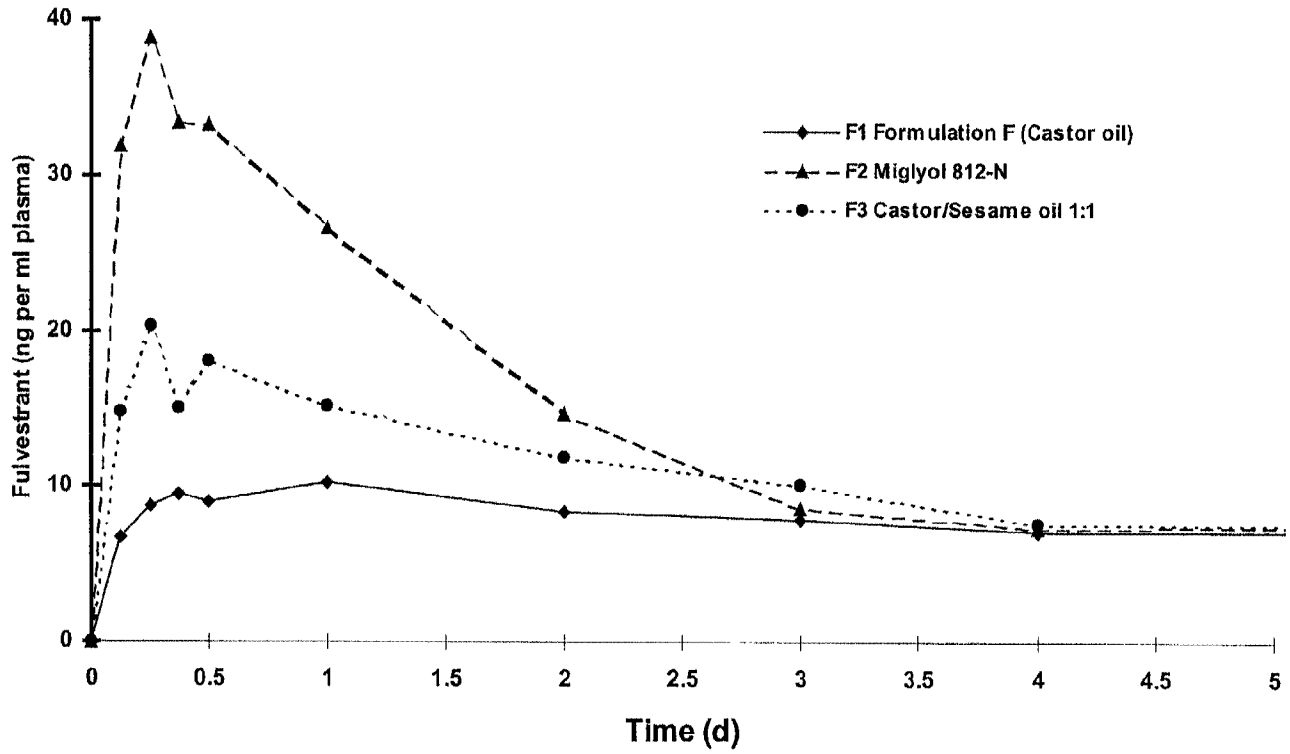

Figure 1

Subclass	ISSUE CLASSIFICATION
Class	

PATENT NUMBER

U.S. UTILITY Patent Application

O.I.P.E.	PATENT DATE
SCANNED TR GTH3 Q.A. HT	

APPLICATION NO.	CONT/PRIOR	CLASS	SUBCLASS	ART UNIT.	EXAMINER
09/756291	F	514	172	1617	

APPLICANTS: John Evans
Rosalind Gruncy

TITLE: Formulation

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PTO-2040
12/99

ISSUING CLASSIFICATION

ORIGINAL		CROSS REFERENCE(S)	
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)
INTERNATIONAL CLASSIFICATION			
			☐ Continued on Issue Slip Inside File Jacket

☐ TERMINAL DISCLAIMER	DRAWINGS			CLAIMS ALLOWED	
	Sheets Drwg.	Figs. Drwg.	Print Fig.	Total Claims	Print Claim for O.G.
☐ The term of this patent subsequent to _____ (date) has been disclaimed.	(Assistant Examiner) (Date)			NOTICE OF ALLOWANCE MAILED	
☐ The term of this patent shall not extend beyond the expiration date of U.S Patent. No. _____	(Primary Examiner) (Date)			ISSUE FEE	
				Amount Due	Date Paid
☐ The terminal ____months of this patent have been disclaimed.	(Legal Instruments Examiner) (Date)			ISSUE BATCH NUMBER	

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SEARCHED

Class	Sub.	Date	Exmr.
514	177	3/02	SH
514	178	3/02	↓
Update	search	11/02	SH
Update	search	8/03	SH

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

SEARCH NOTES
(INCLUDING SEARCH STRATEGY)

	Date	Exmr.
East	3/02	SH
Registry	↓	↓
Caplus		
Medline		
Biosis		
Uspatfull		
Update search	11/02	SH
Benzyl benzoate solvent steroids	↓	↓
Update search	8/03	SH
Inventor search	↓	↓

(RIGHT OUTSIDE)

ISSUE SLIP STAPLE AREA (for additional cross references)

NH
-20-01

POSITION	INITIALS	ID NO.	DATE
FEE DETERMINATION			
O.I.P.E. CLASSIFIER		6	2-3-01
FORMALITY REVIEW	NH	959	02/20/01
RESPONSE FORMALITY REVIEW	Tequest	925	05-09-01

INDEX OF CLAIMS

✔ ..... Rejected
= ..... Allowed
— (Through numeral)... Canceled
÷ ..... Restricted
N ..... Non-elected
I ..... Interference
A ..... Appeal
O ..... Objected

Claim	Date									
Final	Original	1-17-01	3/6/02	11/21/02	8/24/03					
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If more than 150 claims or 10 actions staple additional sheet here

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

jc809 U.S. PTO 01/09/01

REQUEST FOR FILING APPLICATION
Under Rule 53(a), (b) & (f)
(No Filing Fee or Oath/Declaration)
(Do NOT use for Provisional or PCT Applications)
Use for Design or Utility Applications

PATENT APPLICATION

RULE 53(f) NO DECLARATION

Hon. Commissioner of Patents
Washington, DC 20231

Atty. Dkt. PM 275507 (M#) | PHM70635/US (Client Ref)

Date: January 9, 2001

jc928 U.S. PTO 09/756291 01/09/01

Sir:

1. This is a Request for filing a new Patent Application(☐ Design ☒ Utility) entitled:

2. (Complete) Title: FORMULATION

without a filing fee or Oath/Declaration but for which is enclosed the following:

3. ☒ Abstract 1 page(s).

4. 22 Pages of Specification (only spec. and claims); 5. ☐ Specification in non-English language

6. 23 Numbered claim(s); and

7. ☒ Drawings: 1 sheet(s) ☐ 1 set informal; 8. ☒ formal of size: ☒A4 ☐11"

9. **DOMESTIC/INTERNATIONAL** priority is claimed under 35 USC 119(e)/120/365(c) based on the following provisional, nonprovisional and/or PCT international application(s):

Application No.	Filing Date	Application No.	Filing Dat
(1)		(2)	
(3)		(4)	
(5)		(6)	

10. **FOREIGN** priority is claimed under 35 USC 119(a)-(d)/365(b) based on filing in Great Britain

Application No.	Filing Date	Application No.	Filing Dat
(1) 0000313.7	January 10, 2000	(2) 0008837.7	April 12, 2000
(3)		(4)	
(5)		☐ See 3rd page for additional priorities	

11. 2 (No.) Certified copy (copies): ☒ attached; ☐ previously filed (date) _____ in U.S. Application No. / filed on _____

12. ☐ This is a reissue of Patent No. _____

13. ☐ See top first page re prior Provisional, National, International application(s) (X box only if info is there and do not complete corresponding item 14 or 15.)

14. ☐ **Amend the specification** by inserting before the first line -- This is a ☐ Continuation-in-Part ☐ Divisional ☐ Continuation ☐ Substitute Application (MPEP 201.09) of:

14(a) ☐ National Appln. No. / filed .- - (M#)

14(b) ☐ International Appln. No. PCT/ filed _____ which designated the U.S., and that International Application ☐ was ☐ was not published under PCT Article 21(2) in English.--

15. ☐ **Amend the specification** by inserting before the first line: --This application claims the benefit of U.S. Provisional Application No. 60/ _____ , filed _____ .--

16. Extension to date: ☐ concurrently filed ☐ not needed ☐ previously filed

17. ☐ Small Entity Status is claimed (**pr** -filing confirmation **required**)

17(a) ☐ Attached: (No.) Small Entity Statement(s). (Since 9/8/00 Small Entity Statement not essential to make claim)

17(b) ☐ See **NONPUBLICATION REQUEST** under Rule 213(a) attached (PAT-258)

18. ☐ Prior application is assigned to

by Assignment recorded _____ Reel _____ Frame _____

19. ☐ **Attached:**

20. This application is made by the following named inventor(s) **(Double check instructions for accuracy.):**
(Listing of inventor(s) not a requirement, but list if known)

(1) Inventor	John	R.	**EVANS**
	First	Middle Initial	Family Name
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(2) Inventor	Rosalind	U	**GRUNDY**
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(include Zip Code)	SK10 2NA		

(3) Inventor			
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Residence			
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Mailing Address			
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(4) Inventor			
	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(5) Inventor			
	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

21. NOTE: FOR ADDITIONAL INVENTORS, check box ☐
and attach sheet with same information regarding additional inventors.

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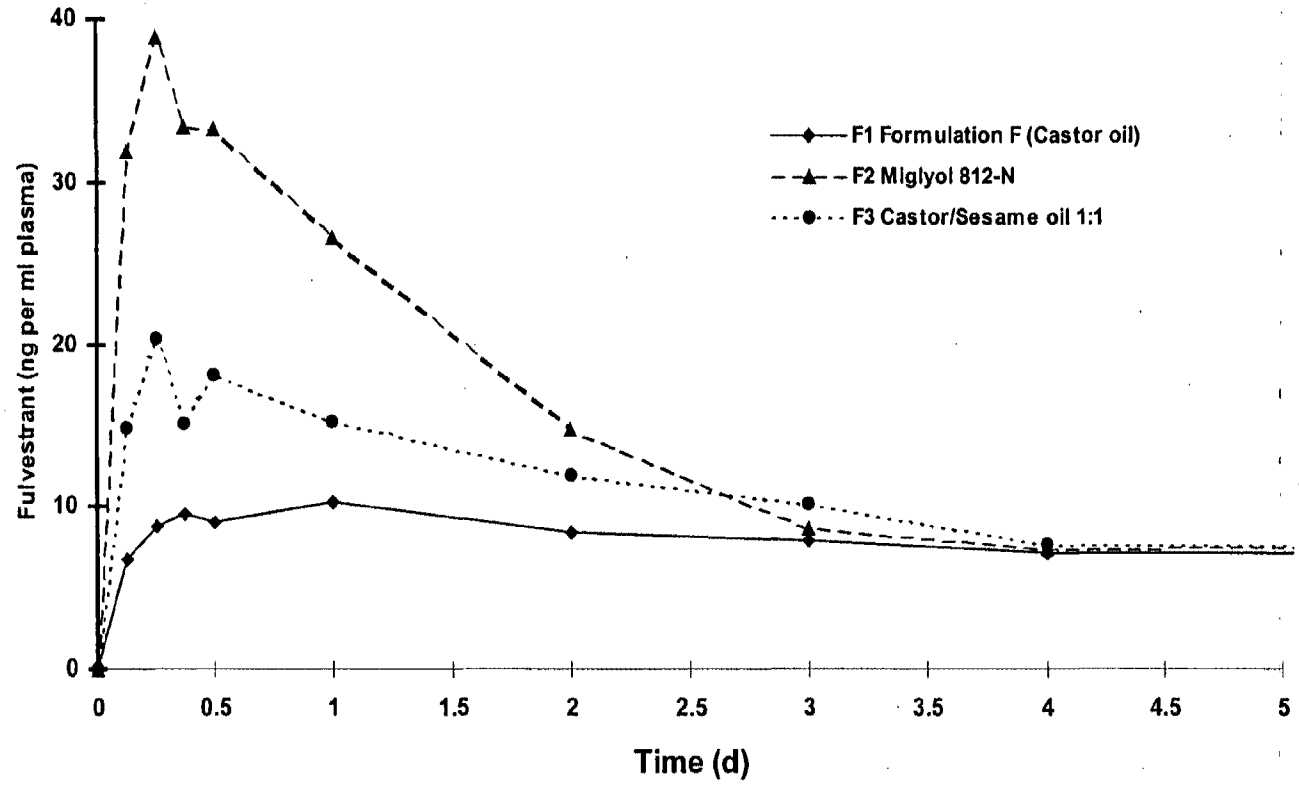


Figure 1

APPLICATION UNDER UNITED STATES PATENT LAWS

Atty. Dkt. No. PM 275507/PHM 70635/US
(M#)

Invention: FORMULATION

Inventor (s): EVANS, John R.
GRUNDY, Rosalind U.

Pillsbury Winthrop LLP
Intellectual Property Group
1100 New York Avenue, NW
Ninth Floor
Washington, DC 20005-3918
Attorneys
Telephone: (202) 861-3000

This is a:

- ☐ Provisional Application
- ☒ Regular Utility Application
- ☐ Continuing Application
  - ☒ The contents of the parent are incorporated by reference
- ☐ PCT National Phase Application
- ☐ Design Application
- ☐ Reissue Application
- ☐ Plant Application
- ☐ Substitute Specification
  Sub. Spec Filed _____
  in App. No. ____/____
- ☐ Marked up Specification re
  Sub. Spec. filed _____
  In App. No ____/____

SPECIFICATION

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

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

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.

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

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

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

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

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.

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.

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.

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

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

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.

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

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

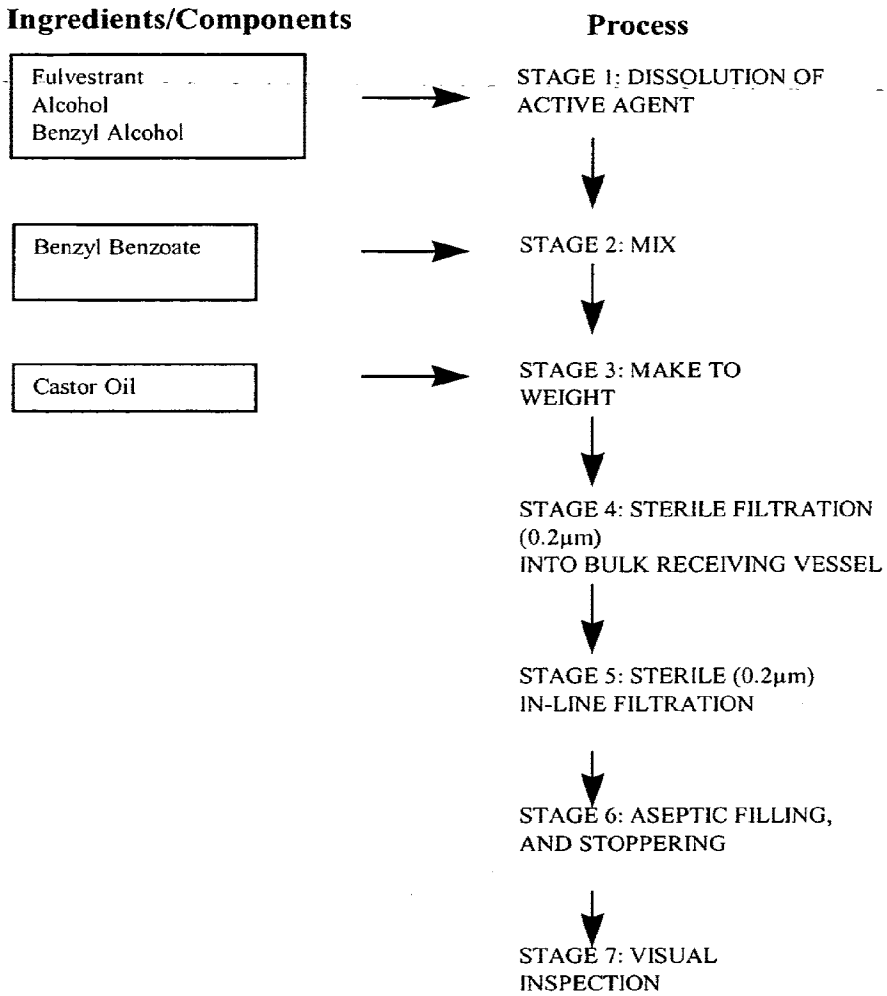
10% weight per volume of ethanol

15% weight per volume of benzyl benzoate

250mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

FLOW DIAGRAM OF MANUFACTURING



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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 .

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} .

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.

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.

Application or Docket Number

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 2000

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 =	* 0
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	355.00	OR	BASIC FEE	710.00
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	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=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

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

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

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

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
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.

CLAIMS ONLY

SERIAL NO.	FILING DATE
APPLICANT(S)	

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2		1				
3		1				
4	1					
5		4				
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TOTAL IND.	2					
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TOTAL CLAIMS	29					

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TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that by virtue of an assignment registered under the Patents Act 1977, the application is now proceeding in the name as substituted.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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Signed P. Mahoney

Dated 22 November 2000

GB0000313.7

By virtue of a direction given under Section of the Patents Act 1977, the application is proceeding in the name of

ASTRAZENECA AB,
Incorporated in Sweden,
S-151 85 Sodertalje,
Sweden [ADP No. 07822448003]

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A
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Request for grant of a patent

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The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

10 JAN 2000

1. Your reference — PHM 99-154

2. Patent application number *(The Patent Office will fill in this part)* — 0000313.7

10JAN00 E603670-1 002934
P01/7700 0.00-0000313.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca UK Ltd
15 Stanhope Gate
LONDON W1Y 6LN
Great Britain

SECTION 30(1) PRIORITY APPLICATION FILED 6.7.00

Patents ADP number *(if you know it)* — 6254007002

7810294001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — FORMULATION

5. Name of your agent *(if you have one)* — BROWN, Andrew Stephen

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Global Intellectual Property
AstraZeneca PLC
Mereside, Alderley Park
Macclesfield Cheshire, SK10 4TG
Great Britain

Patents ADP number *(if you know it)* — 7259252002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

(this more (b))

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Continuation sheets of this form

Description	13
Claim(s)	2
Abstract	-
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature J.M. Marshall Date 10-Jan-2000

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs Joanne M Marshall - 01625 516485

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

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e) Once you have filled in the form you must remember to sign and date it.

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 benzyl benzoate.

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 now referred to as Selective Estrogen Receptor-Downregulators (SERDs). 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 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 nonproprietory 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 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 are formulations use oil as a solvent and wherein also additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

Table 1 - OIL BASED LONG - ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMPANY	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	FREQUENCY
SUSTANON 100			Androgen	Organon	ABPI Data Sheet Comp.	Arachis oil		*10%		1ml	2 weeks
PROLUTON DEPOT	Hydroxy-progesterone hexanoate		Progestogen	Shering HC	ABPI Data Sheet Comp.	Castor oil	up to 46%			1-2ml	1 week
TOCOGESTAN			Progestogen	Theramax	Dict. Vidal	Ethyl oleate	*40%			2ml	< 1week
TROPHOBOLENE			Mixed	Theramax	Dict. Vadal	Olive oil	*45%			1ml	2 - 4 weeks
NORISTERAT			Contraceptive	Schering HC	ABPI Data Sheet Comp.	Castor Oil	YES			1ml	8 weeks
BENZO-GYNOESTRYL			Estradiol	Roussel	Dict. Vidal	Arachis Oil		YES	YES	1ml	1 week
PROGESTERONE -RETARD			Progestogen	Pharlon	Dict. Vidal	Castor Oil	YES			2ml	1 week
GRAVIBINAN			Mixed	Schering HC	Dict. Vidal	Castor Oil	YES			1-2ml	1 - 2 weeks
PARABOLAN			Androgen	Negma	Dict. Vidal	Arachis oil		*5%	*3%	1.5ml	2 weeks
DELESTROGEN	Estradiol valerate	20mg/ml 40mg/ml	Estrodiol	BMS	J.Pharm. Sci (1964) 53(8) 891	Castor Oil	78% 58%	20% 40%	2% 2%		
DELALUTIN	17-Hydroxy progesterone	250mg/ml	Progestrogen	DMS	J.Pharm. Sci.(1964) 53(8) 891	Castor Oil	YES	YES	up to 2%		

BzBz = benzylbenzoate BzOH = benzylalcohol EtOH = ethanol Dict. Vidal = Dictionnaire Vidal
% are w/v and * are approximate as measured directly from a single sample

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

Below in Table 2 is a list showing 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

* castor oil varies according to supplier and also may vary between batches

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 steoidal compounds is known and is attributed to the high number of hydroxy groups of riconoleic 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 single 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 adminster a dose significantly high enougth 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, far exceeding the above guidelines, and would have to be administered as two seperate injections.

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.

It is desired to maintian only the minimum amount of excipients necessary for the preformance of the formulation. In Japan injectable formulations containing high concentrations of ethanol may not be approved for sale since a significant number of Japanese are intolerant to ethanol. In addition within Muslin countries high ethanol containing products may not be culturally acceptable. Therefore, there is a need to minimise the amount of alcohols present within such parenteral formulations.

We have surprisingly found that the introduction of benzyl benzoate to the castor oil allows the amount of alcohol needed to solubilise fulvestrant into a concentration of at least 50 mgml^{-1} to be significantly reduced - see Table 3 below. The finding is surprising since the solubility of fulvestrant in benzylbenzoate - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in benzyl benzoate than the solubility of fulvestrant in castor oil.

Therefore, we present as a feature of the invention a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate per volume of formulation and a sufficient amount of a ricinoleate vehicle, taking

into account the addition of any further optional pharamaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

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

1. The total volume of the formulation is 5ml, 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 5ml, or less.

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

Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; at least 10% w/v, 11% w/v, 12% w/v, 13% w/v, 14% w/v, 15% w/v and, preferably, at least 16% w/v. Maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ; 22% w/v or less, 20% w/v or less and 18%w/v or less.

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 alsohols 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.

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 possibley other organic solvents, for example alcohol 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 benzyl benzoate present in any of the above formulations are; at least 10% w/v, 11% w/v, 12% w/v, 13% w/v, 15% w/v, 16% w/v, 17% w/v, 18% w/v, 19% w/v and 20% w/v. Maximal concentrations of benzyl benzoate 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.

It will be understood by the skilled person that the benzyl benzoate will be of a quality that it will meet pharmacopeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

By the use of the term ricinoleate vehicle we mean an oil which has as a majority proportion (at least 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. Conveniently the ricinoleate vehicle 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/inflamation was due to the presence of fulvestrant in the form of solid particles. The release profile appeared to be controlled by the extent of inflammation/irritation present at the injection site and therefore diffficult 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.

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 the benzyl benzoate is always present at the injection site during the extended release period.

We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and benzyl benzoate, 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 is still achieved.

By use of the term "therapeutically significant levels" we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, idealy at least 3 $ngml^{-1}$ and no more than 8.5 $ngml^{-1}$ of fulvestrant are achieved in the patient.

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 32 days $\pm$ 4 days.

Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate 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 50$mgml^{-1}$ of fulvestrant.

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

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.

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

Formulation Example

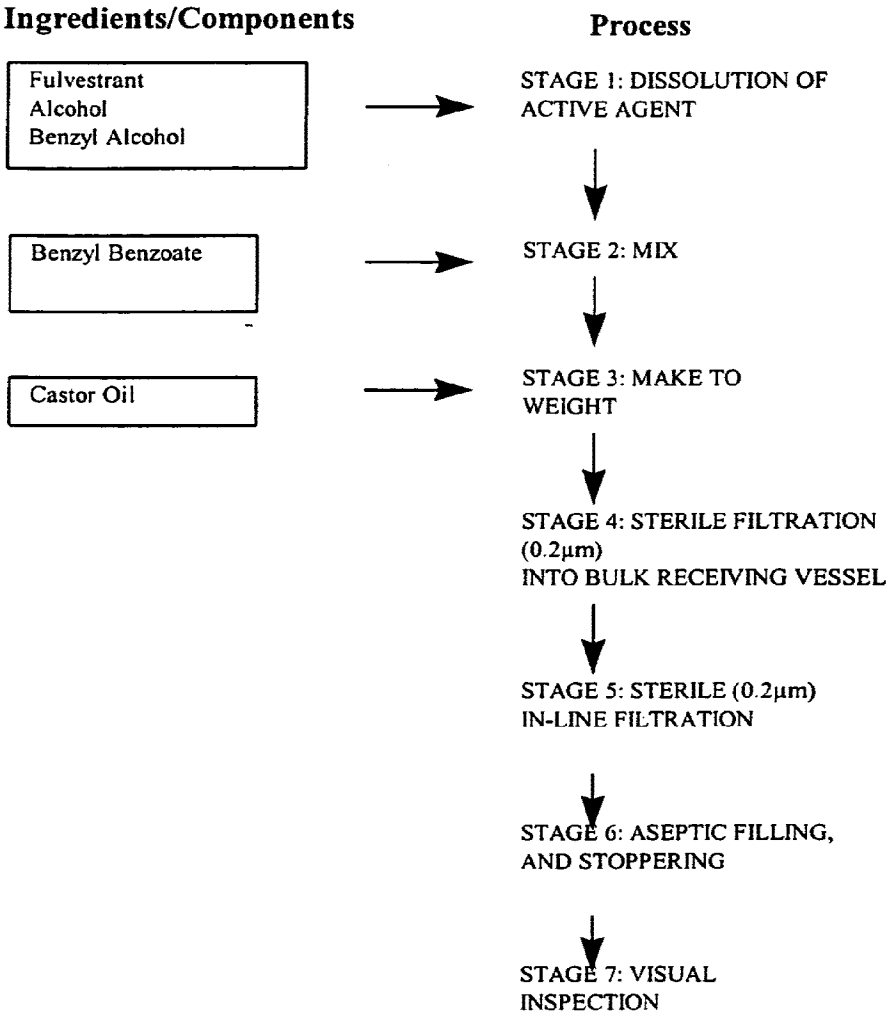
Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid 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 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 choosen 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

FLOW DIAGRAM OF MANUFACTURING



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Claims

1. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate per volume of formulation and a sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharamaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

2. A pharmaceutical formulation as claimed in claim 1 which contains 22% w/v or less of a pharmaceutically-acceptable alcohol.

3. A pharmaceutical formulation as claimed in claim 1 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

4. A pharmaceutical formulation as claimed in claim 1 which contains and 18%w/v or less of a pharmaceutically-acceptable alcohol.

5. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 60% w/v or less of benzyl benzoate.

6. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 50%w/v or less of benzyl benzoate.

7. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 45% w/v or less of benzyl benzoate.

8. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 40% w/v or less of benzyl benzoate.

9. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 35% w/v or less of benzyl benzoate.

10. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 30% w/v or less of benzyl benzoate.

11. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 25% w/v or less of benzyl benzoate.

12. A pharmaceutical formulation as claimed in any claim from 1 to 11 wherein the total volume of the formulation is 5ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.

13. A pharmaceutical formulation as claimed in any claim from 1 to 11 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 5ml, or less.

14. A pharmaceutical formulation as claimed in claim 13 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5ml.

15. An extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate 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 $50mgml^{-1}$ of fulvestrant.

Application No: _____

Pillsbury Madison & Sutro

Inventor: J. EVANS et al

Filed: 1/9/01

Client & Ref. #: ASTRAZENECA (PHM70635/US)

CL.# 9901 M# 27550 7

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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 benzyl benzoate.

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 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 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 are formulations which use oil as a solvent and wherein also additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

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 oil		0.1ml		1ml	3 weeks
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250mgml^{-1}	Progestogen	Schering HC	ABPI Data Sheet Comp.1999	Castor oil	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 oil	45%			1ml	15 to 30 days
NORISTERAT	Norethisterone oenanthoate	200mg	Contraceptive	Schering HC	ABPI Data Sheet Comp.1999	Castor Oil	YES			1ml	8 weeks
BENZO-GYNOESTRYL	Estradiol hexahydrobenzoate	5mg	Estradiol	Roussel	Dict. Vidal 1998	Arachis Oil				1ml	1 week
PROGESTERONE -RETARD	Hydroxy progesterone caproate	250mgml^{-1}	Progestogen	Pharlon	Dict. Vidal 1999	Castor Oil	YES			1 or 2ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate Hydroxyprogesterone caproate	5mg ml^{-1} 250mg ml^{-1}	Mixed	Schering HC	Dict. Vidal 1995	Castor Oil	YES			1 or 2ml	1 - 2 weeks

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

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

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

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

Below in Table 2 is a list showing 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

* castor oil varies according to supplier and also may vary between batches

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 riconoleic 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 single 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.

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, far exceeding the above guidelines, and would have to be administered as two separate injections.

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.

It is desired to maintain only the minimum amount of excipients necessary for the performance of the formulation. In Japan injectable formulations containing high concentrations of ethanol may not be approved for sale since a significant number of Japanese are intolerant to ethanol. In addition within Muslin countries high ethanol containing products may not be culturally acceptable. Therefore, there is a need to minimise the amount of alcohols present within such parenteral formulations.

We have surprisingly found that the introduction of benzyl benzoate to the castor oil allows the amount of alcohol needed to solubilise fulvestrant into a concentration of at least 50 $mgml^{-1}$ to be significantly reduced - see Table 3 below. The finding is surprising since the solubility of fulvestrant in benzylbenzoate - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in benzyl benzoate than the solubility of fulvestrant in castor oil.

Therefore, we present as a feature of the invention a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate per volume of formulation and a 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 45$mgml^{-1}$ of fulvestrant.

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

1. The total volume of the formulation is 5ml, or less, and the concentration of fulvestrant is at least 45$mgml^{-1}$.

2. The total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 5ml, or less.

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

Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; 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. Maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ; 22% w/v or less, 20% w/v or less and 18%w/v or less.

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.

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 alcohol 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 benzyl benzoate present in any of the above formulations are; 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. Maximal concentrations of benzyl benzoate 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.

It will be understood by the skilled person that the benzyl benzoate will be of a quality that it will meet pharmacopoeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

By the use of the term ricinoleate vehicle we mean an oil which has as a majority proportion (at least 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. Conveniently the ricinoleate vehicle 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 controlled by the extent of inflammation/irritation present at the injection site and therefore 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.

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 the benzyl benzoate is always present at the injection site during the extended release period.

We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and benzyl benzoate, 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 is still achieved.

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 $ngml^{-1}$ and no more than 8.5 $ngml^{-1}$ of fulvestrant are achieved in the patient.

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 32 days $\pm$ 4 days.

Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate 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 50$mgml^{-1}$ of fulvestrant.

By the use of the term "optional pharmaceutically-acceptable excipients" we refer to possible additional excipients commonly used in the formulation field including, for example, an antioxidant preservative, a colorant or a surfactant. 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.

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.

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

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 believe that the compound will also share with fulvestrant similar physical properties and therefore the current invention will also have application with this compound.

Formulation Example

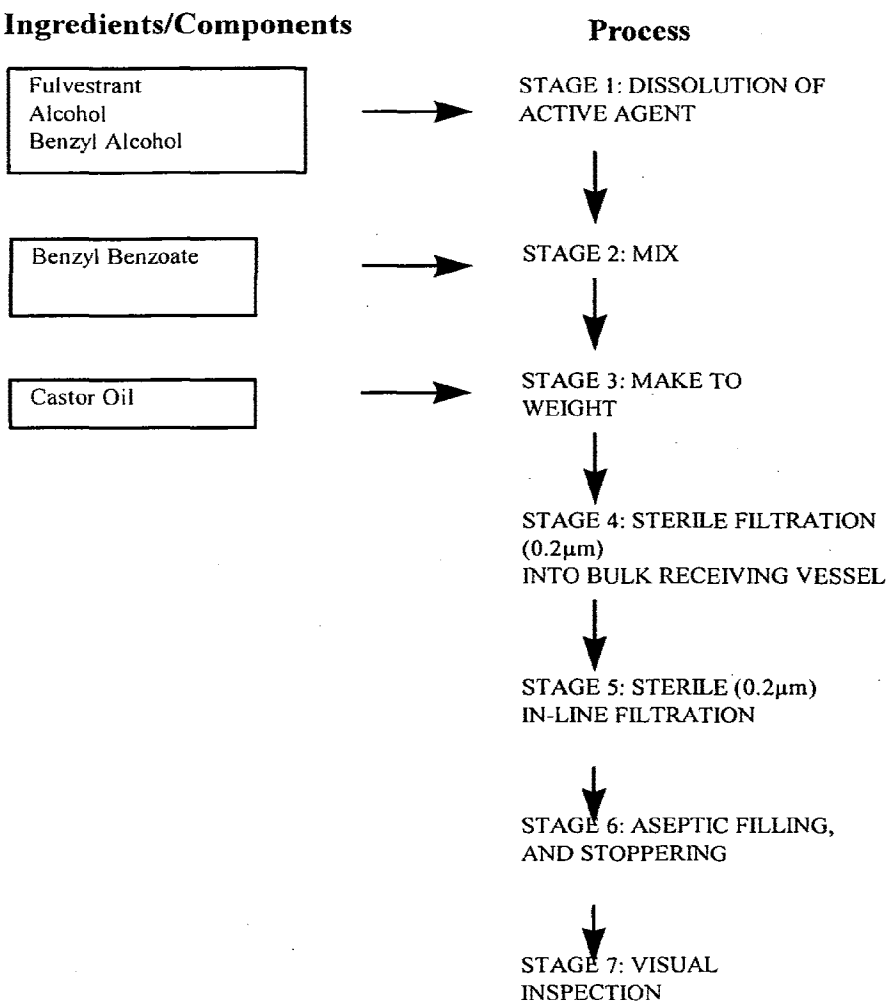
Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid 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 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

FLOW DIAGRAM OF MANUFACTURING



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.

Claims

1. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate per volume of formulation and a 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.

2. A pharmaceutical formulation as claimed in claim 1 which contains 22% w/v or less of a pharmaceutically-acceptable alcohol.

3. A pharmaceutical formulation as claimed in claim 1 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

4. A pharmaceutical formulation as claimed in claim 1 which contains and 18%w/v or less of a pharmaceutically-acceptable alcohol.

5. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 60% w/v or less of benzyl benzoate.

6. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 50%w/v or less of benzyl benzoate.

7. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 45% w/v or less of benzyl benzoate.

8. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 40% w/v or less of benzyl benzoate.

9. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 35% w/v or less of benzyl benzoate.

10. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 30% w/v or less of benzyl benzoate.

11. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 25% w/v or less of benzyl benzoate.

12. A pharmaceutical formulation as claimed in any claim from 1 to 11 wherein the total volume of the formulation is 5ml, or less, and the concentration of fulvestrant is at least 45mgml^{-1}.

13. A pharmaceutical formulation as claimed in any claim from 1 to 11 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 5ml, or less.

14. A pharmaceutical formulation as claimed in claim 13 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5ml.

15. An extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate 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 50mgml^{-1} of fulvestrant.

Application No: _____
Pillsbury Madison & Sutro
Inventor: J. EVANS et al
Filed: 1/9/01
Client & Ref. #: ASTRAZENECA (PAM70635/US)
CL.# 9901 M# 275507

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/756,291	01/09/2001	John R. Evans	PM 275507 PHM70635/US

CONFIRMATION NO. 5974

FORMALITIES LETTER

OC000000005780626

Pillsbury Winthrop LLP
Intellectual Property Group
Ninth Floor
1100 New York Avenue, NW.
Washington, DC 20005-3918

Date Mailed: 02/20/2001

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

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 $ **710** *to complete the basic filing fee and/or file a small entity statement claiming such status (37 CFR 1.27).*
- Total additional claim fee(s) for this application is $432.
  - **$162** for **9** total claims over 20.
  - **$270** for multiple dependent claim surcharge.
- The oath or declaration is missing.
- 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 balance due by applicant is $ 1272.**

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

NK

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

FILING COMPLETION UNDER RULE 53(f)

(NOT PCT Applications)
For Design, Provisional, or Utility Applications

PATENT APPLICATION

COMPLETION Under Rule 53(f)

In re PATENT APPLICATION of
Inventor(s): EVANS, John R. et al

Attn: Application Division

Appln. No.:	09	756,291	Atty.Dkt.	P	275507	PHM 70635/US
	Series Code ⇧	Serial No. ⇧			M#	Client Ref

Filed: January 9, 2001
Title: FORMULATION

Hon. Commisioner of Patents
Washington,DC 20231

Date: March 27, 2001

Sir:

The following **completes the filing** under Rule 53(f) of the above-identified patent application:

1. **Notice to File Missing Parts** ☒ copy attached ☐ not yet received

2. ☒ Signed Declaration attached. ☒ Original ☐ Facsimile/Copy

(Always "X" box 2 if filling signed Declaration and
"X" box 2A only if top box of the Declaration is X'd and file application copy, or
"X" box 2B only if none of the top three boxes of the Declaration is X'd.)

2A. ☐ Attached: Original signed Declaration with attached specification (including claim(s)) which is a copy of specification and claim(s) originally filed to secure the above filing date.

2B. ☐ The original application as filed in the PTO on the above filing date is the application which each inventor executed by signing the attached Rule 63 Declaration.

3. ☐ Specification originally filed in non-English language; hence verified translation attached of:
   a. ☐ Abstract
   b. [#] pages of Specification(only spec. & claims)
   c. ☐ Drawing(s) _____ No of Sheets
      ☐ Fig(s). _____

4. ☐ Letter filing formal drawing attached.

5. ☒ Attached is an assignment and cover sheet. Please return the recorded assignment to the undersigned.

6. **DOMESTIC/INTERNATIONAL** priority is claimed under 35 USC 119(e)/120/365(c) based on the following provisional, nonprovisional and/or PCT international application(s):

Application No.	Filing Date	Application No.	Filing Date
(1)		(2)	
(3)		(4)	
(5)		(6)	

7. **FOREIGN** priority is claimed under 35 USC 119(a)-(d)/365(b) based on filing in Great Britain

8.

Application No.		Filing Date	Application No.		Filing Date
(1)	0000313.7	January 10, 2000	(2)	0008837.7	April 12, 2000
(3)			(4)		
(5)			(6)		

Completion Under Rule 53(b)

9. 2 (No.) Certified copy (copies): ☐ attached; ☒ previously filed (date) January 9, 2001
in U.S. Application No. 09/756,291 filed on January 9, 2001

10. Small Entity Status ⌀ ☒ is Not claimed ☐ is claimed (file PAT-256 if this is the first claim of Small Entity Status)

11. ☐ Attached:

12. ☐ Preliminary Amendment:

THE FOLLOWING FILING FEE IS BASED ON CLAIMS AS FILED LESS ANY ABOVE CANCELLED

				Large/Small Entity		Fee Code
13. Basic Filing Fee . . . . . .Design Application Not Design Application				$320/$160 $710/$355	 +710	106/26 101/201
14. Total Effective Claims	29	minus 20 =	9	x $18/$9	+162	103/203
15. Independent Claims	2	minus 3 =	0	x $80/$40	+0	102/202
16. If any proper multiple dependent claim (ignore improper) is present, (Leave this line blank if this is a reissue application)				$270/$135	+270	104/204
17. Surcharge for filing Declaration/filing fee late				$130/$65	+130	105/205
18.				FILING FEE ENCLOSED =	$1272	
19. **Original due date:** April 20, 2001						
20. **Petition is hereby made** to extend the original due date to cover the date this response is filed for which the requisite fee is attached			(1 mo) (2mos) (3mos) (4mos)	$110/$55 = $390/$195 = $890/$445 = $1390/$695 =	+0	115/215 116/216 117/217 118/218
21. If "non-English" box 3 is X'd, add Rule 17(k) processing fee				$130	+0	139
22. If "assignment" box 5 is X'd, add recording fee.				$40	+40	581
23. Petition Fee for				$130	+0	
24.				TOTAL FEE ENCLOSED =	$1312	

Our Deposit Account No. 03-3975
Our Order No. 9901 (C#) 275507 (M#)

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 (missing or insufficiencies only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown in the heading hereof for which purpose a duplicate copy of this sheet is attached. **This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed.**

Pillsbury Winthrop LLP
Intellectual Property Group

1100 New York Avenue, NW
Ninth Floor
Washington, DC 20005-3918
Tel: (202) 861-3000
Atty/Sec: DJB/mhn

By Atty: Donald J. Bird **Reg. No.** 25323
Sig:
Fax: (202) 822-0944
Tel: (202) 861-3027

NOTE: File in duplicate with PTO receipt (PAT-103A) and attachm nts

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
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APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/756,291	01/09/2001	John R. Evans	PM 275507 PHM70635/US

CONFIRMATION NO. 5974

FORMALITIES LETTER

OC000000005780626

Pillsbury Winthrop LLP
Intellectual Property Group
Ninth Floor
1100 New York Avenue, NW.
Washington, DC 20005-3918

Date Mailed: 02/20/2001

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

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 $ **710** *to complete the basic filing fee and/or file a small entity statement claiming such status (37 CFR 1.27).*
- Total additional claim fee(s) for this application is $432.
  - **$162** for **9** total claims over 20.
  - **$270** for multiple dependent claim surcharge.
- The oath or declaration is missing.
- 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 balance due by applicant is $ 1272.**

09756291 710.00 BP
130.00 BP
162.00 BP
270.00 BP

03/29/2001 ABDITOM 00000006 09756291
01 FC:101
02 FC:105
03 FC:103
04 FC:104

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

NK

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

Z70635/US

FOR UTILITY/DESIGN CIP/PCT NATIONAL/PLAN 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

#3 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 City	State/Foreign Country	Country of Citizenship
Macclesfield, Cheshire	United Kingdom	British
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
ROSALIND	U	GRUNDY
Residence City	State/Foreign Country	Country of Citizenship
Macclesfield, Cheshire	United Kingdom	British
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 11/99(

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trad mark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/756,291	01/09/01	EVANS J	PM 275507 PH

HM22/0801

PILLSBURY WINTHROP LLP
INTELLECTUAL PROPERTY GROUP
NINTH FLOOR
1100 NEW YORK AVENUE, NW.
WASHINGTON DC 20005-3918

EXAMINER	
STILLER,K	
ART UNIT	**PAPER NUMBER**
1617	4

DATE MAILED: 08/01/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/756,291	EVANS ET AL.	
	Examiner	Art Unit	
	Karl Stiller	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 1 MONTH(S) 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 the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- 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) 1-23 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) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-23 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).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ 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.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

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-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-20 and 23, drawn to a pharmaceutical formulation and syringe or vial, comprising fulvestrant, a pharmaceutically acceptable alcohol, a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle, and a ricinoleate vehicle, classified in Class 514, Subclass 169.

II. Claims 21-22, drawn to a method of treating a benign or malignant disease of the breast or reproductive tract in a human, comprising administering , classified in Class 514, Subclass 169.

Inventions of Group I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the process of using the product as claimed to treat benign or malignant diseases of the breast or reproductive tract in a human can be practiced with a materially different product, such as fulvestrant, for example, in a peanut oil vehicle, alone.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Election of Species

In addition, if applicant elects Group II above, Claim 21 is generic to a plurality of disease states or conditions comprising benign or malignant diseases of the breast or reproductive tract. Applicants are required to elect an individual benign or malignant disease of the breast or reproductive tract to be treated in a mammal, e.g., breast cancer, benign prostatic hyperplasia, genital warts, etc., as a specie under 35 U.S.C. 121 to which the claims shall be restricted if no generic claim is finally held to be allowable, even through this requirement is traversed.

Claim 21 is generic to a plurality of disclosed patentably distinct species comprising benign or malignant diseases of the breast or reproductive tract. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

The search for all species of all benign or malignant diseases of the breast or reproductive tract presents an undue burden on the office due to their separate and distinct fields of search. Note that the search is not limited to the patent files. Claim 21 is drawn to the treatment of many benign or malignant diseases of the breast or reproductive tract, for example, breast cancer, benign prostatic hyperplasia, and genital warts. The search field for treatment of breast cancer, benign prostatic hyperplasia, and

readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

A telephone call was made to Donald Bird on July 25, 2001 to request an oral election to the above restriction requirement, but did not result in an election being made.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karl Stiller whose telephone number is 703-306-3219. The examiner can normally be reached Monday through Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie can be reached at 703-308-4612. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4556 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Stiller: ks
July 26, 2001

MINNA MOEZIE, J.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

US 0975629106P1

Creation date: 01-15-2004
Indexing Officer: TTRAN30 - TRANG TRAN
Team: OIPEBackFileIndexing
Dossier: 09756291

Legal Date: 02-01-2002

No.	Doccode	Number of pages
1	LET.	3
2	A...	2
3	IDS	2
4	FOR	14
5	FOR	5
6	FOR	9
7	FOR	8
8	FOR	4
9	FOR	4
10	FOR	14
11	FOR	11
12	FOR	4
13	FOR	4
14	NPL	8
15	NPL	9
16	NPL	10
17	NPL	11
18	NPL	10
19	NPL	6
20	NPL	6
21	NPL	4
22	NPL	6
23	NPL	6
24	NPL	6
25	NPL	6
26	NPL	8
27	NPL	3
28	NPL	4
29	NPL	3
30	NPL	4
31	NPL	8

GRU 1617

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: Stiller, K.

Commissioner of Patents
Washington, D.C. 20231

Sir:

TRANSMITTAL OF RSPONSE TO RESTRICTION REQUIREMENT AND INFORMATION DISCLOSURE STATEMENT

1. Transmitted herewith is a Response to responding to the One-Month Office Action dated August 1, 2001.

2. Additional papers enclosed:

☒ Information Disclosure Statement
☒ Form PTO-1449, 48 references included

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 petitions for an extension of time, the fees for which are set out in 37 C.F.R. § 1.17(a), for the total number of months checked below:

Total Months Requested	Fee for Extension	[Fee for Small Entity]
☒ five months	$ 1,960.00	$ 980.00

Extension of time fee due with this request: $1,960.00

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

4. Constructive Petition

☒ 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 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).

5. Fee Calculation (37 C.F.R. §1.16)

CLAIMS AS AMENDED						
	Claims Remaining After Amendment		Highest No. Previously Paid	Present Extra	at Rate of	Total Fees
Total Claims (37 C.F.R. §1.16(c))	29	minus	20	0	x $18.00 each=	$ 0.00
Independent Claims (37 C.F.R.§1.16(b))	2	minus	3	0	x $84 each=	$ 0.00
[ ] First presentation of Multiple dependent claim(s)				**	$280.00	$ 0.00
SUB-TOTAL =						$ 0.00
Fee for Five (5) Month Extenstion of Time						$ 1,960.00
Fee for Information Disclosure Statement						$ 0.00
Fee for Terminal Disclaimer						$ 0.00
Reduction by ½ for filing by a small entity						$ 0.00
TOTAL FEE =						$ 1,960.00

6. Fee Payment

☐ No fee is to be paid at this time.

☒ Please charge Deposit Account No. 50-0310 for Five Month Extension of Time Fee.

☒ 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: By: _____

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PATENT
ATTORNEY DOCKET NO.: 056291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of)
)
EVANS et al.) Group Art Unit: 1617
)
Appln. No.: 09/756,291) Examiner: Stiller, K.
)
Filed: January 9, 2001)
)
FOR: FORMULATION)

Commissioner of Patents
Washington, D.C. 20231

Sir:

RESPONSE TO RESTRICTION REQUIREMENT

This is in response to the restriction requirement set forth in the one-month Office Action dated August 1, 2001, the time for responding to which has been extended by the petition and authorization for fee payment submitted herewith.

In response to the restriction requirement, applicants elect the invention of Group II, claims 21-22, drawn to the method of treatment. In response to the further request for an election of a species of benign or malignant disease within Group II, applicants

provisionally elect the species "breast cancer" for initial examination in this application. The elected species falls within the scope of claims 21 and 22.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

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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: Stiller, K.

Commissioner of Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT

Attached is a Form PTO-1449 listing the enclosed documents.

The present Information Disclosure Statement is being filed before the mailing date of the first Office Action on the merits, 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, 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.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

By: _____

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(84) Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE

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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.

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^{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 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]-

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).

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.

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

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

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.

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.

TABLE V

Treatm nt	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'
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.

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.

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.

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
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BREVET SPÉCIAL DE MÉDICAMENT

P.V. n° 91.773 N° 6.241 M
Classification internationale : A 61 k // C 07 c

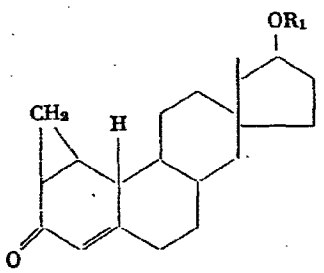
Médicament renfermant de la 1.2α-méthylène-19-nor-testostérone.

Société dite : SCHERING AKTIENGESELLSCHAFT résidant en Allemagne.

Demandé le 19 janvier 1967, à 15h 4m, à Paris.
Délivré par arrêté du 12 août 1968.
(*Bulletin officiel de la Propriété industrielle* [*B.S.M.*], n° 38 du 16 septembre 1968.)

(*Brevet résultant de la division de la demande de brevet, P.V. n° 81.067, déposée le 21 octobre 1966.*)

La présente invention a pour objet un médicament contenant, comme substance active, la 1.2α-méthylène-19-nortestostérone et des esters de ce composé, répondant à la formule générale :



dans laquelle R_1 représente l'hydrogène ou un reste acyle physiologiquement admissible.

Comme restes acyles, on peut envisager tous ceux qui dérivent des acides couramment utilisés pour les estérifications dans la chimie des stéroïdes. Les restes acyles des acides carboxyliques aliphatiques, en particulier ceux ayant de 1 à 12 atomes de carbone, conviennent particulièrement bien. Il est bien entendu que ces acides peuvent être insaturés, ramifiés, polybasiques ou porter les substituants habituels, par exemple des groupe hydroxylés ou amino, ou des atomes d'halogènes. Conviennent également des acides cyclo-aliphatiques, aromatiques, des acides mixtes, aromatiques-aliphatiques ou des acides hétérocycliques, lesquels peuvent également porter des substituants courants. On peut citer, comme acides préférés pour la constitution du reste R_1, par exemple l'acide acétique, l'acide propionique, l'acide oenanthique, l'acide caproïque, l'acide undécylique, l'acide triméthyl-acétique, les acides halogéno-acétiques, l'acide cyclopentyl-propionique, l'acide phényl-acétique, l'acide phénoxy-acétique, les acides dialkyl-amino-acétiques, l'acide pipéridine-acétique, l'acide succinique, l'acide benzoïque, etc.

Les composés utilisés de préférence comme substance active présentent les caractéristiques physiques suivantes :

L'acétate de la 1.2α-méthylène-19-nor-testostérone fond à 134-135,5 °C et présente dans son spectre ultra-violet une extinction ε_{241} de 14 400;

Le dichloracétate de la 1.2α-méthylène-19-nor-testostérone fond à 145-146 °C et présente dans son spectre ultra-violet une extinction ε_{240} de 14 500;

Le propionate de la 1.2α-méthylène-19-nor-testostérone fond à 113-114 °C et présente dans son spectre ultra-violet une extinction ε_{240} de 14 300;

L'œnanthate de la 1.2α-méthylène-19-nor-testostérone se présente sous forme d'huile et il y a dans son spectre ultra-violet une extinction ε_{239} de 13 900;

La 1.2α-méthylène-19-nor-testostérone fond à 219-222 °C et présente dans son spectre ultra-violet une extinction ε_{240} de 14 400.

Les substances actives du présent médicament se préparent de préférence conformément à la demande de brevet français n° 81.067 déposée le 21 octobre 1966 au nom de la demanderesse : on introduit de manière connue une double liaison Δ^4 dans des 1.2α - méthylène - 19 - nor - 3 - oxo - stéroïdes, après quoi, si on le désire, on acyle ou on saponifie les produits primaires ainsi obtenus.

Les nouveaux composés se signalent par une remarquable activité anabolisante et simultanément par une dissociation particulièrement favorable entre l'activité anabolisante souhaitée et l'activité androgène secondaire non recherchée, comme le montre le tableau ci-dessous, dans lequel l'acétate de 1.2α-méthylène-19-nor-testostérone (III) et le propionate de 1.2α-méthylène-19-nor-testostérone (II) sont comparés au composé étalon bien connu

qu'est le propionate de testostérone (I). Les résultats indiqués dans le tableau ont été déterminés sur le rat castré, après application par voie sous cutanée, conformément à l'essai couramment utilisé pour l'étude des propriétés anabolisantes et androgènes. Dans cet essai, on utilise comme valeur de comparaison la dose donnant au releveur de l'anus (M. levator ani) un poids de 50 mg au moins pour 100 g de poids corporel du rat (activité anabolisante). Comme mesure de l'activité androgène, on a indiqué dans le tableau le poids en mg des vésicules séminales pour 100 g de poids corporel du rat.

TABLEAU

Substance	Dose	Poids du releveur de l'anus	Poids de vésicules séminales
	(mg)	(mg)	mg
I. Propionate de testostérone	1	56	529
II. Propionate de 1.2α-méthylène-19-nor-testostérone	0,1	55	147
III. Acétate de 1.2α-méthylène-19-nor-testostérone	0,3	51	165

Il ressort du tableau que les composés actifs II et III, conformes à l'invention possèdent, par rapport au composé de comparaison I, non seulement un renforcement très considérable et imprévisible de l'activité anabolisante, mais aussi, simultanément, un déplacement extrêmement favorable du rapport entre les activités anabolisante et androgène, A ce déplacement favorable du rapport entre les activités s'ajoute l'avantage supplémentaire que les esters des acides aliphatiques à longue chaîne, comme l'acide œnanthique, présentent une activité anabolisante à effet retard, ce qui est très souhaitable.

Les essais cliniques ont rapporté aux constatations pharmacologiques la confirmation attendue. C'est ainsi qu'on a pu montrer, au moyen de l'étude de bilans métaboliques chez l'homme que, par exemple, le propionate de 1.2α-méthylène-19-nor-testostérone manifeste, après injection quotidienne en intra-musculaire de 5 à 10 mg ,une bonne activité anabolisante. Sous l'action du traitement, il se fixe quotidiennement d'environ 2 à 3 g d'azote de plus que dans la période antérieure à l'institution dudit traitement. Des études effectuées sur l'évolution ultérieure du bilan métabolique il ressort que l'œnanthate présente un effet retard marqué. La toxicité des substances actives est très éloignée de la dose thérapeutique qu'on peut pratiquement envisager. On n'a pas observé de phénomènes secondaires, en particulier d'intolérance.

On peut utiliser les nouvelles substances actives dans tous les cas où il est nécessaire de stimuler l'anabolisme des protéines au moyen d'agents à activité anabolisante. On peut citer comme exemples les domaines d'indication suivants : convalescences, atteintes de l'état général, maladies consomptives, maladies cachectisantes, anorexies, poids insuffisant, épuisements, traitements radiothérapiques, anémies, traitements prolongés par les corticoïdes, ostéoporose, affections rénales chroniques, etc.

Les substances actives conformes à la présente invention peuvent être utilisées, en association avec les véhicules bien connus employés en pharmacie galénique, pour la fabrication de médicaments ayant une activité anabolisante, administrables en particulier par voie parentérale mais aussi par voie orale. Parmi les formes de présentation utilisables, on peut citer par exemple des ampoules pour injection par voie intramusculaire.

Les exemples qui suivent ont pour but d'illustrer la présente invention, dont ils ne sauraient en aucune manière limiter la portée.

Exemple 1. — 1 ml correspond à 5 mg de substance active.

On dissout 0,5 g de propionate de 1.2α-méthylène-19-nor-testostérone dans un mélange d'huile de ricin et de benzoate de benzyle (7 : 3) jusqu'à un volume de 100 ml, on vesre dans des ampoules, à raison de 1 ml par ampoule. On stérilise ensuite de manière connue.

Au lieu de benzoate de benzyle. on peut également utiliser l'alcool benzylique.

Exemple 2. — 1 ml correspond à 10 mg de substance active.

On dissout 1 g de propionate de 1.2α-méthylène-19-nor-testostérone dans un mélange d'huile de sésame et de benzoate de benzyle (7 : 3) jusqu'à un volume de 100 ml, on verse dans des ampoules, à raison de 1 ml par ampoule. On stérilise ensuite de manière connue.

Exemple 3. — 1 ml correspond à 50 mg de substance active.

On dissout 5 g d'œnanthate de 1.2α-méthylène-19-nor-testostérone dans l'huile de sésame jusqu'à un volume de 100 ml, on verse dans des ampoules à raison de 1 ml par ampoule, puis on stérilise de manière connue.

Pour l'utilisation par voie orale, on peut envisager des comprimés, des dragées, des suspensions, des capsules, etc.

Exemple 4. — Comprimés contenant 5 mg d'acétate de 1.2α-méthylène-19-nor-testostérone.

Composition pour un comprimé :

5,000 mg d'acétate de 1.2α-méthylène-19-nor-testostérone (micronisé);
36,000 mg de lactose (pharmacopée allemande, DAB 6);
71,565 mg d'amidon de maïs (pharmacopée USA, USP XVI);
6,000 mg de talc (DAB 6);
1,400 mg de gélatine blanche (DAB 6);
0,024 mg de l'ester méthylique de l'acide p-hydroxybenzoïque (DAB 6, 3e addition);
0,011 mg de l'ester propylique de l'acide p-hydroxybenzoïque (DAB 6, 3e addition).

120,000 mg

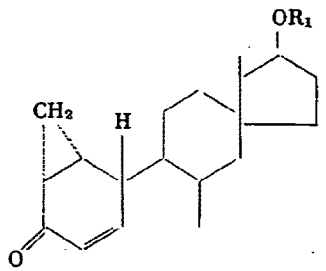
L'amidon de maïs, le lactose, le talc et la gélatine servent de charges, et les esters méthylique et propylique de l'acide o-hydroxy-benzoïque servent d'agents de conservation.

On prépare les comprimés de la manière habituelle sur une presse à comprimés.

[Diamètre : 7 mm avec entaille pour fragmentation; épaisseur : 2,7 à 2,8 mm; dureté : 3 kg; dissociation dans l'eau à 20 °C : une minute].

RÉSUMÉ

1° Médicament anabolisant renfermant, comme substance active, de la 1.2α-méthylène-19-nor-testosrérone et des esters de ce composé, répondant à la formule générale :



dans laquelle :

R_1 représente l'hydrogène ou un reste d'acide physiologiquement admissible;

2° Des variétés du médicament spécifié sous 1°, présentant les particularités suivantes, prises séparément ou selon les diverses combinaisons possibles :

a. Le médicament contient de la 1.2α-méthylène-19-nor-testostérone;

b. Le médicament contient de l'acétate de 1.2α-méthylène-19-nor-testostérone;

c. Le médicament contient du dichloracétate de 1.2α-méthylène-19-nor-testostérone;

d. Le médicament contient du propionate de 1.2α-méthylène-19-nor-testostérone;

e. Le médicament contient de l'œnanthate de 1.2α-méthylène-19-nor-testostérone;

f. La substance active est associée à des excipients couramment utilisés en pharmacie galénique;

g. Le médicament contient la substance active dans les solutions huileuses pour injection;

h. Le médicament contient d'environ 0,5 à 100 mg de substance active par unité de prise;

i. Le médicament contient d'environ 0,1 à environ 20 % de substance active.

Société dite : SCHERING AKTIENGESELLSCHAFT

Par procuration :

Jean CASANOVA (Cabinet ARMENGAUD jeune)

AVIS DOCUMENTAIRE SUR LA NOUVEAUTÉ

Documents susceptibles de porter atteinte à la nouveauté du médicament : *néant.*

Documents illustrant l'état de la technique en la matière :

L'article de F. Neumann et collab. paru dans la revue allemande *Arzneimittel-Forschung*, n° 10, octobre 1965, p. 1168-1170; 1176.

Pour la vente des fascicules, s'adresser à l'IMPRIMERIE NATIONALE, 27, rue de la Convention, Paris (15e).

L16 ANSWER 76 OF 81 HCAPLUS COPYRIGHT 2000 ACS
AN 1971:130391 HCAPLUS
DN 74:130391
TI 1,2.alpha.-Methylene-19-nortestosterone pharmaceutical compositions
PA Schering A.,G.
SO Fr. M., 3 pp.
CODEN: FMXXAJ
DT **Patent**
LA French
IC A61K; C07C
CC **63 (Pharmaceuticals)**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI FR----6241		19680916	FR	19670119

GI For diagram(s), see printed CA Issue.
AB 1,2.alpha.-Methylene-19-nortestosterone esters (I) show good anabolic activity with little **androgenic** activity, and are useful in stimulating protein anabolism in cases of general convalescence, anorexia, anemia, and general debilitating circumstances. Compns. contg. I are administered i.m. or orally. I (R = Ac) (II) m. 134-5.5.degree.; I (R = COCHCl2) m. 145-6.degree.; I (R = COEt) (III) m. 113-14.degree.; I (R = COC6H13) (IV), **oil**; I (R = H) m. 219-22.degree.. A soln. for injection contained 0.5 g III in 100 ml of a mixt. of **benzyl benzoate** and **castor oil** (3:7), 1 ml being used per injection. An-other contained 5 g IV in 100 ml sesame **oil**. Tablets each contained 5 mg II with the usual excipients.
ST nortestosterone methylene anabolic

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PATENT SPECIFICATION

817.241

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Index at acceptance:—Class 81(1), B2(N:S:Z).

Int rnational Classification:—A61k.

COMPLETE SPECIFICATION

Oily Solutions for Parenteral Administration containing Adreno-Cortical Hormones

We, FRANCESCO VISMARA, S.p.A., an Italian Body Corporate, of Casatenovo, Como, Italy, and ALBERTO ERCOLI, an Italian Citizen, of Via Circo 12, Milan, Italy, do hereby declare the invention, for which we 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 is concerned with improvements in or relating to pharmaceutical compositions, more particularly with oily solutions for parenteral administration of adreno-cortical hormones.

The preparation of oily solutions of cortical hormones, such as cortisone and hydrocortisone, or of their corresponding Δ^1-dehydro-derivatives, 9-halogen and/or 6-methyl-derivatives, in sufficiently high concentrations required for many therapeutic purposes has been a problem.

It is well known, in fact, that these hormones, as well as their esters which may be used in therapy, are very sparingly soluble in the oily solvents which are commonly employed as vehicles for parenteral use e.g. olive oil, cottonseed oil, sesame oil, arachis oil or ethyl oleate. For this reason these hormones are usually administered parenterally in aqueous suspension or orally. Both these forms of administration have shown, however, a number of significant disadvantages.

Aqueous suspensions are not always well tolerated. The crystalline deposit is usually absorbed from the site of the injection at too slow a rate. The poor absorption may cause phenomena of local intolerance. Aqueous suspensions may also give rise, especially in prolonged treatments, to irritations at the site of injection, which sometimes form abscesses.

Oral administration does not always assure regularity as well as constancy of action, and does not guarantee a complete uptake of the drug. Furthermore prolonged administration of anti-inflammatory hormones by oral route frequently causes gastritis which may complicate into ulcers which are particularly dangerous because of their silentness.

An object of the present invention is to provide compositions of adreno-cortical hormones in the form of oily solutions, in order to reduce the disadvantages of the two above-mentioned forms of administration.

Another object of the invention is to provide oily solutions with a high hormonal concentration which are of considerable importance in the treatment of certain diseases such as leukemia, where high doses of the hormone are required.

It has now been found that very satisfactory parenterally acceptable solutions of adreno-cortical hormones may be prepared by using esters of ricinoleic acid with certain mono and polyhydric alcohols as solvents; such solutions may of course contain other adjuvants which are not esters but which are parenterally acceptable and pharmaceutically compatible therewith such as antioxidants, wetting and dispersing agents and the like.

According to the present invention there is provided an oily composition adapted for parenteral administration comprising an adreno-cortical hormone in solution in a liquid vehicle consisting of a parenterally acceptable ester of ricinoleic acid with a monohydric or polyhydric alcohol containing two or three carbon atoms per molecule with or without other parenterally acceptable compatible adjuvants which are not esters.

By the term "adreno-cortical hormone" is to be understood steroid compounds having adreno-cortical activity. Such compounds include not only those present in nature but also related compounds which are believed not to be present in nature but which have similar activity to a greater or lesser degree. Thus in addition to including naturally-occurring compounds such as cortisone and hydrocortisone it includes derivatives thereof such as prednisone and prednisolone. Moreover, the term also

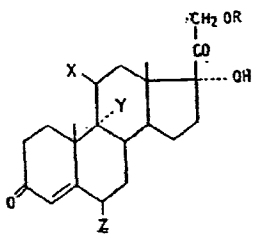
[Price 3s. 6d.]

includes 21-esters of any naturally occurring or synthetic adreno-cortical hormones.

Esters of ricinoleic acid with glycerol, propylene glycol or ethyl alcohol are preferred because of their high solubilizing power and of their good local tolerance.

The oily solutions according to the invention are well-tolerated, well-absorbed at the site of injection and accompanied by relatively few side-effects, even in cases where high doses are administered. They possess a high therapeutic value which makes them active at small doses not otherwise effective, as, for instance, in the liver glycogen deposition test where, at equal doses, prednisone in an oily solution has been shown to have an activity five times higher than that of the oral form, (that is in order to obtain the same increase in liver glycogen, an oral dose five times higher than that administered parenterally in oily form must be given).

Although the adreno-cortical hormone used in the oily composition according to the invention may be any desired such compound it is preferred to use a compound of the general formula: —



where

X is ketonic oxygen or a hydroxyl group,
Y is a hydrogen or a halogen atom,
Z is a hydrogen atom or a methyl group and
R is hydrogen or an acyl group or a Δ^1 or a $\Delta^{1:4}$-dehydro-derivative thereof.

If desired, one may use mixtures of adreno-cortical hormones.

It is preferred that the oily compositions according to the invention should contain the adreno-cortical hormone in an amount from 0.1 to 5% by weight of the liquid vehicle.

The vehicles used in the composition according to the invention can be used either individually or in admixture with other such vehicles in various proportions. These vehicles can also be diluted if desired with a further ester component consisting of a parenterally acceptable ester of an alcohol with a carboxylic acid other than ricinoleic acid, said ester containing at least six carbon atoms per molecule, such as olive oil, sesame oil, ethyl oleate, or benzyl benzoate.

The mixtures, for example with ethyl oleate, have a solubilising power inferior to that of pure ricinoleates; on the other hand, they have the advantage of a lower viscosity, so that injection becomes easier.

Tables 1 and 2 show the solubilities of cortisone, prednisone and prednisolone and of some of their esters in the ricinoleic acid esters as compared with their respective solubilities in olive oil or sesame oil.

TABLE 1

	Cortisone acetate mg/cc	Cortisone trimethyl-acetate mg/cc	Cortisone oenanthate mg/cc	Cortisone cyclopentyl-propionate mg/cc	Cortisone phenyl-propionate mg/cc
Olive oil	0.1	0.1	8	3	3
Glyceryl ricinoleate	5	3	60	40	30
Ethyl ricinoleate	3		60	40	26
Glyceryl ricinoleate + Ethyl ricinoleate		2.5 b		40 a	
Glyceryl ricinoleate + Ethyl oleate 1:1	4	2.5	50	30	25

a) = Glyceryl ricinoleate : ethyl ricinoleate = 1 : 1

b) = Glyceryl ricinoleate : ethyl ricinoleate = 1 : 2

TABLE 2

	Prednisone mg/cc	Prednisone acetate mg/cc	Prednisone trimethyl-acetate mg/cc	Prednisone oenanthate mg/cc	Prednisone cyclopentyl-propionate mg/cc	Prednisolone mg/cc	Prednisolone oenanthate mg/cc
Sesame oil	2	2	1	3	2	1	6
Glyceryl ricinoleate	12	10	8	12	10	25	60
Ethyl ricinoleate	10		7			20	40
Glyceryl ricinoleate + Ethyl ricinoleate	8	9	4	10	10		32
Glyceryl ricinoleate + Ethyl oleate 1:1		— 7	3.8	9	8	16	

The adreno-cortical hormones can be dissolved in the ricinoleic acid esters alone or in admixture with other esters in various proportions as stated above. Moreover different esters of the same hormone or various esters of different hormones can be dissolved simultaneously in the same vehicle or in a mixture of different vehicles. By a suitable mixture of a number of esters of the same hormone or of different hormones, oily compositions can be obtained with a high hormonal concentration.

The solutions thus obtained show a substantially normal viscosity after the addition of stabilisers, such as, for example, propyleneglycol or benzyl alcohol and they are practically stable and more advantageous and effective than the aqueous suspensions previously proposed and also than oral therapy. They ensure, in fact, a higher constancy of action with more marked effects and a greater uptake of the drug.

Therapy with such oily solutions has given very favourable results. The oily compositions of the cortical hormones and, particularly, those of the anti-inflammatory hormones, have been found to possess a generally superior therapeutic value to that obtained by aqueous suspensions or by the oral route.

In most conditions of acute and chronic articular rheumatism, infectious diseases, allergic syndromes etc., injectable preparations have been found to give optimal clinical remissions with doses lower than those normally required by the oral route; for example: 15 mgms. of prednisone in oily solution have given results comparable with those obtainable with 20—25 mgms. of the same hormone administered by the oral route. This constitutes an appreciable advantage, even from the economic point of view.

The efficacy of the oily solutions can also be shown by the results obtained in the palliative treatments of certain types of neoplastic diseases, which results are quite as encouraging as they are unexpected. The oily solutions of the cortical hormones have proved to be particularly useful in giving some measure of relief in cases of pulmonary carcinoma, prostatic cancer, breast cancer and, though less frequently, in uterine cancer, besides of course in those cases of lymphoma, and leukemia

group of malignant tumours, where the therapy with cortisone and cortisone-like steroids is already used. In all these cases a rapid improvement is observed in the general conditions of the patient with an increase in appetite and a restoration of the vital forces. The effect of this treatment on pain is also notable; thus the quantity of morphine required can be appreciably reduced and, in some cases, may even not be necessary.

Although the liquid vehicle used in the compositions according to the invention has been defined in somewhat narrow terms, it should be understood that one may, if desired, add to the composition other pharmocological substances in addition to the adreno-cortical hormones. Substances of this nature include, for example sex hormones and products related to steroid hormones.

Moreover, one may add to the composition desired pharmaceutically acceptable adjuvants such as antioxidants and conserving or antiseptic agents (such as mono- or polyhydric phenols and ethers thereof) to assist the blending and prolong the stability of the components of the composition.

In order that the invention may be well understood, the following examples are given by way of illustration only.

EXAMPLE 1

Cortisone trimethylacetate (5 g.) was ground to a fine powder and suspended in a two litre mixture of glyceryl and ethyl ricinoleates. 5 mg/litre of propyl gallate and nordihydroguaiaretic acid (in equal parts) were added. The mixture was heated on a water-bath with occasional shaking of the suspension so as to obtain a clear and homogeneous solution. The resultant solution was then transferred into neutral glass 2 cc ampoules, each ampoule thus containing 5 mg. of cortisone trimethylacetate. The ampoules, sealed under nitrogen, were sterilised at a temperature of 120°C., for 30 minutes. A number of the ampoules were used for biological experiments. The remainder were maintained for some weeks in the ice-chest and then for some months at room temperature. The ampoules thus treated remained perfectly clear and homogeneous, even after many months had elapsed from the date of their preparation. The addition of small crystals of cortisone trimethylacetate failed to cause either opalescence or the formation of a crystalline precipitate.

The comparison of the biological activity of the oily solution of cortison trimethylacetate was carried out with an aqueous suspension of cortisone acetate at the same concentration (mg/cc), using the test of the survival of adrenalectomised rats treated with one single injection of the steroid. The test was carried out on male rats, 30 days old and weighing 60 gr each. Bilateral adrenalectomy was carried out under ether narcosis, according to the Grollman's technique. 3—4 hours after the adrenalectomy, the animals were subdivided into two groups of ten animals each. All the animals of one group were treated with one single injection of 2.5 mg of cortisone acetate in aqueous suspension. All the animals of the other group were treated with one single injection of 2.5 mg of cortisone trimethylacetate in oily solution. A third group of ten adrenalectomised animals served as controls. The results obtained are shown in the following table.

TABLE 3

Days after intervention	Number of living animals		
	Untreated	Treated with 2.5 mg of cortisone acetate in aqueous suspension	Treated with 2.5 mg of cortisone trimethyl-acetate in oily solution
5	2	10	10
6	0	8	10
7		8	10
8		8	10
9		4	10
10		4	10
11		4	10
12		2	7
13		0	7
14			6
15			3
16			2

EXAMPLE 2

Cortisone oenanthate (500 g., m.p. 138—140°C.), cortisone cyclopentylpropionate (300 g. m.p. 154—156°C.) and cortisone phenylpropionate (200 g., m.p. 173—175°C.) were suspended in a 20 litre mixture of glyceryl triricinoleate and ethyl oleate (1 : 1), containing nordihydroguaiaretic acid in the proportion of 10 mg/litre. The mixture was stirred mechanically, the internal temperature being kept at 100°C so as to obtain a clear and homogeneous solution. This solution was then introduced into 2 cc. ampoules, so that each one contained exactly 100 mg of the mixture of the cortisone esters (50 mg/cc). The ampoules, sealed under nitrogen, were sterilised at a temperature of 120°C for about 30 minutes. With the exception of some of these ampoules, which were used for biological experiments, the remainder were maintained for a few weeks, at about 0°C in an ice-chest, then for some months at room temperature. None of the ampoules thus treated showed any turbidity or precipitate even a few months after the date of their preparation.

EXAMPLE 3

A mixture of cortisone trimethylacetate (100 g., m.p. 260—262°C.), dehydrocorticosterone trimethylacetate (100 g., m.p. 186—187°C.) and desoxycorticosterone trimethylacetate (100 g., m.p. 200—202°C.) was dissolved at a temperature of about 80°C, in a 40 litre solution of ethyl ricinoleate diluted with 10% of ethyl oleate and containing, in the proportion of 8 mg/litre, nordihydroguaiaretic acid and propyl gallate in equal parts.

The clear solution was then introduced into 4000 containers of 10 cc. capacity so that each contained 75 mg of the active substances (7.5 mg/cc). This oily solution is very efficient in the treatment of Addisonians and in adrenocortical deficiencies.

EXAMPLE 4

Prednisone oenanthate (30 g., m.p. 176—178°C.) was admixed with 2.5 litres of a propylenyl ricinoleate solution containing propyl gallate in the proportion of 8 mg/litre in a 5-litre neutral glass flask. The flask was heated on a water-bath, the suspension being occasionally shaken and the temperature slowly raised until dissolution was complete. The clear and homogeneous solution thus obtained was introduced into 2 cc. ampoules so that each ampoule contained exactly 24 mg. of prednisone oenanthate. The ampoules were closed in a nitrogen atmosphere, sterilised and then maintained for some weeks in the ice-chest. The solution inside the ampoules remained quite clear and homogeneous and was practically uncongealable.

In the same way, prednisone cyclopentylpropionate (75 g., m.p. 188—190°C) were dissolved in 7.5 litres of a mixed solution of glyceryl and ethyl ricinoleates, to which had been added, in the proportion of 5 mg/litre, nordihydroguaiaretic acid. The solution thus obtained was introduced into 10 cc. containers. (Each container thus contained 100 mg of prednisone cyclopentylpropionate). A few months after the date of preparation the solution inside the containers was still perfectly homogeneous. There was no formation of any precipitate, even after the addition of seed crystals of prednisone cyclopentylpropionate.

In the same manner as above prednisone was dissolved in a mixture of glyceryl and ethyl ricinoleates (1:1). The biological activity of the prednisone, administered parenterally, in oily solution, was compared with that of prednisone administered orally. The comparison was carried out on albino rats and the action on thymus, adrenals and body weight was observed.

The liposoluble prednisone was administered in doses of 50—100—200—400γ and the orally administered prednisone in doses of 100—200—400—600—1000γ. This treatment was continued for five consecutive days; on the 6th day the animals were sacrificed; the adrenals and thymus were removed and weighed immediately. The results are shown in the table below.

TABLE 4

Treatment	Animals No.	Body weight change %	Adrenals weight mg	Thymus weight mg
Controls	31	107.7 ± 1.26	13.1 ± 0.36	89.4 ± 4.79
Prednisone i.m.				
400 × 5	12	85.2 ± 1.29	7.7 ± 0.21	16.1 ± 0.26
200 × 5	23	90.2 ± 2.92	8.9 ± 0.37	22.3 ± 1.17
100 × 5	12	103.8 ± 3.10	11.6 ± 0.60	36.9 ± 5.19
50 × 5	6	102.6 ± 2.92	13.1 ± 0.54	57.7 ± 6.08
Prednisone per os				
1000 × 5	6	106.1 ± 2.23	11.0 ± 0.81	23.1 ± 1.95
600 × 5	6	105.6 ± 2.50	13.0 ± 0.44	41.0 ± 2.59
400 × 5	12	108.4 ± 2.69	12.4 ± 0.56	43.2 ± 4.12
200 × 5	19	109.3 ± 1.44	12.8 ± 0.88	51.6 ± 3.74
100 × 5	6	104.8 ± 2.23	13.6 ± 0.89	50.0 ± 6.16

These results show that, with regard to the activity on thymus, adrenals and body weight, the prednisone preparation in oily solution administered intramuscularly is much more active than the orally administered prednisone.

EXAMPLE 5

Hydrocortisone acetate (15 g., m.p. 219—220°) was dissolved by heating in 1.5 litres of propylenyl ricinoleate, prepared by esterification of ricinoleic acid with propylene glycol. The solution (containing 10 mg of hydrocortisone acetate per cc) was introduced into 2 cc ampoules which were then sealed under vacuum and sterilized in an autoclave.

The ampoule solution was biologically tested —after diluting 1:10 with sesame oil—for its effects on the survival of adrenalectomised rats and it was found to be very effective.

EXAMPLE 6

Prednisolone (100 g., m.p. 240—242°C) was dissolved by heating in a mixture of ethyl ricinoleate and ethyl oleate (1:1) to give a concentration of 15 mg/cc. Multidose containers (10 cc.) were filled with this solution in the usual manner, sealed and sterilised.

This oily solution of prednisolone was used to treat a number of cases of malignant neoplasia. Tumours of the breast, tumours of the uterine portio and of the skin and primitive tumours of the bone were treated. Subjective

improvements were observed for two or three months. The patients reported a definite feeling of well-being, disappearance of pain, increase in appetite, and euphoria. The oily solution of prednisolone was well tolerated, well absorbed at the site of injection, and accompanied by no undesirable side-effects, even in cases where high doses were administered.

EXAMPLE 7

In the same manner as in Examples 1—6, oily solutions for use in parenteral administration were prepared with other steroids using glyceryl, propylenyl and ethyl ricinoleates singly and in admixture as the liquid vehicle.

Among the steroids made up into such preparations were 9α-fluoro derivatives of prednisone and prednisolone and their corresponding Δ^6-dehydro or 6-methyl derivatives, i.e.: 9α-fluoro - $\Delta^{1:4}$ - pregnadiene - 11β:17α:21-triol-3:20-dione; $\Delta^{1:4:6}$ - pregnatriene - 11β:17α:21 - triol - 3:20 - dione; 9α-fluoro-$\Delta^{1:4:6}$-pregnatriene - 11β:17α:21 - triol - 3:20-dione; 9α - fluoro - 6 - methyl - $\Delta^{1:4}$ - pregnadiene-11β:17α:21-triol-3:20-dione.

EXAMPLE 8

Prednisone trimethylacetate (8 g.) was ground to a fine powder and suspended in a two litre mixture of glyceryl and ethyl ricinoleates, 5 mg/litre of propyl gallate and nordihydroguaiaretic acid (in equal parts) were then added. The mixture was heated on a water-bath, the suspension being occasionally shaken and the temperature slowly raised until a clear and homogeneous solution was obtained. This solution was then transferred into neutral glass 2 cc ampoules, each ampoule thus having 8 mg. of prednisone trimethylacetate. The ampoules, sealed under nitrogen and sterilised, were maintained for some weeks in an ice-chest and then for some months at room temperature. The ampoules thus treated remained perfectly clear and homogeneous, even after many months had elapsed from the date of their preparation. Even the addition of small crystals of prednisone trimethylacetate caused neither opalescence nor crystalline precipitation.

The biological activity of prednisone trimethylacetate in the above vehicle was compared to that of the prednisone orally administered. On the turpentine granuloma test prednisone trimethylacetate in oily solution showed an antiinflammatory power clearly superior to that of the prednisone, administered by oral route.

EXAMPLE 9

Prednisone trimethylacetate (35 g., m.p. 274—278°C.), prednisone oenanthate (80 g., m.p. 176—178°C.) and prednisone cyclopentylpropionate (75 g., m.p. 188—190°C.) were suspended in a 10 litre mixture of glyceryl triricinoleate and ethyl oleate (1:1), containing nordihydroguaiaretic acid in the proportion of 10 mg/litre. The mixture was stirred mechanically, the internal temperature being kept at 100°C. so as to obtain a clear and homogeneous solution. This solution was then introduced into 2 cc. ampoules, so that each contained exactly 38 mg of the mixture of the prednisone esters (19 mg/cc.). The ampoules, sealed under nitrogen, were sterilised at a temperature of 120°C for about 30 minutes. After a few weeks at about 0°C. they were maintained for some months at room temperature. None of the ampoules thus-treated showed any turbidity or precipitate even a few months after the date of their preparation.

The oily solution of the prednisone esters was biologically tested—after a dilution 1:10 with sesame oil—for its effects on the survival of the adrenalectomised rats and it was found to be very effective.

EXAMPLE 10

A mixture of prednisone trimethylacetate (15 g.), prednisolone trimethylacetate (55 g.) and 9α-fluoro-prednisolone trimethylacetate (30 g.) was dissolved, at a temperature of about 80°C., in a 5 litre solution of ethyl ricinoleate containing 10% of ethyl oleate and nordihydroguaiaretic acid and propyl gallate, in equal parts, in the proportion of 8 mg/litre.

The clear solution was then introduced into 500 containers of 10 cc. each, so that each contained 200 mg. of the trimethylacetate mixture.

In the same manner, prednisone oenanthate (20 g.) and prednisolone oenanthate (80 g.) were dissolved in a 2 litre solution of glyceryl ricinoleate (50 mg/cc).

EXAMPLE 11

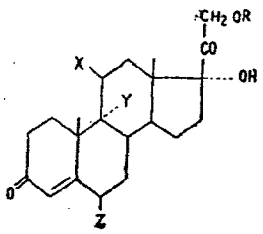
Prednisone (4 g.) and prednisolone (8 g.) were dissolved by heating in 500 cc. of propylenyl ricinoleate, prepared by the esterification of ricinoleic acid with propylene glycol. The solution thus prepared (containing 24 mg/cc of hormones mixture) was assayed on the spontaneous mammary tumour of mice. In several cases a temporary inhibition or retardation of the growth, and also hardening of the tumour was observed.

WHAT WE CLAIM IS:—

1. An oily composition adapted for parenteral administration comprising an adreno-cortical hormone as herein defined in solution in a liquid vehicle consisting of a parenterally acceptable ester of ricinoleic acid with a monohydric or polyhydric alcohol containing two or three carbon atoms per molecule with or without other parenterally acceptable compatible adjuvants which are not esters.

2. An oily composition as claimed in claim 1 in which said alcohol is ethyl alcohol, propylene glycol or glycerol.

3. An oily composition as claimed in claim 1 or 2 in which said adreno-cortical hormone is one having the general formula:—



where

X is ketonic oxygen or a hydroxyl group

Y is hydrogen or a halogen atom

Z is a hydrogen atom or a methyl group and

R is hydrogen or an acyl group or a Δ^1 or a $\Delta^{1:6}$-dehydro-derivative thereof.

4. An oily composition as claimed in any of the preceding claims in which a mixture of adreno-cortical hormones is used.

5. An oily composition as claimed in any of the preceding claims in which a mixture of said ricinoleic esters is used.

6. A modification of an oily composition as claimed in any of the preceding claims in which the liquid vehicle also contains a further ester component consisting of a parenterally acceptable ester of an alcohol with a carboxylic acid other than ricinoleic acid, said ester containing at least six carbon atoms per molecule.

7. An oily composition as claimed in claim 6 in which said ester is olive oil, sesame oil, ethyl oleate or benzyl benzoate.

8. A composition as claimed in any of the preceding claims in which pharmacologically active substances other than adreno-cortical hormones are present.

9. An oily composition as claimed in any of the preceding claims containing an anti-oxidant.

10. An oily composition as claimed in any of the preceding claims in which the adreno-cortical hormone is used in an amount of 0.1 to 5% by weight of the liquid vehicle.

11. An oily composition substantially as herein described with reference to any of the examples.

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(54) OILY DEPOT SOLUTIONS OF GESTAGENS FOR INTRAMUSCULAR INJECTION

(71) We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, do hereby declare the invention, for which we 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:-

The present invention is concerned with oily unsaturated depot solutions of gestagens, as hereinafter defined, for intramuscular injection and with their manufacture and use.

Depot preparations capable of being used for injection have already been known. As compared with preparations capable of being used for oral administration, they have the advantage that a single injection is sufficient for one or more months, whereas, for example, tablets must be taken daily. A depot effect is often brought about by adding the active substance to a carrier substance that slowly releases the active substance. An additional depot effect can be achieved by using a derivative of the active substance that decomposes to the active substance only in the body.

Depot preparations of gestagenic substances are used, for example, as contraceptive agents. Thus, for example, an oily solution of 17α-ethynyl-19-nor-testosterone oenanthate (norethisterone oenanthate) has been a clinically approved depot contraceptive for some years. At a dosage of 200 mg in 1 ml of castor oil/benzyl benzoate (6:4) the action lasts for 12 weeks. However, it has been found that the number of pregnancies is somewhat greater than in the case of taking oral tablets daily, and that undesired pregnancies occur especially shortly before the end of the injection-period. Moreover, it has been desired to obtain an action lasting for 13 weeks (3 months) because then the application-period can be calculated more easily in relation to the menstrual cycle.

It has now been found that a lengthening of the depot effect occurs when the volume of the injection solution is increased, while retaining the quantity of gestagen to be administered.

Female beagle hounds weighing about 13 kg were each injected simultaneously in the right and left M. glutaeus with 200 mg of 14.15-^{3}H-marked norethisterone oenanthate and 4-^{14}C-marked norethisterone oenanthate, respectively, in 1.8 ml and in 0.6 ml of castor oil/benzyl benzoate (6:4). During 13 weeks the ^{14}C- and ^{3}H-activity in the blood, plasma, urine and faeces was measured. The separation of the marked substances in proportion to the release from the depot showed up to 7 weeks after application no systematic difference between the selected volumes of application. There was found only a very small percentage reduction in the release during the initially high rates of release from the larger volumes. From the 8th week onwards the quantities of the marking applied with the larger volumes predominated. In the 13th week after application the release from the injection-volumes was increased in favour of the 1.8 ml solution by three and a half times, that is to say, in the 13th week there was observed, as compared with the smaller volumes, a rate of release about 3.5 times higher.

The measured quantities for the 13th week are given in the accompanying drawing.

It could not have been foreseen that, by increasing the volume of the solution while using the same quantity of gestagen, after intramuscular injection a retarded release of gestagen and therewith a lengthening of the duration of action would occur.

Owing to the lengthening of the period of action by increasing the injection-volume, a quantity of 200 mg of norethisterone oenanthate is sufficient for a reliable protection against conception for 3 months in women of child-bearing age. For a shorter or longer

period than 3 months smaller or larger quantities, respectively, of the gestagen are required. Generally, 50 to 500 mg, and preferably 200 to 400 mg, of norethisterone oenanthate, or corresponding quantities of another appropriate depot gestagen, are used in 1 to 6 ml, and preferably 2 to 4 ml, of oily solution. Lengthening of the period of action occurs even with a small increase in the volume; however, an advantageous increase in the volume of solvent is one and a half to three times (that is the concentration of active substance is 1/3 to 2/3 of that normally employed). A greater increase in the volume of solvent is basically possible within the scope of the present invention, but it is not recommended because such large volumes applied intramuscularly lead to trouble.

The present invention accordingly provides an oily solution of a gestagen, as hereinafter defined, the solution being suitable for use as a depot preparation by intramuscular injection and containing the gestagen in a maximum concentration as hereinafer defined.

The gestagen is understood herein to exclude any one of the following compounds, namely progesterone, 17α-hydroxy-progesterone and esters of 17α-hydroxy-progesterone.

The maximum concentration of the gestagen in the oily solution is understood herein to be a concentration having a gestagenic activity, as measured by its effect on the cervical mucus of a human female, corresponding to the gestagenic activity of substantially 133.33 mg per ml of norethisterone oenanthate in the same solvent.

The gestagen is advantageously present in a concentration that is 1/3 to 2/3 of the concentration of the gestagen normally used in an oily solution suitable for use as a depot preparation by intramuscular injection. In other words, a "preferred range of concentration" for the gestagen in the oily solution is a concentration having a gestagenic activity, as measured by its gestagenic effect on the cervical mucus of a human female, corresponding to the gestagenic activity of substantially 66.67 to 133.33 mg per ml of norethisterone oenanthate in the same solvent.

There are a number of properties of the cervical mucus of a human female affected by the administration of a gestagen which are well known to the gynaecologist, so that one or more such parameters can be used to correlate the gestagenic effect.

Gestagens are also known as gestogens, progestins, progestogens and progestational substances.

The present invention also provides a process for the manufacture of an oily solution of the present invention, wherein the gestagen is dissolved in an amount of the solvent sufficient to form a substantially saturated solution of the gestagen, the resulting solution is diluted with a further amount of the solvent and the resulting diluted solution is filtered under sterile conditions, and, if desired, the resulting solution is introduced into at least one ampoule under aseptic conditions and sterilized. The ampoule may have a capacity of 1, 2, 3 or 4 ml.

As gestagens there come into consideration one or more of these compounds that themselves, owing to their chemical structure, already display a protracted action when injected intramuscularly and for which, owing to their spectrum of action, a long lasting treatment is indicated. Such compounds are, for example, lipophilic steroid hormones and in this case especially steroid alcohols in the form of their esters. Oily solutions of these steroids having a gestagenic activity may be used, for example, for the control of fertility in human beings and animals or the treatment of menopausal complaints in women.

As gestagenic steroid hormones (gestagens) there may be mentioned, for example, esters of 19-nor-17-hydroxy-progesterone, and also esters of 17-hydroxy-progesterone derivatives, for example 17-esters of 6α-methyl-17-hydroxy-progesterone, 6-methyl-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-16α-methyl-17-hydroxy-progesterone, 6,16α-dimethyl-6-dehydro-17-hydroxy-progesterone, 1α,2α-methylene-6-chloro- or -6-fluoro-6-dehydro-17-hydroxy-progesterone or also esters of 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-18-methyl-19-nor-testosterone, 17α-ethynyl-Δ^4-oestrene-3,17β-diol or 17α-ethynyl-Δ^4-oestren-17β-ol. The gestagenic steroid hormone is advantageously 17α-ethynyl-19-nor-testosterone oenanthate.

The esters are derived from acids, for example carboxylic acids, capable of forming physiologically tolerable esters. Preferred are the esters of organic carboxylic acids containing at least 4 carbon atoms. The acids may belong to the aliphatic, cycloaliphatic, aromatic, aromatic-aliphatic or heterocyclic series. These acids may also be unsaturated and/or di- or poly-basic and/or substituted in the usual manner. As examples of substituents there may be mentioned alkyl, hydroxyl, alkoxy, oxo or amino groups or halogen atoms. There may be mentioned, for example, the following esters: butyrates, valerates, caproates, oenanthates, pelargonates, undecanoates, benzoates, β-cyclopentylpropionates and phenylacetates.

A 3-keto group present in the steroid hormone may be functionally converted and present, for example, as an enol-ester or enol-ether group. In the case of an enol-ester

group there also come into consideration the ester groups already mentioned above, but also acetates and propionates. In the case of an enol-ether group, the ether residue may be, preferably, a lower alkyl group, for example a methyl or ethyl group. Also suitable are cycloalkyl groups, for example a cyclopentyl or cyclohexyl group.

The effective dose of the gestagen in the oily solutions of the present invention depends on the purpose of the treatment, on the nature of the active substance and the desired duration of the action. It is, for example, for 17α-ethynyl-19-nor-testosterone oenanthate in the control of fertility in women for 3 months 200 mg. Instead of 17α-ethynyl-19-nor-testosterone oenanthate, there may be used comparable depot gestagens. The quantity of comparable gestagens administered and the frequency of their administration may be such that their gestagenic activity, as measured, for example, by their effect on the cervical mucus of a human female, corresponds to that produced by the administration of 200 mg of 17α-ethynyl-19-nor-testosterone oenanthate every three months.

The volumes intramuscularly injected of the oily solutions of the present invention are normally 1 to 6 ml. The oily solutions are thus advantageously made up in unit dosage form, each dosage unit having a volume within the range of from 1 to 6 ml, for example a volume of 1, 2, 3 or 4 ml. Each dosage unit may be contained in an ampoule.

It is advantageous for every 1 to 6 ml of the oily solutions of the present invention to contain 50 to 500 mg of the gestagen, and more especially for every 2 to 4 ml of the solutions to contain 200 to 400 mg of the gestagen.

As oily solvents there are suitable those known to the expert for such purposes, for example sesame oil and castor oil. For increasing the solubility of the gestagen there may be added to the oily solvents solubilizers, for example benzyl benzoate or benzyl alcohol. In addition to those mentioned above other vegetable oils, for example linseed oil, cottonseed oil, sunflower oil, ground nut oil, olive oil and wheat oil, may be used. Also suitable are synthetic oils, for example polyethylene glycol, triglycerides of higher saturated fatty acids and monoesters of higher fatty acids. A mixture of castor oil/benzyl benzoate in the ratio by volume of 6:4 is preferred as solvent.

As indicated above, the oily solutions of the present invention can be used as contraceptives.

The present invention accordingly further provides a method of contraception, wherein there is administered by intramuscular injection in a contraceptive dose to a female mammal, advantageously a female of the human species, an oily solution of a gestagen, as hereinbefore defined, the solution being suitable for use as a depot preparation by intramuscular injection and containing the gestagen in a maximum concentration as hereinbefore defined.

The various details of the oily solutions of the present invention discussed above also, of course, apply to the oily solutions used in the method of contraception of the present invention. Thus, for example, an advantageous embodiment of the method of contraception of the present invention is the administration by intramuscular injection to a human female every 13 weeks of 1 to 6 ml of the oily solution, the 1 to 6 ml containing 50 to 500 mg of the gestagen, and preferably of 2 to 4 ml of the oily solution, the 2 to 4 ml containing 200 to 400 mg of the gestagen.

The present invention further provides a contraceptive pack which comprises an oily solution of a gestagen, as hereinbefore defined, together with instructions, the instructions requiring the administration by intramuscular injection of the solution in a contraceptive dose to a female mammal, advantageously a female of the human species, and the solution being suitable for use as a depot preparation by intramuscular injection and containing the gestagen in a maximum concentration as hereinbefore defined.

The various details of the oily solutions of the present invention discussed above further apply to the oily solutions contained in the contraceptive packs of the present invention. Thus, the instructions in the packs advantageously require that there is administered to a human female every 13 weeks 1 to 6 ml of the oily solution, the 1 to 6 ml containing 50 to 500 mg of the gestagen, and preferably 2 to 4 ml of the oily solution, the 2 to 4 ml containing 200 to 400 mg of the gestagen.

The following Examples illustrate the invention:-

Example 1

2000 mg of 17α-ethynyl-19-nor-testosterone oenanthate were dissolved in a mixture of castor oil/benzyl benzoate (6:4 by volume), and the solution was then made up with a further amount of the same solvent to 20 ml. The solution was filtered under sterile conditions, and was introduced in the usual manner into 2 ml-ampoules under aseptic conditions. The ampoules were finally sterilized for 2 hours at 120°C.

Example 2

2000 mg of 17α-ethynyl-19-nor-testosterone oenanthate were dissolved in a mixture of castor oil/benzyl benzoate (6:4 by volume), and the solution was then made up with a further amount of the same solvent to 30 ml. The solution was filtered under sterile conditions, and was introduced in the usual manner into 3 ml-ampoules under aseptic conditions. The ampoules were finally sterilized for 2 hours at 120°C.

WHAT WE CLAIM IS:-

1. An oily solution of gestagen, as hereinbefore defined, the solution being suitable for use as a depot preparation by intramuscular injection and containing the gestagen in a maximum concentration as hereinbefore defined.
2. A solution as claimed in claim 1, wherein the gestagen is present in a preferred range of concentration as hereinbefore defined.
3. A solution as claimed in claim 1 or 2, which contains as the solvent a mixture of castor oil and benzyl benzoate.
4. A solution as claimed in claim 3, wherein the castor oil and benzyl benzoate are present in the mixture in the ratio by volume of 6:4.
5. A solution as claimed in any one of claims 1 to 4, wherein the gestagen is at least one lipophilic steroid.
6. A solution as claimed in claim 5, wherein the lipophilic steroid is a physiologically tolerable carboxylic acid ester of a steroid alcohol.
7. A solution as claimed in claim 6, wherein the carboxylic acid contains at least 4 carbon atoms.
8. A solution as claimed in any one of claims 1 to 7, wherein the gestagen is an ester of 19-nor-17-hydroxy-progesterone, 6α-methyl-17-hydroxy-progesterone, 6-methyl-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-16α-methyl-17-hydroxy-progesterone, 6,16α-dimethyl-6-dehydro-17-hydroxy-progesterone, 1α,2α-methylene-6-chloro- or -6-fluoro-6-dehydro-17-hydroxy-progesterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-18-methyl-19-nor-testosterone, 17α-ethynyl-Δ^4-oestrene-3,17β-diol or 17α-ethynyl-Δ^4-oestren-17β-ol.
9. A solution as claimed in claim 8, wherein the gestagen is 17α-ethynyl-19-nor-testosterone oenanthate.
10. A solution as claimed in any one of claims 1 to 9, wherein every 1 to 6 ml of the solution contains 50 to 500 mg of the gestagen.
11. A solution as claimed in claim 10, wherein every 2 to 4 ml of the solution contains 200 to 400 mg of the gestagen.
12. A solution as claimed in any one of claims 1 to 11, which is in unit dosage form.
13. A solution as claimed in claim 12, wherein each dosage unit has a volume within the range of from 1 to 6 ml.
14. A solution as claimed in claim 13, wherein each dosage unit has a volume of 1, 2, 3 or 4 ml.
15. A solution as claimed in any one of claims 12 to 14, wherein each dosage unit is contained in an ampoule.
16. A solution as claimed in claim 1 having a composition substantially as described in Example 1 or 2 herein.
17. A process for the manufacture of an oily solution as claimed in any one of claims 1 to 16, wherein the gestagen is dissolved in an amount of the solvent sufficient to form a substantially saturated solution of the gestagen, the resulting solution is diluted with a further amount of the solvent and the resulting diluted solution is filtered under sterile conditions, and, if desired, the resulting solution is introduced into at least one ampoule under aseptic conditions and sterilized.
18. A process as claimed in claim 17, conducted substantially as described in Example 1 or 2 herein.
19. A method of contraception, wherein there is administered by intramuscular injection in a contraceptive dose to a female mammal an oily solution of a gestagen, as hereinbefore defined, the solution being suitable for use as a depot preparation by

intramuscular injection and containing the gestagen in a maximum concentration as hereinbefore defined.

20. A method as claimed in claim 19, wherein the gestagen is present in the oily solution in a preferred range of concentration as hereinbefore defined.

21. A method as claimed in claim 19 or 20, wherein the oily solution contains as the solvent a mixture of castor oil and benzyl benzoate.

22. A method as claimed in claim 21, wherein the castor oil and benzyl benzoate are present in the mixture in the ratio by volume of 6:4.

23. A method as claimed in any one of claims 19 to 22, wherein the gestagen is a physiologically tolerable, lipophilic carboxylic acid ester of a steroid alcohol.

24. A method as claimed in claim 23, wherein the carboxylic acid contains at least 4 carbon atoms.

25. A method as claimed in any one of claims 19 to 24, wherein the gestagen is an ester of 19-nor-17-hydroxy-progesterone, 6α-methyl-17-hydroxy-progesterone, 6-methyl-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-16α-methyl-17-hydroxy-progesterone, 6,16α-dimethyl-6-dehydro-17-hydroxy-progesterone, 1α-2α-methylene-6-chloro- or -6-fluoro-6-dehydro-17-hydroxy-progesterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-18-methyl-19-nor-testosterone, 17α-ethynyl-18-methyl-19-nor-testosterone, 17α-ethynyl-Δ^4-oestrene-3,17β-diol or 17α-ethynyl-Δ^4-oestren-17β-ol.

26. A method as claimed in claim 25, wherein the gestagen is 17α-ethynyl-19-nor-testosterone oenanthate.

27. A method as claimed in any one of claims 19 to 26, wherein the female mammal is a female of the human species.

28. A method as claimed in claim 27, wherein there is administered to the human female every 13 weeks 1 to 6 ml of the oily solution, the 1 to 6 ml containing 50 to 500 mg of the gestagen.

29. A method as claimed in claim 28, wherein there is administered to the human female every 13 weeks 2 to 4 ml of the oily solution, the 2 to 4 ml containing 200 to 400 mg of the gestagen.

30. A method as claimed in claim 29, wherein there is administered to the human female every 13 weeks the contents of an ampoule having a composition substantially as described in Example 1 or 2 herein.

31. A contraceptive pack which comprises an oily solution of a gestagen, as hereinbefore defined, together with instructions, the instructions requiring the administration of intramuscular injection of the solution in a contraceptive dose to a female mammal and the solution being suitable for use as a depot preparation by intramuscular injection and containing the gestagen in a maximum concentration as hereinbefore defined.

32. A pack as claimed in claim 31, wherein the gestagen is present in the oily solution in a preferred range of concentration as hereinbefore defined.

33. A pack as claimed in claim 31 or 32, wherein the oily solution contains as the solvent a mixture of castor oil and benzyl benzoate.

34. A pack as claimed in claim 33, wherein the castor oil and benzyl benzoate are present in the mixture in the ratio by volume of 6:4.

35. A pack as claimed in any one of claims 31 to 34, wherein the gestagen is a physiologically tolerable, lipophilic carboxylic acid ester of a steroid alcohol.

36. A pack as claimed in claim 35, wherein the carboxylic acid contains at least 4 carbon atoms.

37. A pack as claimed in any one of claims 31 to 36, wherein the gestagen is an ester of 19-nor-17-hydroxy-progesterone, 6α-methyl-17-hydroxy-progesterone, 6-methyl-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-16α-methyl-17-hydroxy-progesterone, 6,16α-dimethyl-6-dehydro-17-hydroxy-progesterone, 1α,2α-methylene-6-chloro- or -6-fluoro-6-dehydro-17-hydroxy-progesterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-18-methyl-19-nor-testosterone, 17α-ethynyl-Δ^4-oestrene-3,17β-diol or 17α-ethynyl-Δ^4-oestren-17β-ol.

38. A pack as claimed in claim 37, wherein the gestagen is 17α-ethynyl-19-nor-testosterone oenanthate.

39. A pack as claimed in any one of claims 31 to 38, wherein the oily solution is in unit dosage form.

40. A pack as claimed in any one of claims 31 to 39, wherein the female mammal is a female of the human species.

41. A pack as claimed in claim 40, wherein the instructions require that there is administered to the human female every 13 weeks 1 to 6 ml of the oily solution, the 1 to 6 ml containing 50 to 500 mg of the gestagen.

42. A pack as claimed in claim 41, wherein the instructions require that there is administered to the human female every 13 weeks 2 to 4 ml of the oily solution, the 2 to 4 ml containing 200 to 400 mg of the gestagen.

43. A pack as claimed in claim 31, wherein the oily solution is in unit dosage form, each dosage unit being contained in an ampoule and the ampoule having a composition substantially as described in Example 1 or 2 herein, and the instructions require that there is administered to a human female every 13 weeks one of the dosage units.

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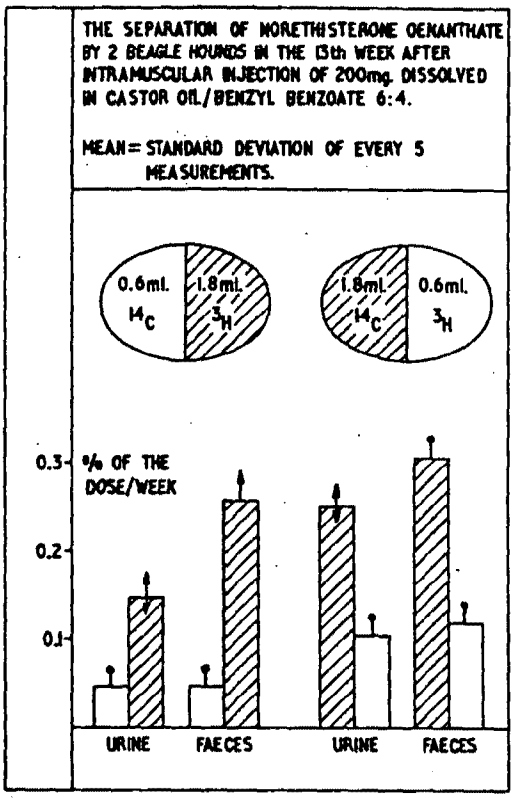
THE SEPARATION OF NORETHISTERONE OENANTHATE BY 2 BEAGLE HOUNDS IN THE 13th WEEK AFTER INTRAMUSCULAR INJECTION OF 200mg. DISSOLVED IN CASTOR OIL/BENZYL BENZOATE 6:4.
MEAN = STANDARD DEVIATION OF EVERY 5 MEASUREMENTS.
0.6ml. ^{14}C
1.8ml. ^{3}H
1.8ml. ^{14}C
0.6ml. ^{3}H
% OF THE DOSE/WEEK
0.3
0.2
0.1
URINE
FAECES
URINE
FAECES

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PATENT SPECIFICATION (11) 1 207 571

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(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

[Price 5s. 0d. (25p)]

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

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.

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NO DRAWINGS.

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Int. Cl.:—A 61 k 3/00.

COMPLETE SPECIFICATION.

Medicinal Preparations for the Treatment of Prostatic Hypertrophy.

We, SCHERING AKTIENGESELLSCHAFT, a body corporate organised according to the laws of Germany, of 170—172 Mullerstrasse, Berlin N.65, Germany, do hereby declare the invention, for which we 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 medicinal preparations for the treatment of hypertrophic conditions of the prostrate.

It is an object of the present invention to achieve with respect to hypertrophic conditions of the prostate at least palliative relief, i.e. relief of pain, although frequently, the medicinal preparations of the invention will cause a reduction in the size of the prostate and improvement in the urinary flow.

Accordingly, this invention provides a medicinal preparation for intra-muscular injection in the treatment of hypertrophic conditions of the prostate, which comprises a solution of a 17-ester of 19-nor-17α-hydroxy-progesterone in an oily solvent.

The 17-ester present in the medicinal preparations of the invention is preferably 19 - nor - 17α - hydroxy - progesterone - 17 - caproate. Other advantageous 17-esters of 19-nor-17α-hydroxy-progesterone are the formate, acetate, butyrate, caprylate and cyclopentyl-propionate.

In the hypertrophy of the prostate, which is characterised by its long duration, within two or three months after starting the administration of a medicinal preparation of the present invention a marked improvement is observed, particularly with respect to the irritating effects which occur. Pollakisuria and nocturia are significantly reduced. Furthermore, the flow of urine is normalized and the residual volume of urine is significantly reduced or completely eliminated.

[*Price* 4s. 6d.]

Apart from the desired slow release or depot effect of, for example, 19-nor-17α-hydroxy-progesterone-17-caproate, it is a particular advantage of the preparations of the present invention that for the successful treatment of hypertrophy of the prostate a dosage of the active ingredient of from 100 to 200 mg per week will give positive results. In contrast thereto, attempts to treat hypertrophy of the prostate with other steroid compounds generally require doses of from about 2 to 3 grams per week which are administered intramuscularly in the form of oily solutions. Even assuming a high solubility of the active steroid of 250 mg per 1 ml of oil, administration of these other steroids requires the intra-muscular injection of from at least 8 to 12 ml of oil, which generally causes undesirable side effect, such as oil infiltration, hardening at the point of injection, painful reddening and inflammation or even abcesses of long duration at the points of infiltration.

A further advantage of the esters present in the preparations of the present invention, and particularly 19-nor-17α-hydroxy-progesterone caproate, is that they do not have an oestrogenic or androgenic side effect and only a slight antigonadotropic effect.

In the treatment of hypertrophy of the prostate with the preparations of this invention between 50 and 1000 mg of the 19-nor-17α-hydroxy-progesterone ester are injected intramuscularly several times per week, and th preferred treatment will be the administration of 250 mg between 2 and 3 times per week for the purpose of relieving pain, reduction of the size of prostate and improvement in the urinary flow. The administration of this medication should be continued as long as the condition of the patient requires.

The medicinal preparations of this inven-

tion are made, for example, by dissolving the 19-nor-17α-hydroxy-progesterone ester in an oily solvent, such as castor oil, by the methods known in galenic pharmacology. If desired, the solvent powder of the oily solvents can be increased by the addition of diluents or solution promoters, for example, benzyl benzoate.

The resulting solutions, which may contain, for instance, 250 mg of the active agent per millilitre, are then charged under sterile conditions into ampoules having a capacity of 1 to 2 millilitres. A preferred preparation according to the present invention is a solution of 19-nor-17α-hydroxy-progesterone-17-caproate in a mixture of 6 parts by volume of castor oil and 4 parts by volume of benzyl benzoate, the solution containing 100 mg of the caproate per millilitre of solution.

The 19 - nor - 17α - hydroxy - progesterone esters are made by the esterification of 19-nor-17α-hydroxy-progesterone with the appropriate organic carboxylic acids by methods in themselves known, for example, by the esterification of 19-nor-17α-hydroxy-progesterone with caproic acid/caproic anhydride and saponification of the 3-enol-ester group, intermediately formed, in acid solution or, in aqueous sodium hydroxide solution. The isolated 19-nor-17α-hydroxy-progesterone caproate, after recrystallization from isopropyl ether, melts at 123—124°C.

The following Examples illustrate methods of making certain of the 17-esters of 19-nor-17α-hydroxy-progesterone to be incorporated in the medicinal preparations of the invention:

Example 1

300 mg of 19-nor-17α-hydroxy-progesterone are dissolved in a mixture of 17 cc of acetic anhydride and 42 cc of 95% formic acid which has been standing for 6 hours at 0°C. 345 mg of p-toluene sulphonic acid · 1 H_2O are added under ice cooling and nitrogen atmosphere. The reaction mixture is allowed to stand for 16 hours at room temperature. The clear solution is poured into a mixture of pyridine in ice water and filtered under suction after 1 hour to obtain the crude 17α-hydroxy-norprogesterone-formate as a precipitate. The precipitate is dried and recrystallized from isopropyl ether. There is thus obtained a yield of 265 mg of pure 19-nor-17α-hydroxy-progesterone-17-formate melting at 198—199.5°C.

U.V. $\epsilon_{239}=17{,}000$.

Example 2

380 mg of p-toluene sulphonic acid · 1 H_2O are added to a suspension of 316 mg of 19-nor-17α-hydroxy-progesterone in 16 cc of acetic anyhydride. The esterification is completed after 4 hours at 37°C. The excess of acetic anhydride is decomposed with pyridine in ice water and the 3-enol-17-diester is extracted with ether. The ethereal extract is washed until neutral, dried over sodium sulphate and concentrated. The residue was dissolved in 35 cc of methanol, reacted with 0.35 cc of concentrated hydrochloric acid and heated under refluxing for 1 hour. The methanolic solution is diluted with water and extracted with ether. The ethereal extract is washed with water until neutral and dried over sodium sulphate and then concentrated. The substance is recrystallized from isopropyl ether for purification. There is thus obtained a yield of 250 mg of pure 19-nor-17α-hydroxy-progesterone-17-acetate melting at 214—216°C.

U.V. $\epsilon_{239}=17{,}000$.

Example 3

1.32 grams of p-toluene sulphonic acid · 1 H_2O are added to a solution of 1.0 gram of 19-nor-17α-hydroxy-progesterone in 32 cc of caproic anhydride under stirring and under a nitrogen atmosphere. After 3 hours at 37°C. the reaction is completed. The clear light-yellow solution is taken up in a mixture of 1.43 cc of concentrated hydrochloric acid in 143 cc of methanol, and heated under refluxing and under nitrogen for 1 hour. The excess of caproic acid is removed by steam distillation and the residue is extracted with ether. The ethereal extract is washed with water until neutral, dried over sodium sulphate and concentrated. The precipitated crude product is recrystallized from isopropyl ether.

The yield amounts to 1.1 grams of pure 19 - nor - 17α - hydroxy - progesterone - 17 - caproate melting at 123—124°C.

U.V. $\epsilon_{239}=17{,}540$.

Example 4

0.66 gram of p-toluene sulphonic acid · 1 H_2O are added to a suspension of 0.5 gram of 19-nor-17α-hydroxy-progesterone in 20 cc of butyric anhydride under stirring and under a nitrogen atmosphere. After 4 hours at 37°C, 70 cc of methanol and 0.7 cc of concentrated hydrochloric acid are added to the clear solution, and the whole is cooked for 1 hour under refluxing and under a nitrogen atmosphere. The reaction mixture is extracted with ether, the ethereal extract is washed until neutral, dried over sodium sulphate and concentrated.

Recrystallization from isopropyl ether results in pure 19-nor-17α-hydroxy-progesterone-17-butyrate.

U.V. $\epsilon_{239}=17{,}200$.

Example 5

920 mg of p-toluene sulphonic acid $\cdot 1 H_2O$ are added to a suspension of 0.7 gram of 19-nor-17α-hydroxy-progesterone in 30 cc of caprylic anhydride under a nitrogen atmosphere. After 3 hours of stirring at 37°C the solution is diluted with 100 cc of methanol, and after the addition of 1 cc of concentrated hydrochloric acid, the whole is heated for 1 hour under refluxing. The excess of caprylic acid is removed by steam distillation. The residue is taken up in ether, the ethereal extract is washed until neutral, dried over sodium sulphate and concentrated.

The thus obtained oil is dissolved in isopropyl ether, purified with activated carbon and the thus obtained colourless solution is again concentrated to dryness. The resulting oily residue is found upon elemental analysis and upon tests under ultra-violet and infra-red light to be pure 19-nor-17α-hydroxy-progesterone-17-caprylate.

U.V. $\epsilon_{239}=17{,}100$.

Example 6

1 gram of 19-nor-17α-hydroxy-progesterone is added to a mixture heated to a temperature of 80°C of 4 cc of cyclopentyl-propionic acid and 1 cc of trifluoroacetic anhydride. After 35 minutes of reaction at the same temperature the clear solution is added to water, the precipitated oil is taken up in ether, the ethereal extract is first washed with a saturated sodium carbonate solution, and subsequently with water until neutral. It is then dried over sodium sulphate and concentrated. The resulting crude oil is dissolved in isopropyl ether, purified with activated carbon, and the resulting colourless solution is concentrated to dryness. The colourless oily residue can definitely be identified as 19-nor-17α-hydroxy-progesterone-17-cyclopentylpropionate.

U.V. $\epsilon_{239}=17{,}400$.

A medicinal preparation of the present invention may be prepared, for example, from 25 mg of 19-nor-17α-hydroxy-progesterone-17-caproate by dissolving the latter in 0.6 ml of castor oil and 0.4 ml of benzyl benzoate, or by dissolving the above caproate or other ester of 19-nor-17α-hydroxy-progesterone in 1.0 ml of sesame oil. The oily solution is then passed through a sterile filter. Ampoules are filled with the solution under aseptic conditions. After the ampoules have been sealed they are sterilised by heating for one hour at 120°C.

Generally it is desirable to use for intramuscular administration for the treatment hypertrophy of the prostate, oily solutions containing between 50 and 250 mg of the 19-nor-17α-hydroxy-progesterone ester per millilitre.

WHAT WE CLAIM IS:—

1. A medicinal preparation for intramuscular injection in the treatment of hypertrophic conditions of the prostate, which comprises a solution of 17-ester of 19-nor-17α-hydroxy-progesterone in an oily solvent.

2. A medicinal preparation as claimed in claim 1, wherein the solution also contains a solution promoter.

3. A medicinal preparation as claimed in claim 2, wherein the solution promoter is benzyl benzoate.

4. A medicinal preparation as claimed in any one of claims 1 to 3, wherein the solvent comprises castor oil.

5. A medicinal preparation as claimed in claim 4, wherein the solvent is a mixture of 6 parts by volume of castor oil and 4 parts by volume of benzyl benzoate.

6. A medicinal preparation as claimed in any one of claims 1 to 5, which contains about 100 milligrams of the 17-ester per millilitre of the solution.

7. A medicinal preparation as claimed in any one of claims 1 to 6, wherein the said ester is a 19-nor-17α-hydroxy-progesterone-17-caproate.

8. A medicinal preparation as claimed in any one of claims 1 to 6, wherein the said ester is the 17-formate, 17-acetate, 17-butyrate, 17-caprylate or 17-cyclopentyl-propionate of 19-nor-17-α-hydroxy-progesterone.

9. A medicinal preparation as claimed in any one of claims 1 to 8, which contains from 50 to 250 milligrams of the 17-ester per millilitre of the solution.

ABEL & IMRAY,
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ADAMS & ADAMS,
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Pretoria.

A & A Ref: 57058

Patents Form No. 1A.

REPUBLIC OF SOUTH AFRICA

THE PATENTS ACT, 1952, AS AMENDED.

APPLICATION FOR A PATENT UNDER INTERNATIONAL ARRANGEMENTS

(WITH AUTHORISATION OF AGENT)

change I.t.o. request 7/10/70.

Application No. 68/1014

FOR OFFICIAL USE ONLY

Full Name(s) of Applicant(s): SCHERING AKTIENGESELLSCHAFT, a Body Corporate organized and existing according to the laws of the Federal Republic of Germany,

Address(es) of applicant(s): 170-172 Müllerstrasse, 1 Berlin 65, Germany and Waldshaese 14, D 4619 Bergkamen, Germany

Full name(s) of inventor(s): KARL-HEINZ KIMBEL

I/We do hereby declare that I am/we are in possession of an invention the title of which is

"CONTRACEPTIVE PREPARATIONS"

I am/We are the assignee(s)~~/legal representative(s)~~ of the inventor(s). Application(s) for protection for the invention has/have been made in the following country/countries and on the following official dates i.e.:—

1. (country) Germany	(date) 28th February, 1967	(number) Sch 40 314 IVa/30
2. (country)	(date)	(number)
3. (country)	(date)	(number)

The said application or each of the said applications was the first application in a convention country in respect of the relevant invention by me/us or by any person from whom I/we derive title. To the best of my/our knowledge and belief there is no lawful ground for objection to the grant of a patent to me/us on this application. I/We pray that a patent be granted to me/us for the invention in priority over other applicants and that such patent shall have the official date of the first application in a convention country i.e. 28th February, 1967

~~I/We hereby appoint the persons and qualified staff of the firm of ADAMS & ADAMS, jointly and severally to act for me/us in all matters relating to this application and any letters patent granted thereon~~

Dated this 15th day of February, 1968

PATENT ATTORNEY.

Address for service:
C/o ADAMS & ADAMS,
ALLIED BUILDING,
PRETORIA.

Table of Classification	
Class	Sub-class

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Signature of Applicant/s and Capacity

PATENTS
FORM NO. 3

A. & A. Ref. No. 57058

ADAMS & ADAMS
PATENT ATTORNEYS
ALLIED BUILDING
PRETORIA

REPUBLIC OF SOUTH AFRICA

The Patents Act, 1952

COMPLETE SPECIFICATION

68/1014

Here insert (in full) name, address of applicant(s) as in application form.

(a) SCHERING AKTIENGESELLSCHAFT, a Body Corporate organized and existing according to the laws of the Federal Republic of Germany of 170-172 Müllerstrasse, 1 Berlin 65, Germany, and Waldshaasse 14, D 4619 Bergkamen, Germany.

Here insert title (verbally agreeing with that in the application form.)

(b) "CONTRACEPTIVE PREPARATIONS"

I/WE do hereby declare this invention, the manner in which and the method by which it is to be performed, to be particularly described and ascertained in and by the following statement:-

The present invention is concerned with contraceptive preparations.

Hormonal methods of contraception have been known, for example the oral administration of Enovid, Ovulen and Anovlar (Registered Trade Marks) and similar combinations of oestrogenic and gestagenic active principles. Experiments have also been made with corresponding preparations for administration by injection in which the active components provide a depot from which they are slowly liberated.

The disadvantage of the latter method is, in particular, the unpredictability of onset, the duration and the extent of withdrawal bleeding. The published experiments, in which a prolonged-action oestrogen and a prolonged-action gestagen are administered together in the first week of the menstrual cycle by injection to suppress ovulation by means of an adequately high oestrogen and progesterone level, have shown that the reduction of the progesterone concentration in the body is not uniform enough to enable the onset of withdrawal bleeding to be predicted within a span of a few days, which is generally possible in the case of natural menstruation.

The disadvantage of oral administration lies in the fact that a tablet has to be taken daily, which means a comparativel high intake of hormones. This gives rise to undesirable side-effects, for example vomiting, increase in weight and so forth.

The present invention is based on the discovery of a new method of contraception in which a combination of a gestagen, in a comparatively small dose, and a depot-oestrogen is administered after the 10th day, preferably in the second half, of the menstruation cycle.

Accordingly, the present invention provides a contraceptive preparation suitable for parenteral administration or administration by implantation, which comprises a

depot oestrogen and a comparatively small concentration of a gestagen.

The contraceptive preparations of the present invention may be administered, preferably in the form of oily solutions, parenterally, preferably intramuscularly or subcutaneously. However, it is also possible to administer the preparations by implantation.

It is further possible to administer the depot oestrogen and the gestagen singly, for example the gestagen orally and the oestrogen parenterally or by implantation. Accordingly, the present invention also provides a contraceptive preparation which is made up in two parts ready for administration, the one part comprising a diluent and a unit dose of a depot oestrogen and the other part comprising a diluent and approximately 0.5 to 100 mg of a gestagen.

In the new contraceptive method using the preparations of the present invention the comparatively small dose of the gestagen ensures reliable onset of withdrawal bleeding, that is to say, predictable within a span of a few days, as in natural menstruation, and the simultaneous injection of a depot-oestrogen inhibits ovulation and/or nidation in at least the following menstruation cycle by change within the female reproductive system.

Furthermore, the contraceptive action can be determined for a given period of time by appropriate variation of the concentration of active principles. When using a preparation of the present invention it is possible, by a single administration of the preparation, to prevent conception for a period covering one or more menstrual cycles, that is to say for a period of from approximately four weeks to six months or even longer, it being possibl to bring about withdrawa

bleeding within a few days after administration, without termination of the contraceptive action, by the additional parenteral or even oral administration of a gestagen.

As has already been stated, the oestrogenic and gestagenic components are preferably administered together. For this purpose the active principles are dissolved in one of the solvents known to be suitable for parenteral injection, with which a man skilled in the art will be familiar, filtered under sterile conditions and introduced into ampoules under aseptic conditions. Preference is given to oily solvents, for example sesame oil or castor oil. A diluent or a solubilizer, for example benzyl benzoate, may be added to the oil solutions to increase the solubility of the active principles.

In addition to the above-mentioned solvents, it is also possible to use vegetable oils, for example linseed oil, cottonseed oil, sunflower oil, peanut oil, olive oil and wheat oil. Also suitable are synthetic solvents, for example glycol, lactic acid esters and benzyl alcohol. Naturally, the selection of solvents given above is by no means complete. It is not necessary to provide a complete list, because a man skilled in the art will know which of the known solvents to choose for a specific purpose.

It is generally preferable to administer the contraceptive preparation at four-week intervals to imitate the regular menstrual cycle. If the interval between administratio is prolonged, for example, to several months, either on the advice of a physician or at the patient's request, only one withdrawal bleeding takes place, the complete contraceptive protection, during the interval between times of administration unless additional gestagen is given.

All substances having a prolonged oestrogenic action may be used as the oestrogen component. The period of activity should preferably be at least about 14 days. The oestrogen used is preferably administered in such doses and at such intervals that the suppression of ovulation achieved with the preparations of the present invention is at least equal to that achieved with a daily oral administration of 0.05 mg of ethynyl-oestradiol. Furthermore, the oestrogen used is preferably of the kind that produces a longer period of ovulation inhibition than orally administered ethynyl-oestradiol. Preferred oestrogen components are, in particular oestradiol esters, for example oestradiol oenanthate, oestradi undecylate, oestradiol palmitate, oestradiol butyrate and oestradiol benzoate.

The decision as to which oestrogen is the most suitable active principle to use in the preparations depends largely on the desired period of contraceptive protection. If the protective action is to cover only one menstrual cycle, in other words about four weeks, it may be quite adequate to administer oestradiol valerate, which, as is known, is liberated from a depot for only a comparatively short period.

The contraceptive preparations of the present invention suitable for parenteral administration or administration by implantation are, like the two-part preparations of the present invention, advantageously in unit dosage form. The amount of oestrogen in the unit dosage form preparations is within the range of from 0.5 to 500 mg, per unit dose. The choice of oestrogen is advantageously such that a dose of preferably 5 to 50 mg, per unit dose, is sufficient to ensure the successful use of the preparations of the present inventio

When using oestradiol oenanthate to give contraceptive protection for a period of one menstrual cycle (about four

weeks), a dose of 10 mg is generally sufficient. If the period of contraception is to be prolonged and the preferred dosage limit of 50 mg has to be exceeded, the oestrogen component may be increased to 250 mg.

Substances suitable for use as the gestagen component in the preparations of the present invention are all those which, when administered in a comparatively small dose, bring about predictable withdrawal bleeding similar in intensity and duration to normal menstruation. Preferred gestagens are those having a medium or long period of activity. The preferred concentration in the unit dosage form preparations is within the range of from 10 to 100 mg. A concentration within the range of from 0.5 to 50 mg, per unit dose, is adequate in the case of the highly active gestagens. As examples of gestagens that may be used in the preparations of the present invention there may be mentioned: progesterone and the physiologically tolerable 3-enolesters thereof, hydroxy-progesterone-caproate, hydroxy-nor-progesterone-caproate, medroxy-progesterone-acetate, nor-ethyndrone caproat and 17α-ethynyl-18-homo-19-nor-testosterone. Also suitable are 17α-hydroxy-progesterone derivatives, for example 17α-hydroxy-19-nor-progesterone, 6α-methyl-17α-hydroxy-progesterone, 6-methyl-6-dehydro-17α-hydroxy-progesterone, 6-chloro-6-dehydro-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6,16-dimethyl-6-dehydro-17α-hydroxy-progesterone, 6-methyl-6-dehydro-16-methylene-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16-methylene-17α-

hydroxy-progesterone, 1,2-methylene-6-chloro-dehydro-17α-hydroxyprogesterone, 1,2-methylene-6-fluoro-6-dehydro-17α-hydroxy-progesterone, 17α-ethynyl-testosterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-$\Delta^{5(10)}$-oestren-17β-ol-3-one, 17α-methyl-19-nor-testosterone, 17α-ethynyl-Δ^{4}-oestrene-3β,17β-diol, 17α-ethynyl-Δ^{4}-oestren-17β-ol, 17α-alkyl-Δ^{4}-oestren-17β-ols and the physiologically tolerable straight-chain or branched esters thereof, for example acetates, valerates, butyrates, oenanthates and undecylates. The ester group may be substituted in the usual manner, for example, by one or more substituents selected from halogen atoms and hydroxyl, carbonyl, keto, amino and similar groups.

Having now particularly described and ascertained .....
.....said invention and in what manner the same is
to be performed, ...we... declare that what ...we... claim is:

~~What we claim is:~~

1. A contraceptive preparation suitable for parenteral administration or administration by implantation, which comprises a depot oestrogen and a comparatively small concentration of a gestagen.

2. A contraceptive preparation as claimed in claim 1, which is in a form suitable for subcutaneous or intramuscular injection.

3. A contraceptive preparation as claimed in claim 1 or 2, which is in the form of an oily solution.

4. A contraceptive preparation as claimed in claim 3, containing sesame oil or castor oil as solvent.

5. A contraceptive preparation as claimed in claim 3 or 4, wherein the preparation also contains a diluent or a solubilizer.

6. A contraceptive preparation as claimed in claim 5, wherein the diluent or solubilizer is benzyl benzoate.

7. A contraceptive preparation as claimed in claim 3, containing a mixture of castor oil and benzyl benzoate as solvent.

8. A contraceptive preparation as claimed in any one of claims 1 to 7, where is in unit dosage form.

9. A contraceptive preparation as claimed in claim 8, containing 0.5 to 500 mg, per unit dose, of the depot oestrogen and approximately 0.5 to 100 mg, per unit dose, of the gestagen.

10. A contraceptive preparation as claimed in claim 8, containing 5 to 50 mg, per unit dose, of the depot oestrogen and 10 to 50 mg, per unit dose, of the gestagen.

11. A contraceptive preparation as claimed in any one of claims 1 to 10, wherein the depot oestrogen is oestradiol oenanthate, oestradiol undecylate, oestradiol palmitate, oestradiol dibutyrate or oestradiol benzoate.

12. A contraceptive preparation as claimed in any one of claims 1 to 11, wherein the gestagen is hydroxy-progesterone caproate, hydroxy-nor-progesterone caproate, medroxy-progesterone acetate or nor-ethyndrone caproate.

13. A contraceptive preparation as claimed in any one of claims 1 to 11, wherein the gestagen is 17α-hydroxy-19-nor-progesterone, 6α-methyl-17α-hydroxy-progesterone, 6-methyl-6-dehydro-17α-hydroxy-progesterone, 6-chloro-6-dehydro-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6,16-dimethyl-6-dehydro-17α-hydroxy-progesterone, 6-methyl-6-dehydro-16-methylene-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16-methylene-17α-hydroxy-progesterone, 1,2-methylene-6-chloro-6-dehydro-17α-hydroxy-progesterone, 1,2-methylene-6-fluoro-6-dehydro-17α-hydroxy-progesterone, 17α-ethynyl-testosterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-$\Delta^{5(10)}$-oestren-17β-ol-3-one, 17α-methyl-19-nor-testosterone, 17α-ethynyl-Δ^{4}-oestrene-3β,17β-diol 17α-ethynyl-Δ^{4}-oestren-17β-ol or a 17α-alkyl-Δ^{4}-oestren-17β-ol or a physiologically tolerable ester thereof.

14. A contraceptive preparation as claimed in claim 13, wherein the ester is an acetate, valerate, butyrate, caproate, oenanthate or undecylate.

15. A contraceptive preparation as claimed in any one of claims 1 to 11, wherein the gestagen is progesterone or a physiologically tolerable 3-enolester thereof.

16. A contraceptive preparation as claimed in any one of claims 1 to 11, wherein the gestagen is 17α-ethynyl-18-homo-19-nor-testosterone.

17. A contraceptive preparation which is made up in two parts ready for administration, the one part comprising a diluent and a unit dose of a depot oestrogen and the other part comprising a diluent and approximately 0.5 to 100 mg of a gestagen.

18. A contraceptive preparation as claimed in claim 17, wherein the part comprising a depot oestrogen is in a form suitable for parenteral administration.

19. A contraceptive preparation as claimed in claim 18, wherein the part comprising a depot oestrogen is in a form suitable for subcutaneous or intramuscular injection.

20. A contraceptive preparation as claimed in claim 17, wherein the part comprising a depot oestrogen is in a form suitable for administration by implantation.

21. A contraceptive preparation as claimed in any one of claims 17 to 20, wherein the part comprising a gestagen is in a form suitable for oral administration.

22. A contraceptive preparation as claimed in any one of claims 17 to 21, wherein one of or each of the parts is in the form of an oily solution.

23. A contraceptive preparation as claimed in claim 22 wherein the oily solution contains sesame oil or castor oil as solvent.

24. A contraceptive preparation as claimed in claim 23 wherein the oily solution also contains benzyl benzoate.

25. A contraceptive preparation as claimed in any one of claims 17 to 24, containing 10 to 50 mg of the gestagen.

26. A contraceptive preparation as claimed in any one of claims 17 to 25, containing 0.5 to 500 mg of the depot oestrogen.

27. A contraceptive preparation as claimed in any one of claims 17 to 25, containing 5 to 50 mg of the depot oestro

28. A contraceptive preparation as claimed in any one of claims 17 to 27, wh rein the depot oestrogen is oestradiol oenanthate, oestradiol undecylate, oestradiol palmitate, oestradiol dibutyrate or oestradiol benzoate..

29. A contraceptive preparation as claimed in any one of claims 17 to 28, wherein the gestagen is hydroxy-progesterone caproate, hydroxy-nor-progesterone caproate, medroxy-progesterone acetate or nor-ethyndrone caproate.

30. A contraceptive preparation as claimed in any one of claims 17 to 28, wherein the gestagen is 17α-hydroxy-19-nor-progesterone, 6α-methyl-17α-hydroxy-progesterone, 6-methyl-6-dehydro-17α-hydroxy-progesterone, 6-chloro-6-dehydro-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6,16-dimethyl-6-dehydro-17α-hydroxy-progesterone, 6-methyl-6-dehydro-16-methylene-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16-methylene-17α-hydroxy-progesterone, 1,2-methylene-6-chloro-6-dehydro-17α-hydroxy-progesterone, 1,2-methylene-6-fluoro-6-dehydro-17α-hydroxy-progesterone, 17α-ethynyl-testosterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-$\Delta^{5(10)}$-oestren-17β-ol-3-one, 17α-methyl-19-nor-testosterone, 17α-ethynyl-Δ^{4}-oestrene-3β,17β-diol, 17α-ethynyl-Δ^{4}-oestren-17β-ol or a 17α-alkyl-Δ^{4}-oestren-17β-ol or a physiologically tolerable ester thereof.

31. A contraceptive preparation as claimed in claim 30, wherein the ester is an acetate, valerate, butyrat , caproate, oenanthate or undecylate.

32. A contraceptive preparation as claimed in any one of claims 17 to 28, wherein the gestagen is progesterone or a

physiologically tolerable 3-enolester thereof.

33. A contraceptive preparation as claimed in any one of claims 17 to 28, wherein the gestagen is 17α-ethynyl-18-homo-19-nor-testosterone.

34. A contraceptive preparation, substantially as described herein.

DATED this 15th day of FEBRUARY, 1968.

PATENT ATTORNEY.

MDP/ME

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A&A Ref: 57661

ADAMS & ADAMS,
Allied Building,
Pretoria.

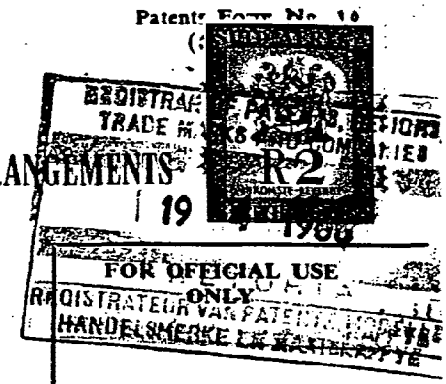
REPUBLIC OF SOUTH AFRICA

Patents Form No. 10

THE PATENTS ACT, 1952, AS AMENDED.

APPLICATION FOR A PATENT UNDER INTERNATIONAL ARRANGEMENTS

(WITH AUTHORISATION OF AGENT)



change I.t.O. request 7-10-70.

Filing date and Application No. 68/2530

Full Name(s) of applicant(s): SCHERING AKTIENGESELLSCHAFT, a Body Corporate organized and existing under the laws of the Federal Republic of Germany, of Berlin and Bergkamen, Germany

Address(es) of applicant(s): ~~address for service~~ Müllerstraße 170/172 and Waldstrasse 14, D4619 Bergkamen Germany.
D 1 Berlin 65, Germany,

Full Name(s) of inventor(s): Joachim Ufer, Karl-Heinz Kimbel and Ursula Lachnit

I/We do hereby declare that I am/we are in possession of an invention the title of which is

"Method for contraception"

I am/We are the assignee(s)/~~legal representative(s)~~ of the inventor(s). Application(s) for protection for the invention has/have been made in the following country/countries and on the following official dates i.e.:-

1.	(country)	Germany	(date) 19th April, 1967	(number)	Sch 40 583 IVa/30h
2.	(country)		(date)	(number)	
3.	(country)		(date)	(number)	

The said application or each of the said applications was the first application in a convention country in respect of the relevant invention by me/us or by any person from whom I/we derive title. To the best of my/our knowledge and belief there is no lawful ground for objection to the grant of a patent to me/us on this application. I/We pray that a patent be granted to me/us for the investion in priority over other applicants and that such patent shall have the official date of the first application in a convention country i.e. 19th April, 1967.

I/We hereby appoint the partners and qualified staff of the firm of ADAMS & ADAMS, jointly and severally, to act for me/us in all matters relating to this application and any letters patent granted thereon.

Dated this 1st day of April 1968

FIRST RECEIVED BY ME IN THE REPUBLIC OF SOUTH AFRICA THIS 8th DAY OF April 1968

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ALLIED BUILDING,
PRETORIA.

FOR SOUTH AFRICA USE ONLY

M. Ufer

SCHERING AKTIENGESELLSCHAFT

Table of Classification	
Class	Sub-Class

Signature of Applicant/s and Capacity

(Dr. Asmis) (Dr. Mattner)
(CONFIDENTIAL CLERKS)

PATENTS
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PATENT ATTORNEYS
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PRETORIA

REPUBLIC OF SOUTH AFRICA

The Patents Act, 1952

COMPLETE SPECIFICATION

68/2530

Here insert (in full) name, address of applicant(s) as in application form. (a)

SCHERING AKTIENGESELLSCHAFT, a Body Corporate organized and existing under the laws of the Federal Republic of Germany, of Berlin and Bergkamen, Germany,
Müllerstrasse 170/172, D 1 Berlin 65, Germany.
and Waldshaese 14, D4619 Bergkamen Germany

Here insert title (verbally agreeing with that in the application form.) (b)

"METHOD FOR CONTRACEPTION"

I/WE do hereby declare this invention, the mann r in which and the method by which it is to be performed, to be particularly described and ascertained in and by the following statement:-

Hormonal methods for contraception are already known, for example the oral application of Enovid (R), Ovulen (R), Anovlar (R) and similar combinations of oestrogenically and gestagenically active principles. Also known are tests with corresponding injection preparations, with which the active principle components have an additional accumulative effect. The action of these known agents is based on the fact that the active principle used inhibits the ovulation. The contraception obtained with these known methods is based therefore on the inactivation of the ovaries and the discontinuation of the bleeding caused by these methods does not correspond to a normal menstruation. Apart from the known undesired side effects, such as for example stomach troubles, vomiting, increase of weight and others, the application of the known methods means a far-reaching interference with the endocrinological conditions of women, as every expert will know.

It has now been found that a reliable contraception can be achieved without a simultaneous suppression of the ovulation, after a single application of a gestagen, when the application of the active principle is made parenterally, with which the duration of activity, namely for a menstruation cycle or a longer period, can be varied by the utilisation of an active principle with an accumulative effect or by variation of the quantity of the dose of the gestagen administered.

The invention relates therefore to a method for contraception without the suppression of ovulation, characterised in that a suitable gestagen is applied parenterally, preferably intramuscularly or subcutaneously or by implantation.

As active principles suitable for the method according to the invention, use can be made of all gestagens which, after parenteral application or implantation, do not cause inhibition of ovulation. With the practical application of the method

according to the invention, the dosing of the active principle is chosen in such a way that the gonadotropin secretion is not or only slightly suppressed.

Particularly suitable are such active principles which, apart from their gestagenic action, have no central inhibiting effect, more particularly an ovulation inhibiting effect, for example esters of hydroxy-progesterone and of 19-nor-hydroxy-progesterone and more particularly the corresponding 17-capronates or 17-oenanthates.

Suitable are also such active principles the desired gestagenic effect (and the anti-oestrogenic effect) of which is considerably dissociated from the undesired ovulation inhibiting effect. For application according to the invention, these active principles are dosed in such small quantities that, on the one hand, the change of the composition and texture of the cervical mucus obtained in this manner is sufficient to effect a reliable contraception and, on the other hand, the threshold dosage of the central inhibiting effect is not exceeded. The following gestagens are mentioned as examples: progesterone and its pharmaceutically effective 3-enol ester or 17 alpha-hydroxy-progesterone derivatives, such as for example the 17-esters of 6alpha-methyl-17alpha-hydroxy-progesterone, 6-methyl-6-dehydro-17alpha-hydroxy-progesterone, 6-chloro-or fluoro-6-dehydro-17alpha-hydroxy-progesterone, 6-chloro- or fluoro-6-dehydro-16alpha- or 16beta-methyl-17alpha-hydroxy-progesterone, 6,16-dimethyl-6-dehydro-17alpha-hydroxy-progesterone, 6-methyl- or 6-chloro-6-dehydro-16-methylene-17alpha-hydroxy-progesterone, 1,2-methylene-6-chloro- or 6-fluoro-6-dehydro-17alpha-hydroxy-progesterone or also 17alpha-ethinyl-18-homo-19-nor-testosterone and their esters.

Applicable in principle are also gestagens of which the

dissociation between the desired gestagenic effect and the undesired ovulation inhibiting effect is relatively close, such as for example nor-ethisterone capronate, 17alpha-ethinyl-testosterone, 17alpha-ethinyl-19-nor-testosterone, 17alpha-ethinyl-delta$^{5(10)}$-oestren-17beta-ol-3-one, 17alpha-methyl-19-nor-testosterone, 17alpha-ethinyl-delta^{4}-oestren-3, 17beta-diol, 17alpha-ethinyl-delta^{4}-oestren-17beta-ol, 17alpha-alkyl-delta^{4}-oestren-17beta-ol and their physiologically effective esters. For the practical application of the method according to the invention, these last-named active principles are however less suitable, because as a result of the considerably smaller dissociation of the gestagenic effect from the ovulation inhibiting effect, they are difficult to dose.

If the gestagens applicable according to the invention are used in the form of their esters, use can be made of all physiologically valuable straight-chain or branched-chain esters, such as for example the acetates, valerianates, butyrates, capronates, oenanthates, undecylates, and the like. Furthermore, the ester residue present can also be substituted in known manner, for example by one or more halogen atoms, hydroxyl, carbonyl, keto amino, and similar groups.

With the application of the method according to the invention in which the active principle is applied about 5 to 7 days after the start of the bleeding, the duration of the activity is at least for the period of a menstruation cycle. With a corresponding dosage of the active principle, or by utilising a gestagen with accumulative effect, also a correspondingly longer duration of activity can be obtained, for example, for 3 to 4 months and more.

More particularly for the active principles of the first

group, without central inhibiting effect, and essentially also for the active principles of the second group (considerable dissociation of the gestangenic from the ovulation inhibiting effect) the active dose is generally between 3-250 mg of gestagen. In many cases, more particularly when the duration of the effect is to be limited to only one menstruation cycle, a dosage of up to about 100 mg is already sufficient. For ensuring contraception for a longer duration by a single application of gestagen, more particularly the gestagens of the first group can be administered in dosages of up to 500 mg.

With the utilisation of 19-nor-17alpha-hydroxy-progesterone capronate, the dose is from 3 to 20 mg, preferably about 5 mg and with the utilisation of 17alpha-hydroxy-progesterone capronate 75 to 150 mg, preferably about 100 mg, when the duration of activity of the method according to the invention is to cover one menstruation cycle.

An advantage of the method according to the invention is that the contraception is brought about without a simultaneous ovulation inhibition and, apart from the modification of the composition and structure of the cervical mucus, all biological and physiological phenomena of the sexual cycle remain uninfluenced. Side effects (which may occur as is known with the application of methods, for example a combination of active principles to be applied orally, in which the resulting contraception is based on the ovulation inhibiting effect of the active principle), for example stomach troubles, vomiting, increase of weight etc., are not observed with the application of the method according to the invention.

For the practical application of the method according to the invention, the active principle is preferably dissolved in a solvent suitable for parenteral injection as known to a skilled

person for such purposes, filtered sterile and filled into ampulla under aseptic conditions. Particularly suitable are oily solvents, such as for example sesame oil or castor oil. Apart from these solvents vegetable oils are also suitable, such as linseed oil, cotton seed oil, sunflower oil, arachid oil, olive oil, wheat oil, etc. For increasing the solubility of the active principles, diluting agents or dissolution promoters, such as for example benzyl benzoate, may be added to the oily solutions.

Apart from the said oily solvents, use can however also be made of synthetic solvents such as, for example, glycol, lactic acid ester, benzul alcohol etc. The possible solvents mentioned above, of course are not exhaustive. This does not seem to be necessary because the expert is in a position, by reason of his professional knowledge, to choose from among the known solvents the most suitable for the purpose.

EXAMPLE 1.

5 g of 19-nor-17alpha-hydroxy-progesterone capronate are dissolved in sesame oil. The solution is made up with sesame oil to 1000 ml, filtered sterile and filled into 1 ml ampullae under aseptic conditions. Thereafter it is after-sterilised for 2 hours at 120°C.

EXAMPLE 2.

20 g of 19-nor-17alpha-hydroxy-progesterone capronate are dissolved in a mixture of castor oil/benzyl benzoate (6 : 4) and the solution is then made up to 1000 ml. The sterile filtered solution is filled in known manner into 1 ml ampullae under aseptic conditions. The ampullae are finally after-sterilised for 2 hours at 120°C.

EXAMPLE 3.

150 g of 17alpha-hydroxy-progesterone capronate are dissolved in a mixture of castor oil/benzyl benzoate (6 : 4) and then made up to 1000 ml of solution. The sterile filtered solution is, in known manner, filled into 1 or 2 ml ampullae under aseptic conditions. The ampullae are then after-sterilised for 2 hours at 120°C.

Having now particularly described and ascertained our said invention and the manner in which the same is to be performed, we declare that what we claim is:

1. A method for achieving contraception without the suppression of ovulation, characterised in that a suitable gestagen is administered parenterally, preferably intra-muscularly or subcutaneously.

2. A method in accordance with claim 1, characterised in that the active principle is administered in oily solution, preferably in sesame oil or castor oil, if desired in the presence of a dissolution promoter or dilution agent, for example benzyl benzoat

3. A method in accordance with claim 1, characterised in that the active principle is administered by implantation.

4. A method in accordance with any one of claims 1 to 3, characterised in that gestagens, which have no additional ovulation inhibiting or central inhibiting effects are used as the active principle.

5. A method in accordance with any one of claims 1 to 4, characterised in that as active principle hydroxy-progesterone or 19-nor-hydroxy-progesterone ester is used.

6. A method in accordance with any one of claims 1 to 5, characterised in that as active principle hydroxy-progesterone or 19-nor-hydroxy-progesterone capronate is dispensed.

7. A method in accordance with any one of claims 1 to 3, characterised in that as active principle, a gestagen is used with sufficient dissociation of the desired gestagenic effect from the undesired central inhibiting effect or ovulation inhibiting effect, at a dosage which with complete contraceptive effect does not reach the threshold dosage of the side effect.

8. A medicament for contraception, containing a gestagen in a dosage which does not suppress or which only slightly suppresses the gonatropin secretion.

9. A medicament in accordance with claim 8, containing an active principle in accordance with claim 5 or 6.

10. A medicament in accordance with claim 8 or 9, containing as active principle 19-nor-17alpha-hydroxy-progesterone capronate at a dosage of 3 to 25 mg, preferably about 5 mg.

11. A medicament in accordance with claim 8 or 9, containing as active principle 17alpha-hydroxy-progesterone capronate at a dosage of 75 to 150 mg, preferably about 100 mg.

12. A method for achieving contraception, substantially as described herein.

13. A medicament for contraception, substantially as described herein.

DATED THIS 19th DAY OF APRIL 1968

PATENT ATTORNEY

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ОПИСАНИЕ ИЗОБРЕТЕНИЯ

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(72) Авторы изобретения М. И. Прокофьев и Е. С. Прокофьева

(71) Заявитель —

(54) СПОСОБ СИНХРОНИЗАЦИИ ПОЛОВОЙ ОХОТЫ У ЦИКЛИРУЮЩИХ СВИНОМАТОК

1

Изобретение относится к животноводству, в частности к препаратам для синхронизации охоты у сельскохозяйственных животных, преимущественно свиноматок.

Известно, что эффективные результаты по синхронизации охоты у свиней получают при использовании нестероидного ингибитора гонадотропной функции гипофиза-металлибура, (33828 дитиокарбомоилгидразин) английского производства. При ежедневном добавлении его к корму в течение 20 дней по 100 *мг* одному животному в день охота наступает у 75—90% свинок на 5—7 или 4—8 день после окончания скармливания. Оплодотворяемость в синхронизированную охоту колеблется от 35 до 82%. Для более точного контроля времени овуляции и охоты через день после окончания скармливания этого препарата инъецируют СЖК, а на 4-й день — ХГ [1].

Недостаток данного способа — необходимость многократных обработок и периодическое появление у свинок побочных явлений, выражающихся, в частности, снижением аппетита.

Известен также способ синхронизации охоты у домашних животных, включающий парентеральное или оральное введение прогестагенных препаратов, например, 17α-оксипрогестерона-капроната в дозе 4—5 *мг* на 1 *кг* живого веса [2, 3].

2

Недостаток этого способа — образование кистозных фолликулов, появление у свиней побочных явлений и высокая трудоемкость обработок, так как препараты приходится вводить многократно.

Цель изобретения — устранение отмеченных недостатков и создание способа, обеспечивающего повышение синхронности проявления охоты у свиноматок.

Это достигается тем, что циклирующим свиньям вводят оксипрогестерон-капронат в смеси с эстрадиол-валерианатом в соотношении 50 : 1 в растворе растительного масла и бензил бензоата (7 : 3) в дозе соответственно 3—4 *мг* оксипрогестерон-капроната и 0,06—0,08 *мг* эстрадиол-валерианата на 1 *кг* живого веса.

Предлагаемый способ осуществляется следующим образом.

Оксипрогестерон-капронат и эстрадиол-валерианат растворяют в смеси растительного масла, например, хлопкового и бензил-бензоата в соотношении 7 : 3 соответственно до 10—12% и 0,20—0,25% концентрации. Полученный раствор стерилизуют в течение 2 *час* на водяной бане при температуре 100° С и охлаждают до комнатной температуры. После этого раствор препарата вводят животным путем однократной внутримышечной инъекции в области шеи или лопатки в количестве

3—4 *мг* оксипрогестерон-капроната и 0,06—0,08 *мг* эстрадиол-валерианата на *кг* живого веса. Вводимый препарат, обладая пролонгирующим действием, тормозит проявление охоты у обработанных свиней в течение 6—20 суток. Через 17—22 суток после обработки охота наступает одновременно у большинства свиней.

При испытании предлагаемого способа после инъекции раствора, содержащего 3—4 *мг* оксипрогестерон-капроната и 0,06—0,08 *мг* эстрадиол-валерианата на 1 *кг* живого веса в остром опыте на 30 свинках была обнаружена овуляция и образование желтых тел между 17 и 22 днями после обработки.

В производственных опытах установлено, что охота наступала у 95—100% свинок одновременно в течение 4—5 суток, начиная с 17—19 дня после обработки. Оплодотворяемость свинок была нормальной: 75% и выше после первого спаривания.

Формула изобретения

Способ синхронизации половой охоты у циклирующих свиноматок, включающий введение им внутримышечно прогестагенного препарата оксипрогестерон-капроната, отличающийся тем, что, с целью повышения синхронности проявления охоты у свиноматок, оксипрогестерон-капронат вводят в смеси с эстрадиол-валерианатом в соотношении 50 : 1, которые предварительно растворяют в смеси растительного масла и бензил-бензоата (7 : 3), в дозе соответственно 3—4 *мг* оксипрогестерон-капроната и 0,06—0,08 *мг* эстрадиол-валерианата на 1 *кг* живого веса.

Источники информации, принятые во внимание при экспертизе:

1. Семенов В. А и Ельчанинов В. В. Синхронизация охоты. — «Свиноводство», 1970, № 12, с. 27.

2. Клинский Ю. Д. и Даровских В. Е. Синхронизация половой функции у сельскохозяйственных животных. — «Сельское хозяйство за рубежом», 1972, № 3, с. 28.

3. Авторское свидетельство № 367866, кл. А 01 К 67/02, 1972.

Составитель А. Алексеенок

Редактор Н. Скворцова Техред Л. Кочемирова Корректор И. Симкина

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ЦНИИПИ Государственного комитета Совета Министров СССР
по делам изобретений и открытий
Москва, Ж-35, Раушская наб., д. 4/5

Тип. Харьк. фил. пред. «Патент»

Soviet Union

AN 1978-09798A [05] WPIX
TI Compsn. for oestrus cycle control in sows - contg. hydroxy-**progesterone** caproate, oestradiol valerate, **oil** and **benzyl benzoate** to improve heat synchronisation.
DC **B01** C03 P14
IN PROKOFEVA, E S
PA (PROK-I) PROKOFEV M I
CYC 1
PI SU----549118 A 19770623 (197805)*
PRAI 1973SU-1904192 19730402
AB SU 549118 A UPAB: 19930901
Heat is synchronised in sows by **intra-muscular injection** of hydroxyprogesterone capronate. Better synchronisation is attained by **injecting** the above capronate mixed with oestradiol valetrate in the ratio 50:1. The **hormones** are dissolved in a 7:3 mixture of vegetable **oil** : **benzyl benzoate** and the dosage employed is 3/4 mg hydroxyprogesterone capronate and 0.06-0.08 mg oestradiol valerate per kg. body wt.

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ОПИСАНИЕ ИЗОБРЕТЕНИЯ

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(71) Заявитель Научно-исследовательский институт животноводства

(54) СПОСОБ СИНХРОНИЗАЦИИ ПОЛОВОЙ ОХОТЫ У САМОК ДОМАШНИХ ЖИВОТНЫХ

1

Изобретение относится к сельскому хозяйству, в частности к животноводству, и может быть использовано в регуляции воспроизводительной функции у самок крупного рогатого скота.

Известен способ синхронизации охоты у домашних животных путем однократной инъекции 17α-оксипрогестерона-капроната [1].

Однако этот способ не обеспечивает высокой точности регулирования сроков проявления охоты, а также существенного сокращения сервис-периода у коров.

Цель изобретения — повышение эффективности синхронизации половой охоты у самок домашних животных.

Для достижения этой цели животным вводят 17α-оксипрогестерон-капронат подкожно в количестве 4—5 мг на 1 кг живой массы за 18—20 дней до осеменения телками и в первый месяц после отела коровам. На 17—18 день после введения этого препарата животным инъецируют 1000—1500 ед. хорионического гонадотропина и 5—10 мг 0,2—0,5%-ного раствора эстрадиола бензоата на одну голову.

При этом растворы хорионического гонадотропина и эстрадиола бензоата вводят одновременно раздельно или перед инъекцией смешивают и вводят в виде эмульсии внутримышечно.

2

Пример 1. Научно-производственный опыт проводят на 35 коровах, 17α-оксипрогестерон-капронат растворяют в смеси растительного масла и бензил-бензоата в соотношении 7:3 до 10%-ной концентрации и вводят коровам однократно подкожно в количестве 4—5 мг на 1 кг живой массы в первый месяц после отела, начиная с 10—15 дня. На 17—18-й день после введения этого препарата животным инъецируют хорионический гонадотропин в 0,9%-ном водном растворе хлористого натрия в количестве 1000—1500 ед. и эстрадиол бензоат, растворенный в растительном масле до 0,2—0,5%-ной концентрации в количестве 5—10 мг на одно животное.

Указанная обработка обеспечивает синхронное проявление охоты у всех коров в течение трех суток и сокращение продолжительности сервис-периода на 42 дня (52,6 дней у обработанных коров по сравнению с 94,5 днями у контрольных).

Пример 2. Телкам опытной группы (46 голов) за 20—30 дней до того, как они достигнут живой массы, необходимой для случки, инъецируют подкожно однократно 17α-оксипрогестерон-капронат в дозе 1500 мг, а затем на 18-й день после первой

обработки вводят 10 мг эстрадиола бензоата и 1000 ед. хорионического гонадотропина. Гормональные препараты растворяют в тех же растворителях, как описано в 1 примере, 41 (89,1%) из 46 телок пришли в охоту в течение двух суток после второй обработки и 16 (39,0%) из 41 телки оплодотворились после первого осеменения замороженной спермой. За две последовательные охоты оплодотворились 42 (91,3%) из 46 телок в опытной группе против 49 (87,5%) из 56 телок в контрольной группе. Продолжительность времени от окончания обработки до оплодотворенном осеменения в группе обработанных телок составила 19,5±6,3 дня против 44,4±5,4 дня в контрольной группе. Таким образом, плодотворное осеменение в группе обработанных телок наступило на 21,1 дня раньше, чем в контрольной группе.

Формула изобретения

1. Способ синхронизации половой охоты у самок домашних животных, преимущественно крупного рогатого скота, включающий введение прогестагенного препарата, предпочтительно 17α-оксипрогестерона-капроната в смеси с растительным маслом и бензилбензоатом, отличающийся тем, что, с целью повышения эффективности способа, 17α-оксипрогестерон-капронат вводят телкам за 18—20 дней до осеменения, а коровам в первый месяц после отела, а затем животным через 17—18 суток дополнительно инъецируют хорионический гонадотропин и эстроген.

2. Способ по п. 1, отличающийся тем, что хорионический гонадотропин вводят в дозе 1000—1500 единиц на одно животное.

3. Способ по п. 1, отличающийся тем, что в качестве эстрогена используют 0,2—0,5%-ный раствор эстрадиол бензоата, который вводят в дозе 5,0—10,0 мг на животное.

4. Способ по п. 1, отличающийся тем, что растворы хорионического гонадотропина и эстрадиола бензоата вводят одновременно раздельно или перед инъекцией смешивают и вводят в виде эмульсии внутримышечно.

Источники информации,
принятые во внимание при экспертизе

1. Авторское свидетельство СССР № 367866, A 61D 7/00, 1973.

Составитель А. Макаров

Редактор Г. Кузьмина Техред А. Камышникова Корректор В. Петрова

Заказ 1782/11 Изд. № 478 Тираж 681 Подписное
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113035, Москва, Ж-35, Раушская наб., д. 4/5

Типография, пр. Сапунова, 2

QR

gc0174

FILE 'WPIX' ENTERED AT 16:21:29 ON 18 APR 2001

L2 1 SU676284/PN

L2 ANSWER 1 OF 1 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1980-23354C [13] WPIX
TI Farm animal, e.g. cow, heat period synchronisation - by injecting 17-alpha-hydroxy-progesterone capronate and later, chorionic gonadotropin and oestrogen.
DC B01 C03
IN BIKKULOV, A S; LEDNEV, P I; PROKOFEV, M I
PA (LIVE-R) LIVESTOCK RES INST
CYC 1
PI SU----676284 A 19790730 (198013)* <--
PRAI 1975SU-2149961 19750626
AB SU 676284 A UPAB: 19930902
Heat of female farm animals, esp. cows, is synchronised for the husbandry purposes by subcutaneously injecting 17 alpha-hydroxyprogesterone capronate mixed with a vegetable oil and benzyl benzoate.

The effectiveness of synchronisation with respect to heifers is enhanced by carrying out the injecting 18-20 days before the fecundation; cows are inoculated within one month after the calving. In both cases, after 17-18 days, an additional injection is applied contg. chorionic gonadotropine and oestrogen.

FULL ESTIMATED COST 2.86 3.06
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A2

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(30) Priority: 12.10.83 GB 8327256

(43) Date of publication of application: 24.04.85 Bulletin 85/17

(84) Designated Contracting States: AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: IMPERIAL CHEMICAL INDUSTRIES PLC, Imperial Chemical House Millbank, London SW1P 3JF (GB)

(72) Inventor: Bowler, Jean, 9 Tatton Drive, Sandbach Cheshire (GB)
Inventor: Tait, Brian Steele, 3, Batemill Close, Macclesfield Cheshire (GB)

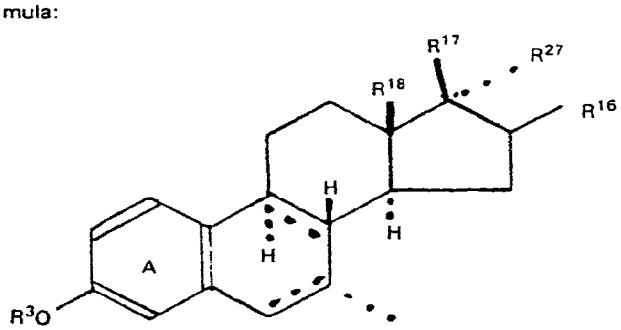
(74) Representative: Slatcher, Reginald Peter et al, Imperial Chemical Industries PLC Legal Department: Patents P.O. Box 6 Bessemer Road, Welwyn Garden City AL7 1HD (GB)

(54) Steroid derivatives.

(57) A steroid derivative of the formula:

ST-A-X-R^1

wherein ST is a 7α-linked steroid nucleus of the general formula:



wherein the double bond(s) carbon atoms 6 and 7 and/or carbon atoms 8 and 9 are optional;
wherein the aromatic ring A may optionally bear one or two halogen or alkyl substituents;
wherein R^3 is hydrogen, alkyl, or acyl;
wherein R^{16} is hydrogen, alkyl or hydroxy;
wherein either R^{17} is hydroxy or acyloxy and R^{27} is hydrogen, alkyl, alkenyl or alkynyl, or R^{17} and R^{27} together form oxo (=O);
wherein R^{18} is alkyl;
wherein A is alkylene, alkenylene or alkynylene optionally fluorinated and optionally interrupted by -O-, -S-, -SO-, $-SO_2-$, -CO-, -NR-, -NRCO-, -CONR-, -COO-, -OCO- or phenylene, wherein R is hydrogen or alkyl;
wherein R^1 is hydrogen, alkyl, alkenyl, cycloalkyl, halogenoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl, arylalkyl, or dialkylaminoalkyl, or R^1 is joined to R^2 as defined below;
and wherein X is $-CONR^2-$, $-CSNR^2-$, $-NR^{12}CO-$, $-NR^{12}CS-$, $-NR^{12}CONR^2-$, $NR^{12}-\overset{NR^{22}}{\overset{\|}{C}}-NR^2-$, $-SO_2NR^2-$, or -CO-; or, when R^1 is not hydrogen, is -O-, $-NR^2-$, $-(NO)R^2-$, $-(PO)R^2-$, $-NR^{12}COO-$; $-NR^{12}SO_2-$, -S-, -SO- or $-SO_2-$;
wherein R^2 is hydrogen or alkyl or R^1 annd R^2 together form alkylene or halogenoalkylene;
wherein R^{12} is hydrogen or alkyl and wherein R^{22} is hydrogen, cyano or nitro;
or a salt thereof when appropriate.

EP 0 138 504 A2

STEROID DERIVATIVES

This invention relates to new steroid derivatives which possess antioestrogenic activity.

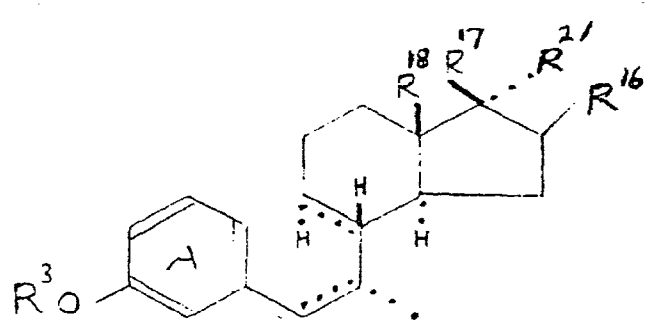
Various oestradiol derivatives are known which bear a carboxyalkyl substituent at the 7α-position. These have been used, when bound via the carboxy group to polyacrylamide resin or to agarose, for the purification of oestrogen receptors (Journal of Biological Chemistry, 1978, 253, 8221); and, when conjugated with bovine serum albumin, for the preparation of antigens (United Kingdom Specification No. 1,478,356).

We have now found that certain 7α-substituted derivatives of oestradiol and related steroids possess potent antioestrogenic activity.

According to the invention there is provided a steroid derivative of the formula:-

$$ST\text{-}A\text{-}X\text{-}R^1$$

wherein ST is a 7α-linked steroid nucleus of the general formula:-



wherein the dotted lines between carbon atoms 6 and 7, and carbon atoms 8 and 9, of the steroid nucleus indicate that there is an optional double bond between carbon atoms 6 and 7, or that there are two optional double bonds between carbon atoms 6 and 7 and carbon atoms 8 and 9;

wherein the aromatic ring A may optionally bear one or two halogen or alkyl substituents;

wherein R^3 is hydrogen or alkyl, alkanoyl, alkoxycarbonyl, carboxyalkanoyl or aroyl each of up to 10 carbon atoms;

wherein R^{16} is hydrogen, alkyl of up to 6 carbon atoms which is preferably in the β-configuration, or hydroxy which is preferably in the α-configuration;

wherein either R^{17} (in the β-configuration) is hydroxy or alkanoyloxy, carboxyalkanoyloxy or aroyloxy each of up to 10 carbon atoms; and R^{27} (in the α-configuration) is hydrogen or alkyl, alkenyl or alkynyl each of up to 6 carbon atoms ;

or R^{17} and R^{27} together form oxo (=O);

wherein R^{18} is alkyl of up to 6 carbon atoms;

wherein A is straight- or branched- chain alkylene, alkenylene or alkynylene each of from 3 to 14 carbon atoms, which may have one or more hydrogen atoms replaced by fluorine atoms, or has the formula

$$-A^1-Y-A^{11}-$$

wherein A^1 and A^{11} are each alkylene or alkenylene, optionally fluorinated, having together a total of 2 to 13 carbon atoms and Y is -O-, -S-, -SO-, $-SO_2-$, -CO- or -NR- wherein R is hydrogen or alkyl of up to 3 carbon atoms;

or A^1 is alkylene or alkenylene, optionally fluorinated, and A^{11} is a direct link or alkylene or alkenylene, optionally fluorinated, such that A^1 and

A^{11} together have a total of 1 to 12 carbon atoms, and Y is -NRCO-, -CONR-, -COO-, -OCO- or phenylene wherein R has the meaning stated above;

wherein R^1 is hydrogen, or alkyl, alkenyl, cycloalkyl, halogenoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl or arylalkyl each of up to 10 carbon atoms, or dialkylaminoalkyl wherein each alkyl is of up to 6 carbon atoms, or R^1 is joined to R^2 as defined below;

and wherein X is $-CONR^2-$, $-CSNR^2_{22}-$, $-NR^{12}-CO-$, $-NR^{12}-CS-$, $-NR^{12}-CONR^2-$, $-NR^{12}-\overset{\overset{NR}{\|}}{C}-NR^2-$, $-SO_2NR^2-$ or $-CO-$;

or, when R^1 is not hydrogen, is $-O-$, $-NR^2-$, $-(NO)R^2-$, $-(PO)R^2-$, $-NR^{12}-COO-$, $-NR^{12}-SO_2-$, $-S-$, $-SO-$ or $-SO_2-$;

wherein R^2 is hydrogen or alkyl of up to 6 carbon atoms, or R^1 and R^2 together form alkylene or halogenoalkylene such that, with the adjacent nitrogen atom, they form a heterocyclic ring of 5 to 7 ring atoms, one of which atoms may be a second heterocyclic atom selected from oxygen, sulphur and nitrogen;

wherein R^{12} is hydrogen or alkyl of up to 6 carbon atoms;

and wherein R^{22} is hydrogen, cyano or nitro;

or a salt thereof when appropriate.

A suitable value for the halogen or alkyl substituent in ring A is, for example, fluoro, chloro, bromo, iodo, methyl or ethyl.

A suitable value for R^3 when it is alkyl, alkanoyl, alkoxycarbonyl, carboxyalkanoyl or aroyl is, for example, methyl, ethyl, acetyl, propionyl, butyryl, pivalyl, decanoyl, isopropoxycarbonyl, succinyl or benzoyl. R^3 is preferably hydrogen or alkanoyl or alkoxycarbonyl each of up to 5 carbon atoms.

A suitable value for R^{16} when it is alkyl is, for example, methyl or ethyl. R^{16} is preferably hydrogen.

A suitable value for R^{17} when it is alkanoyloxy, carboxyalkanoyloxy or aroyloxy is, for example, acetoxy, propionyloxy, succinyloxy or benzoyloxy. R^{17} is preferably hydroxy.

A suitable value for R^{27} when it is alkyl, alkenyl or alkynyl is, for example, ethyl, vinyl or ethynyl. R^{27} is preferably hydrogen.

A suitable value for R^{18} is methyl or ethyl, especially methyl.

The group ST- is preferably oestra-1,3,5(10)-triene-3,17β-diol, 3-hydroxyoestra-1,3,5(10)-trien-17-one or 17α-ethynyloestra-1,3,5(10)-triene-3,17β-diol, all of which bear the -A-X-R^1 substituent in the 7α-position, or a 3-alkanoyl ester thereof.

One preferred value for the group -A- is a straight-chain alkylene group of the formula

$$-(CH_2)_n-$$

wherein n is an integer of from 3 to 14, especially from 7 to 11, which may have one of the hydrogen atoms replaced by fluorine, for example to provide the group $-(CH_2)_8CHFCH_2-$. A may also be a branched-chain alkylene group, for example the group $-(CH_2)_6CH(CH_3)-$, or a straight-chain alkenylene group, for example of the formula

$$-(CH_2)_2CH=CH(CH_2)_m-$$

wherein m is an integer from 0 to 10, especially from 3 to 7.

A second preferred value for the group A is a group of the formula

$$-A^{1}-Y-A^{11}-$$

wherein A^{1} is straight-chain alkylene or alkenylene each of 2 to 9 carbon atoms, especially alkylene of 4 to 6 carbon atoms, -Y- is phenylene (ortho, meta- or, especially, para-) and A^{11} is a direct link, ethylene or vinylene, especially ethylene.

A suitable value for R^{1} when it is alkyl, alkenyl or cycloalkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, t-pentyl, 2,2-dimethylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1,1-dimethylbutyl, 1,3- dimethylbutyl, n-heptyl, n-nonyl, n-decyl, n-undecyl, allyl, cyclopentyl or cyclohexyl.

A suitable value for R^{1} when it is aryl or arylalkyl is, for example, phenyl, 2-ethylphenyl, p-fluorophenyl, p-chlorophenyl, m-chlorophenyl, p-cyanophenyl, p-methoxyphenyl, benzyl, α-methylbenzyl, p-chlorobenzyl, p-fluorophenethyl or p-chlorophenethyl.

A suitable value for R^{1} when it is halogenoalkyl, carboxyalkyl, alkoxycarbonylalkyl or dialkylaminoalkyl is, for example, 2-chloro-2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, 3-chloropropyl, 2,2-difluorobutyl, 4,4,4-trifluorobutyl, 1H,1H-heptafluorobutyl, 4,4,5,5,5-pentafluoropentyl, 4,4,5,5,6,6,6-heptafluorohexyl, 1H,1H-tridecafluoroheptyl, 5-carboxypentyl, 5-methoxycarbonylpentyl or 3- dimethylaminopropyl.

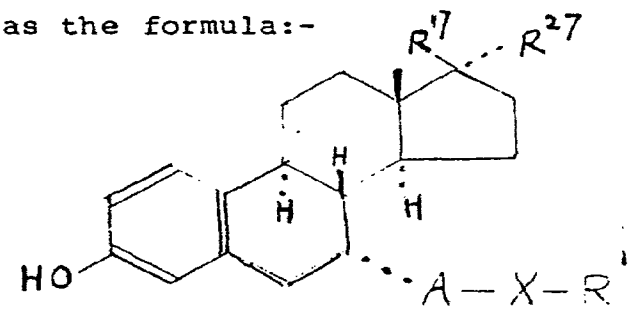
A suitable value for the heterocyclic ring $-NR^{1}R^{2}$ is, for example, pyrrolidino, piperidino, 4-methylpiperidino, 4-ethylpiperidino, 3-methylpiperidino, 3,3-dimethylpiperidino, 4-chloropiperidino, morpholino or 4- methylpiperazino.

A suitable value for R^{2} or R^{12} when it is alkyl is, for example, methyl, ethyl or n-butyl.

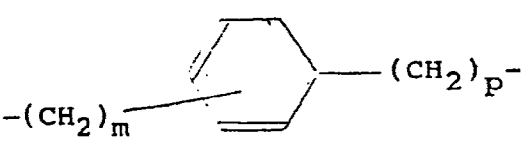
One appropriate salt is an acid-addition salt of a steroid derivative which possesses an amino function, for example a compound wherein Y is -NR-, X is $-NR^2-$ or R^1 is dialkylaminoalkyl. A suitable acid-addition salt is, for example, a hydrochloride, hydrobromide, acetate, citrate, oxalate or tartrate.

Another appropriate salt is a base-addition salt of a steroid derivative which possesses a carboxy function, for example a compound wherein R^1 is carboxyalkyl. A suitable base-addition salt is, for example, a sodium, potassium, ammonium or cyclohexylamine salt.

A preferred steroid derivative of the invention has the formula:-



wherein R^{17} is hydroxy and R^{27} is hydrogen or ethynyl, or R^{17} and R^{27} together form oxo;
wherein -A- is $-(CH_2)_n-$, wherein n is an integer from 3 to 14, especially from 7 to 11, or -A- is



wherein m is an integer from 2 to 9, especially from 4 to 6, and p is 0 to 2, especially 0 or 2;
wherein R^1 is alkyl, fluoroalkyl or cycloalkyl each of up to 10 carbon atoms, or phenyl, chlorophenyl or benzyl, or is linked to R^2 as stated below;
wherein X is $-CONR^2-$, $-NR^{12}CO-$, -S-, -SO- or $-SO_2-$,
wherein R^2 is hydrogen or alkyl of up to 3 carbon

atoms or together with R^1 forms alkylene of 5 or 6 carbon atoms, and wherein R^{12} is hydrogen or alkyl of up to 3 carbon atoms.

A particularly preferred steroid derivative of the invention has the last-mentioned formula wherein the number of carbon atoms in the two groups A and R^1 adds up to between 12 and 16, inclusive, especially 14 if neither R^1 nor A contains a phenyl or phenylene group, and 16 if there is a phenylene group in -A- or a phenyl group in R^1.

Specific steroid derivatives of the invention are hereinafter described in the Examples. Of these, particularly preferred compounds are:

N-n-butyl-N-methyl-, N-2,2,3,3,4,4,4-heptafluorobutyl-N-methyl- and N, N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecamide;

N-n-butyl- and N-2,2,3,3,4,4,4-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-pentafluoropentylsulphonyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)-decyl]- and 7α-[10-(p-chlorobenzylsulphonyl)decyl]oestra- 1,3,5(10)-triene- 3,17β-diol; and

7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

A preferred process for the manufacture of a steroid derivative of the invention wherein X has the formula $-CONR^2-$, $-CSNR^2-$ or $-SO_2NR^2-$ comprises the reaction of a compound of the formula ST^1-A-Z^1, wherein A has the meaning stated above, wherein ST^1 either has the same meaning as stated above for ST, or is an equivalent 7α-linked steroid nucleus which bears one or more protecting groups for functional derivatives, and wherein Z^1 is an activated group

derived from a carboxylic, thiocarboxylic or sulphonic acid, with an amine of the formula HNR^1R^2, wherein R^1 and R^2 have the meanings stated above, whereafter any protecting group in ST^1 is removed by conventional means.

A suitable activated group Z^1 is, for example, a mixed anhydride, for example an anhydride formed by reaction of the acid with a chloroformate such as isobutyl chloroformate.

A suitable protecting group in ST^1 is, for example, an alkyl or aralkyl ether, for example the methyl or benzyl ether, of the 3-hydroxy function, or a tetrahydropyranyl ether of the 17β- hydroxy function.

A preferred process for the manufacture of a steroid drivative of the invention wherein X has the formula -CO- comprises the reaction of an acid of the formula ST^1-A-COOH, wherein ST^1 and A have the meanings stated above, with an organometallic compound of the formula R^1-M, wherein R^1 has the meaning stated above and M is a metal group, for example the lithium group, whereafter any protecting group in ST^1 is removed by conventional means.

A preferred process for the manufacture of a steroid derivative of the invention wherein X has the formula -S-, -O-, $-NR^2-$ or $-(PO)R^2-$ comprises the reaction of a compound of the formula ST^1-A-Z^2, wherein ST^1 and A have the meanings stated above and wherein Z^2 is a displaceable group, with a compound of the formula R^1SH, R^1OH, HNR^1R^2 or R^1R^2P-C_6H_5 wherein R^1 and R^2 have the meanings stated above, whereafter any protecting group in ST^1 is removed by conventional means, and whereafter a phosphonium salt is hydrolysed to the phosphinyl compound.

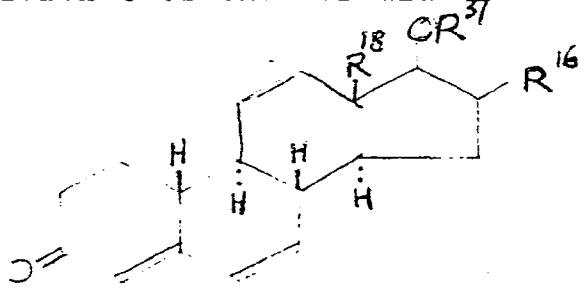
A suitable value for Z^2 is, for example, a halogen atom or a sulphonyloxy group, for example the methanesulphonyloxy or toluene-p-sulphonyloxy group.

A preferred process for the manufacture of a

steroid derivative of the invention wherein X has the formula $-NR^{12}CO-$, $-NR^{12}CS-$, $-NR^{12}CONR^{22}-$, $-NR^{12}-\overset{\overset{NR^{2}}{\|}}{C}-NR^{2}-$, $-NR^{12}COO-$ or $-NR^{12}SO_2-$ comprises the reaction of a compound of the formula $ST^1-A-NHR^{12}$, wherein ST^1, A and R^{12} have the meanings stated above, with an acylating agent derived from an acid of the formula R^1COOH, R^1CSOH, R^1OCOOH or R^1SO_2OH; or, for the manufacture of a urea, with an isocyanate of the formula R^1NCO; or, for the manufacture of a guanidine, with a cyanamide of the formula R^1NR^2-CN, whereafter any protecting group in ST^1 is removed by conventional means.

A suitable acylating agent is, for example, an acyl chloride or acyl anhydride.

The starting materials for use in all the abovementioned processes may be obtained by reacting a steroid derivative of the formula



wherein R^{16} and R^{18} have the meanings stated above and wherein R^{37} is an acyl group, for example the acetyl group, with a compound of the formula

$$Br-A^2-CH_2-O-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{Si}}-C(CH_3)_3$$

wherein A^2 either has the same meaning as stated above for A, or wherein $-A^2-CH_2-$ has the same meaning as stated above for A;

separating the isomers at the 7-position of the steroid nucleus to provide the 7α-isomer; hydrolysing off the dimethyl-t-butylsilyl protecting group; and converting the steroidal part of the molecule to the required structure by conventional reactions. The intermediate product obtained, which has the formula:-

$$ST^1\text{-}A^2\text{-}CH_2OH$$

wherein ST^1 has the meaning stated above, may be oxidised to the corresponding carboxylic acid of the formula $ST^1\text{-}A^2\text{-}COOH$ which provides the starting material for the first or second process of the invention described above;
or it may be converted into a compound of the formula $ST^1\text{-}A^2\text{-}CH_2Z^2$ by reaction with a halogenating agent or a sulphonylating agent to provide the starting material for the third process of the invention described above.

The starting material for the fourth process of the invention described above may be obtained by using the third process of the invention described above except that an amine of the formula $R^{12}NH_2$ is used in place of an amine of the formula HNR^1R^2.

The intermediate of the formula $ST^1\text{-}A^2\text{-}CH_2OH$ may be oxidised to an aldehyde of the formula $ST^1\text{-}A^2\text{-}CHO$ which may then be used, by reaction with an appropriately-substituted hydrocarbyltriphenylphosphonium salt or hydrocarbyltriethylphosphonate, to prepare a starting material wherein -A- is alkenylene.

An alternative process for the manufacture of a steroid derivative of the invention wherein -A- is alkenylene of the formula $-A^3\text{-}CH{=}CH\text{-}A^4-$ comprises the reaction of a compound of the formula:-

ST^1-A^3CHO

wherein ST^1 and A^3 have the meanings stated above, with a triphenylphosphonium salt of the formula:-

$$R^1X-A^4-CH_2-P^+(Ph)_3 \quad Q^-$$

wherein R^1, X and A^4 have the meanings stated above and wherein Q^- is an anion, for example the bromide ion.

The reaction may be carried out in solution in dimethyl sulphoxide in the presence of dimsyl sodium.

The steroidal aldehyde starting material when $-A^3-$ is $-A^2-$ as defined above may be obtained by oxidation of the corresponding alcohol as described above. The steroidal aldehyde starting material wherein $-A^3-$ is a direct link may be obtained from the 3-keto-$\Delta^{4,6}$-inital steroidal starting material described above by reaction with cyanide to give the 3-keto-Δ^4-7α-cyano compound, aromatisation, suitable protection and then reduction of the cyano group to the formyl group.

The phosphonium starting material may be obtained by reaction of triphenylphosphine with a bromide of the formula

$$R^1-X-A^4-CH_2Br.$$

A steroid derivative of the invention wherein ST is a 17β-hydroxy-steroid derivative may be converted by conventional reactions into the corresponding 17-keto steroid derivative, and thence to the corresponding 17β-hydroxy-17α-hydrocarbyl steroid derivative (that is, a steroid derivative of the invention wherein R^{27} is alkyl, alkenyl or alkynyl). Similarly, a steroid derivative of the invention wherein R^3 and/or R^{17}

are other than hydrogen may be obtained from the corresponding compounds wherein R^3 and/or R^{17} are hydrogen by conventional etherification or esterification processes, and these may also be used in reverse to prepare the corresponding hydroxy compounds.

A steroid derivative of the invention wherein A is alkenylene may be hydrogenated to provide the corresponding compound wherein A is alkylene.

A steroid derivative of the invention wherein -X- is $-CH_2NR^2-$ or $-NR^2CH_2-$ may be obtained by the reduction, for example with borane, of the corresponding compound wherein -X- is $-CONR^2-$ or $-NR^2CO-$.

A steroid derivative of the invention wherein -X- is -CSNH- or -NHCS- may be obtained by the reaction of the corresponding compound wherein X is -CONH- or -NHCO- with 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide.

A steroid derivative of the invention wherein X is $-(NO)R^2$, -SO- or $-SO_2-$ may be obtained by the oxidation of the corresponding compound wherein X is $-NR^2-$ or -S-. The conditions for the oxidation will be chosen to provide the desired product; for example aqueous sodium metaperiodate will oxidise the sulphur group to sulphinyl, and m-chloroperbenzoic acid in chloroform solution will oxidise the sulphur group to sulphonyl or the amine to its oxide.

As stated above, a steroid derivative of the invention possesses antioestrogenic activity. This may be demonstrated by its effect in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when a steroid derivative of the invention and oestradiol benzoate are co-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 steroid derivative of the invention.

In particular, a preferred steroid derivative of the invention produces an antioestrogenic effect at a dose which produces no partial agonist effect, unlike the known antioestrogens tamoxifen and clomiphene. When a preferred steroid is coadministered with oestradiol benzoate to a rat as described above, no increase in uterine weight whatsoever is observed at a suitable dose.

A compound with the above pharmacological properties is of value in the treatment of the same conditions in which tamoxifen is beneficial, in particular, in the treatment of anovulatory infertility and in the treatment of breast tumours. It is also of value in the treatment of menstrual disorders.

When used to produce an anti-oestrogenic effect in warm-blooded animals, a typical daily dose is from 0.1 to 25 mg/kg. administered orally or by injection. In man this is equivalent to an oral dose of from 5 to 1250 mg./day. A steroid derivative of the invention is most conveniently administered to man in the form of a pharmaceutical composition.

According to a further feature of the invention, there is provided a pharmaceutical composition comprising a steroid derivative of the invention together wih a pharmaceutically acceptable diluent or carrier.

The composition may be in a form suitable for oral or parenteral administration. A tablet or capsule is a particularly convenient form for oral administration and such a composition may be made by conventional methods and contain conventional excipients. Thus a tablet could 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.

The composition may contain, in addition to the steroid derivative of the invention, one or more antiandrogenic agents or antiprogestational agents.

A composition for oral administration may conveniently contain from 5 to 500 mg. of a steroid derivative of the invention.

The invention is illustrated but not limited by the following Examples:-

Example 1

N-Methylmorpholine (0.24 ml.) and isobutyl chloroformate (0.288 ml.) were successively added to a stirred solution of 11-(17β-acetoxy-3-benzoyloxyoestra-1,3,5(10)-trien-7α-yl)undecanoic acid (1.0 g.) in methylene chloride (17 ml.) which was cooled to -10°C., and after 30 minutes n-butylamine (0.29 ml.) was added and the mixture was stirred at laboratory temperature for 15 minutes. Saturated aqueous sodium bicarbonate solution (20 ml.) was added and the mixture was extracted four times with methylene chloride (50 ml.each time). The combined extracts were washed with water (10 ml.), dried and evaporated to dryness. There was thus obtained as residue 11-(17β-acetoxy-3-benzoyloxy-N-n-butyloestra-1,3,5(10)-trien-7α-yl)undecanamide as an oil.

Aqueous N-sodium hydroxide solution (8 ml.) was added to a stirred solution of the above amide (1.06 g.) in a mixture of methanol (16 ml.) and tetrahydrofuran (8 ml.) and the mixture was stirred at laboratory temperature for 18 hours, neutralised with aqueous N-hydrochloric acid and the organic solvents were removed by evaporation. Water (40 ml.) was added and the mixture was extracted four times with methylene chloride (60 ml. each time). The combined extracts were washed with water (10 ml.), dried and evaporated to dryness and the residue was purified by chromatography

on a silica gel (Merck Kieselgel 60) column using a 13:7 v/v mixture of ethyl acetate and toluene as eluant. There was thus obtained N-n-butyl-11-(3,17β-dihydroxyoestra-1,3,5(10)trien-7α-yl)undecanamide as an oil which was characterised by the following data:-

Proton magnetic resonance spectrum (in $CDCl_3$)

Shift (δ)	Type of peak	No of protons	Assignment
7.16	multiplet	1	) aromatic) protons at) positions) 1, 2 and 4
6.65	"	2	
3.7		1	position 17
3.28	quartet	2	$-CH_2-$ adjacent to $-CO-$
0.90	triplet	3	$-CH_3$ in n-butyl
0.78	singlet	3	position 18

Mass Spectrum

$M^+ = 511.4039$ ($C_{33}H_{53}O_3N$ requires 511.4024)

$M - H_2O = 493$

$M - (CH_2CONHC_4H_9) = 397$

Thin layer chromatography (silica gel plates using a 7.3 v/v mixture of ethyl acetate and toluene)

$R_F = 0.3$

The 11-(17β-acetoxy-3-benzoyloxyoestra-1,3,5(10)-trien-7α-yl)-undecanoic acid used as starting material was obtained as follows:-

A solution of dimethyl-t-butylsilyl chloride (37.3 g.) in tetrahydrofuran (40 ml.) was added to a solution of 11-bromoundecanol (50.18 g.) and imidazole (28.95 g.) in tetrahydrofuran (120 ml.) and the mixture was kept at laboratory temperature for 1.75 hours, diluted with diethyl ether (300 ml.) and filtered. The filtrate was evaporated to dryness and the residue purified by chromatography on silica gel using a 4:1 v/v mixture of petroleum ether (b.p. 60-80°C.) and toluene as eluant.

A solution of the 11-(dimethyl-t-butylsilyloxy)undecyl bromide thus obtained (73.1 g.) in tetrahydrofuran (200 ml.) was added during 2 hours to a stirred suspension of magnesium turnings (4.8 g.) in tetrahydrofuran (20 ml.) under normal conditions for preparation of a Grignard reagent, and the mixture was heated under reflux for 2 hours, diluted with tetrahydrofuran (100 ml.) and cooled to -30°C. Cuprous iodide (19.05 g., dried at 100°C. immediately before use) was added, the mixture was vigorously stirred for 10 minutes and a solution of 6-dehyro-19-nortestosterone acetate (15.48 g.) in tetrahydrofuran (50 ml.) was added. The mixture was stirred for 40 minutes, acetic acid (12 ml.) was added and the mixture was evaporated to dryness. Water (150 ml.) was added to the residue, and the mixture was extracted four times with diethyl ether (300 ml. each time). The combined extracts were washed with water (50 ml.), dried and evaporated to dryness, and the residue was purified by chromatography on a silica gel column using a 24:1 v/v mixture of toluene and ethyl acetate as eluant.

A mixture of 17β-acetoxy-7α-[11-(dimethyl-t-butylsilyloxy)undecyl]oestr-4-ene-3-one thus obtained (11.2 g.), acetic acid (62 ml.), water (31 ml.) and tetrahydrofuran (56 ml.) was stirred at 50°C. for 2.75 hours and was then evaporated to dryness. A solution of the residue in pyridine (56 ml.) and acetic anhydride (28 ml.) was kept at laboratory temperature for 18 hours, cooled to 0°C., water (10 ml.) was added and the mixture was stirred for 45 minutes and then evaporated to dryness. The residue was dissolved in diethyl ether (400 ml.) and the solution was washed with saturated aqueous sodium bicarbonate solution (20 ml.) and then with water (20 ml.), dried and evaporated to dryness.

A solution of the 17β-acetoxy-7α-(11-acetoxyundecyl)oestr-4-ene-3-one thus obtained (8.98 g.) in acetonitrile (50 ml.) was added rapidly to a vigorously stirred suspension of cupric bromide (7.75 g.) and lithium bromide (1.52 g.) in acetonitrile (120 ml.) which was heated under reflux under an atmosphere of argon, and the mixture was stirred and heated for 30 minutes and then cooled. Saturated aqueous sodium bicarbonate solution (200 ml.) was added and the mixture was extracted four times with ethyl acetate (200 ml. each time). The combined extracts were washed with water (50 ml.), dried and evaporated to dryness, and the residue was purified by chromatography on a silica gel column using a 9:1 v/v mixture of toluene and ethyl acetate as eluant.

Aqueous N-sodium hydroxide solution (8 ml.) was added to a stirred solution of the 17β-acetoxy-7α-(11-acetoxyundecyl)oestra-1,3,5(10)-trien-3-ol thus obtained (2.8 g.) in methanol (54 ml.) and the mixture was stirred at laboratory temperature for 70 minutes, neutralised with aqueous N-hydrochloric acid and the methanol was removed by evaporation. The residue was extracted four times with ethyl acetate (60 ml. each time) and the combined extracts

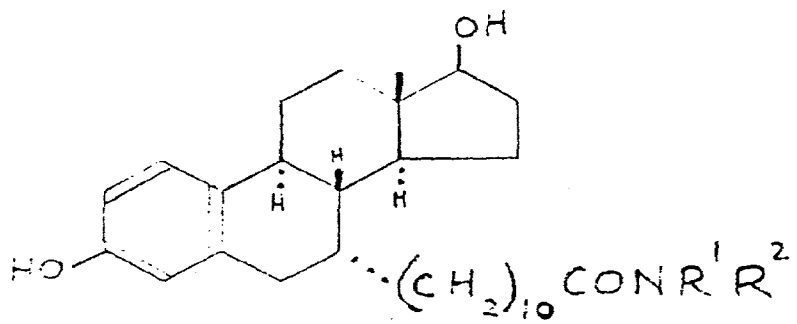
were washed with water (20 ml.), dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 7:3 v/v mixture of toluene and ethyl acetate as eluant.

Aqueous N-sodium hydroxide solution (6 ml.) and benzoyl chloride (0.93 ml.) were added to a stirred solution of the 17β-acetoxy-7α-(11-hydroxy-undecyl)oestra-1,3,5(10)-trien-3-ol thus obtained (1.94 g.) in acetone (20 ml.) which was cooled to 0°C., and the mixture was stirred for 20 minutes and then poured into a mixture of ice-water (200 ml.) and saturated aqueous sodium bicarbonate solution (50 ml.). The mixture was extracted four times with diethyl ether (120 ml. each time) and the combined extracts were washed twice with saturated aqueous sodium bicarbonate solution (15 ml. each time) and then with water (20 ml.), dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 7:3 v/v mixture of toluene and ethyl acetate as eluant.

Jones's reagent (8N-chromic acid solution, 2.3 ml.) was added to a solution of the 17β-acetoxy-3-benzoyloxy-7α-(11-hydroxyundecyl)oestra-1,3,5(10)-triene thus obtained (2.17 g.) in acetone (37 ml.) which was cooled to 0°C. After 15 minutes isopropanol (0.5 ml.) was added and the mixture was evaporated to dryness. Water (40 ml.) was added and the mixture was extracted three times with methylene chloride (60 ml. each time). The combined extracts were washed twice with water (10 ml. each time), dried and evaporated to dryness, and the residue was purified by chromatography on a silica gel column using a 7:3 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained 11-(17β-acetoxy-3-benzoyloxyoestra-1,3,5(10)-trien-7α-yl)-undecanoic acid.

Example 2

The process described in Example 1 was repeated using the appropriate amine in place of n-butylamine. There were thus obtained the compounds described in the following table, all of which were oils the structures of which were confirmed by proton magnetic resonance and mass spectroscopy:-



R^1	R^2	
H	H	*
ethyl	H	
n-propyl	H	
isopropyl	H	+
isobutyl	H	+
t-butyl	H	
3-methylbutyl	H	+
1-methylbutyl	H	
2-methylbutyl	H	+
2,2-dimethylpropyl	H	
n-hexyl	H	
1,1-dimethylbutyl	H	+
1,3-dimethylbutyl	H	
cyclohexyl	H	
2,2,2-trifluoroethyl	H	
2,2,3,3,4,4,4-heptafluorobutyl	H	+
2,2-difluorobutyl	H	
3-chloropropyl	H	

R^1	R^2	
phenyl	H	
4-methoxyphenyl	H	
4-chlorophenyl	H	+
4-cyanophenyl	H	
2-ethylphenyl	H	
benzyl	H	
1-phenylethyl	H	
5-carboxypentyl	H	**
3-dimethylaminopropyl	H	
n-butyl	methyl	
2,2-dimethylpropyl	methyl	
2-methylbutyl	methyl	
n-hexyl	methyl	
2,2,3,3,3-pentafluoropropyl	methyl	
2,2-difluorobutyl	methyl	
4,4,4-trifluorobutyl	methyl	
2,2,3,3,4,4,4-heptafluorobutyl	methyl	+
benzyl	methyl	
n-butyl	ethyl	
n-butyl	n-butyl	
2,2,2-trifluoroethyl	n-butyl	
$-(CH_2)_5-$		
$-(CH_2)_2-N(CH_3)-(CH_2)_2-$		
$-(CH_2)_2CH(CH_3)(CH_2)_2-$		+
$-CH_2CH(CH_3)(CH_2)_3-$		+
$-(CH_2)_2CHCl(CH_2)_2-$		
$-(CH_2)_2CH(C_2H_5)(CH_2)_2-$		
$-(CH_2)_3C(CH_3)_2-CH_2-$		

* A solution of ammonia in tetrahydrofuran was used as starting material.

** Methyl 6-aminohexanoate was used as starting material, the methyl ester being hydrolysed during the second stage of the process.

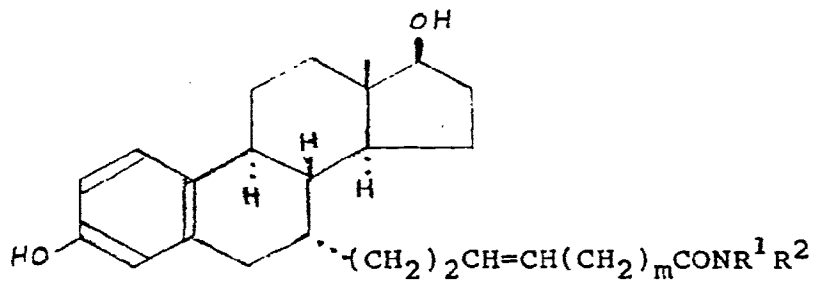
In some cases (indicated + in the above table) the undecanoic acid used as starting material was the 3-hydroxy- rather than the 3-benzoyloxy-compound, which was prepared by a shortened route as follows:-

The 17β-acetoxy-7α-(11-acetoxyundecyl)oestr-4-ene-3-one, prepared as described in the 5th paragraph of Example 1, was hydrolysed to the corresponding 11-hydroxyundecyl compound as described in the 7th paragraph of Example 1, and this product was purified by chromatography on a silica gel column using a 3:2 v/v mixture of toluene and ethyl acetate as eluant. It was then oxidised to the corresponding undecanoic acid as described in the 9th paragraph of Example 1, and this product was purified by chromatography on a silica gel column using a 19:1 v/v mixture of methylene chloride and methanol as eluant. The undecanoic acid was aromatised as described in the 6th paragraph of Example 1, except that the pH of the reaction mixture was adjusted to 3 before extraction into ethyl acetate. The product was purified by chromatography on a silica gel column using a 3:1 v/v mixture of diethyl ether and petroleum ether (b.p. 60-80°C.) as eluant. There was thus obtained, as an oil, 11-(17β-acetoxy-3-hydroxyoestra-1,3,5(10)-trien-7α-yl)undecanoic acid.

Example 3

The process described in Example 1 was repeated except that the appropriate (17β-acetoxy-3-hydroxy-oestra-1,3,5-(10)trien-7α-yl)alkenoic acid and the appropriate amine were used as starting materials. There were thus obtained the compounds described in the following table,

all of which were oils the structures of which were confirmed by proton magnetic resonance and mass spectroscopy:-



m	R^1	R^2
3	n-butyl	H
3	n-heptyl	H
3	n-heptyl	methyl
5	n-butyl	H
5	n-pentyl	H
8	ethyl	H
8	n-butyl	H
10	methyl	methyl

The initial compounds obtained are (17β-acetoxy-3-isobutyloxycarbonyloestra-1,3,5(10)-trien-7α-yl)-alkenamides, the hydroxy group at the 3-position being converted into the carbonate during the first stage of the amide-forming reaction by the isobutyl chloroformate.

The alkenoic acids used as starting materials were prepared by a process exemplified by the following preparation of 8-(17β-acetoxy-3-hydroxy-oestra-1,3,5(10)-trien-7α-yl)octa-5-enoic acid:-

The process described in the first paragraph of Example 1 relating to the preparation of starting

materials was repeated except that dimethyl-t-butylsilyl chloride was reacted with 3-bromopropanol instead of 11-bromoundecanol. The Grignard reagent from this was reacted with 6-dehydro-19-nortestosterone, and the sequence of reactions described in the succeeding five paragraphs of Example 1 was repeated. There was thus obtained 17β-acetoxy-3-benzoyloxy-7α-(3-hydroxypropyl)-oestra-1,3,5(10)-triene.

Pyridinium chlorochromate (0.427 g.) was added to a stirred solution of this oestratriene (0.629 g.) in methylene chloride (13 m.) and the mixture was stirred for 2 hours, diluted with diethyl ether (50 ml.) and filtered through a filter-aid. The filtrate was evaporated to dryness and the residue was purified by chromatography on a silica gel column using a 19:1 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained 3-(17β-acetoxy-3-benzoyloxyoestra-1,3,5(10)-trien-7α-yl)propionaldehyde.

Finely powdered (4-carboxybutyl)triphenylphosphonium bromide (1.4 g.) was degassed by heating in vacuo at 100°C. for 1 hour and was then dissolved in dimethyl-sulphoxide (5 ml.) under an atmosphere of a nitrogen. A 2-molar solution of methanesulphinylmethyl sodium in dimethyl sulphoxide (3.8 ml.) was added dropwise, and a solution of the above aldehyde (0.25 g.) in toluene (2 ml.) was then added. The mixture was stirred for 1 hour and then evaporated to dryness under reduced pressure at a temperature not exceeding 40°C. The residue was shaken with water (5 ml.) and diethyl ether (10 ml.) and the aqueous solution was separated, acidified to pH 3.5 with aqueous 2N-oxalic acid solution and extracted four times with ethyl acetate (10 ml. each time). The combined extracts were washed with water, dried and evaporated to dryness and the residue was purified by chromatography on a silica gel column using a

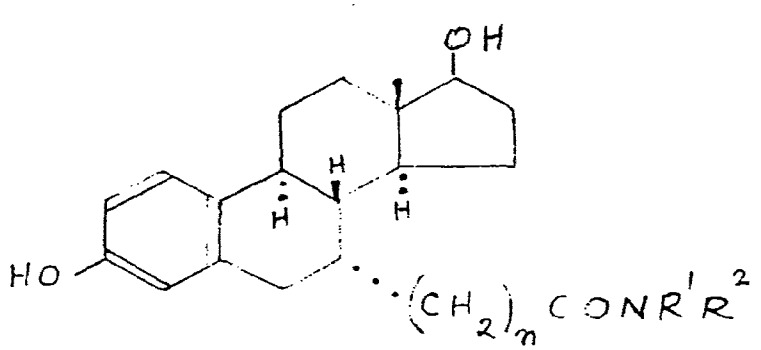
1:1 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained 8-(17β-acetoxy-3-hydroxyoestra-1,3,5-(10)-trien-7α-yl)octa-5-enoic acid.

The corresponding deca-7-enoic, trideca-10-enoic and pentadeca-12-enoic acids were obtained by using (6-carboxyhexyl)- , (9-carboxynonyl)- or (11-carboxyundecyl)-triphenylphosphonium bromide in place of (4-carboxybutyl)-triphenylphosphonium bromide.

Example 4

5% Palladium-on-charcoal catalyst (0.025 g.) was added to a solution of N-n-butyl-8-(3,17β-dihydroxy-oestra-1,3,5(10)-trien-7α-yl)oct-5-enamide (Example 3; 0.05 g.) in ethyl acetate (2.5 ml.) and the mixture was stirred at laboratory temperature under an atmosphere of hydrogen for 1 hour and then filtered. The filtrate was evaporated to dryness and there was thus obtained as oily residue N-n-butyl-8-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)octanamide, the structure of which was confirmed by spectroscopic means.

The process described above was repeated using the appropriate alkenamide described in Example 3 and there were thus obtained as oils the compounds described in the following table, the structures of all of which were confirmed by spectroscopic means;

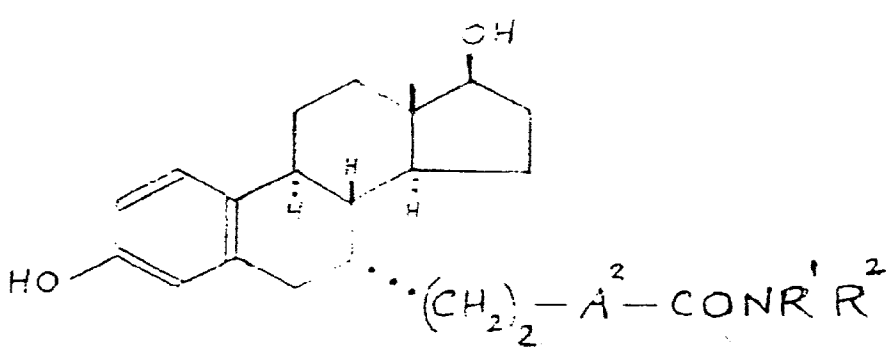


n	R^1	R^2
7	n-heptyl	H
7	n-heptyl	methyl
9	n-butyl	H
9	n-pentyl	H
12	ethyl	H
12	n-butyl	H
14	methyl	methyl

Example 5

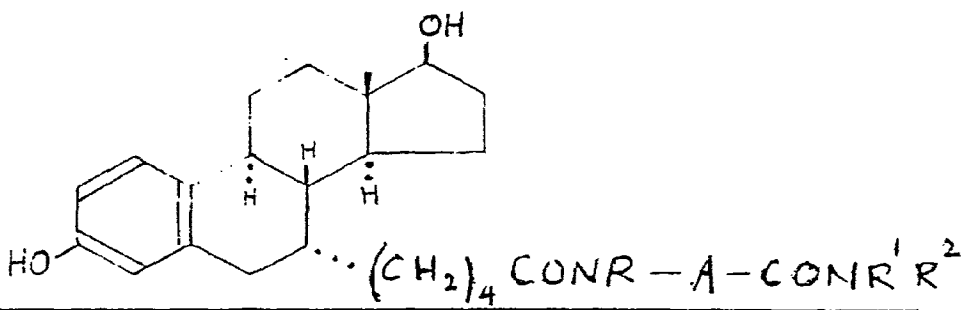
The process described in Example 1 was repeated except that either 3, 17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)pent-2-enoic acid or 3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)pentanoic acid, and the appropriate amine, were used as starting materials. There were thus obtained as oils the compounds described in the following tables, the structures of which were confirmed by proton magnetic resonace and mass spectoscopy.

TABLE I



A^2	R^1	R^2
$-CH_2CH_2-$	n-decyl	H
$-CH_2CH_2-$	n-decyl	methyl
-CH=CH-	n-decyl	H

TABLE 2



R	A	R^1	R^2
H	CH_2	n-heptyl	H
H	$(CH_2)_2$	n-hexyl	H
H	$(CH_2)_3$	n-hexyl	H
methyl	$(CH_2)_3$	n-hexyl	H
methyl	$(CH_2)_3$	n-hexyl	methyl

The pentenoic and pentanoic acids used as starting materials were obtained as follows:-

Sodium hydride (0.069 g.) was added to a stirred solution of triethylphosphonoacetate (0.413 g.) in tetrahydrofuran (10 ml.) which was maintained at 0°C., and the mixture was stirred at that temperature for 1 hour. A solution of 3-(17β-acetoxy-3-benzoyloxyoestra-1,3,5(10)-trien-7α-yl)propionaldehyde (Example 3, second paragraph relating to preparation of starting materials, 0.25 g.) in tetrahydrofuran (5 ml.)

was added and the mixture was stirred at laboratory temperature for 30 minutes, neutralised with acetic acid and evaporated to dryness. The residue was shaken with water (15 ml.), the mixture was extracted three times with ethyl acetate (30 ml. each time) and the combined extracts were washed with water, dried and evaporated to dryness. There was thus obtained as residue ethyl 5-(17β-acetoxy-3-benzoyloxy-oestra-1,3,5(10-trien-7α-yl)pent-2-enoate. Part of this was hydrolysed to the corresponding pent-2-enoic acid with aqueous sodium hydroxide solution for use as one starting material, and part of it was hydrogenated by a similar process to that described in Example 4, and the ethyl 5-(17β-acetoxy-3-benzoyloxyoestra-1,3,5-(10)-trien-7α-yl)pentanoate thus obtained was hydrolysed to the corresponding dihydroxypentanoic acid with aqueous sodium hydroxide solution for use as the other starting material.

The amidoalkylamines used as starting materials for the compounds described in Table 2 were obtained as follows:-

N-n-Hexyl-4-methylaminobutyramide

A solution of 1-methylpyrrolidin-2-one (5 g.) in aqueous 6N-sodium hydroxide solution (50 ml.) containing methanol (0.1 ml.) was heated under reflux for 3 hours, cooled to 0°C. and benzyl chloroformate (9.5 g.) was added dropwise. The mixture was kept at 0°C. for 12 hours and then poured onto a mixture of equal volumes of ice and concentrated aqueous hydrochloric acid. The mixture was extracted with ethyl acetate and the extract was washed with water, dried and evaporated to dryness.

Triethylamine (3.7 ml.) and ethyl chloroformate (2.5 ml.) were successively added to a stirred solution of the 4-(N-benzyloxycarbonyl-N-methylamino)butyric acid thus obtained (6.0 g.) in ethyl

acetate (100 ml.) which was cooled to -20°C., and the mixture was stirred at that temperature for 15 minutes. A solution of n-hexylamine (3.2 ml.) in ethyl acetate (30 ml.) was added and the mixture was allowed to warm up to laboratory temperature and stirred at that temperature for 16 hours, then washed successively with dilute aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried and evaporated to dryness.

A solution of the 4-(N-benzyloxycarbonyl-N-methylamino)-N-n-hexylbutyramide thus obtained (6.6 g.) in ethanol (100 ml.) was shaken with hydrogen in the presence of a 10% palladium-on-charcoal catalyst (0.6 g.) for 18 hours, filtered and evaporated to dryness. There was thus obtained as residual oil N-n-hexyl-4-methylaminobutyramide.

N-n-Hexyl-N-methyl-4-methylaminobutyramide

As above but using N-n-hexyl-N-methylamine in place of n-hexylamine.

Glycine N-n-heptylamide

As above from glycine and benzyl chloroformate (N-benzyloxycarbonylglycine has m.p. 119-121°C.), then triethylamine, ethyl chloroformate and n-heptylamine.

β-Alanine N-n-hexylamide

As above using β-alanine in place of glycine and n-hexylamine in place of n-heptylamine.

N-n-hexyl-4-aminobutyramide

As above using 4-aminobutyric acid in place of glycine and n-hexylamine in place of n-heptylamine.

Example 6

N-Methylmorpholine (0.028 ml.) and isobutyl chloroformate (0.038 ml.) were successively added to a stirred solution of 11-(3-benzyloxy-17β-hydroxyoestra-1,3,5(10)-trien-7α-yl)undec-10-enoic acid (0.109 g.) in tetrahydrofuran (3 ml.) which was cooled to -10°C. The

mixture was stirred at -10°C. for 30 minutes, N-methyl-isobutylamine (0.05 ml.) was added and the mixture was stirred at laboratory temperature for 2 hours. Saturated aqueous sodium bicarbonate solution (5 ml.) was added and the mixture was extracted 3 times with methylene chloride (10 ml. each time). The combined extracts were washed with water (2 ml.), dried and evaporated to dryness, and there was thus obtained as oily residue N-isobutyl-N-methyl-11-(3-benzyloxy-17β-hydroxyoestra-1,3,5(10)-trien-7α-yl)undec-10-enamide.

A 10% palladium-on-charcoal catalyst (0.03g.) was added to a solution of the above compound (0.105 g.) in ethyl acetate (10 ml.) and the mixture was stirred at laboratory temperature under an atmosphere of hydrogen for 5 hours, and then filtered. The filtrate was evaporated to dryness and there was thus obtained as oily residue N-isobutyl-N-methyl-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide, the structure of which was confirmed by proton magnetic resonance spectroscopy and elemental analysis.

The undecenoic acid used as starting material was obtained as follows:-

Diethyl aluminium cyanide (100 ml. of a 1.2 molar solution in toluene) was added to a stirred solution of 6-dehydro-19-nortestosterone acetate (9 g.) in tetrahydrofuran (400 ml.) and the mixture was stirred at laboratory temperature for 1 hour and then poured into a mixture of ice (1000 ml.) and aqueous 2N-sodium hydroxide solution (500 m.). The mixture was extracted 3 times with methylene chloride (300 ml. each time) and the combined extracts were washed with water (100 ml.), dried and evaporated to dryness. The residue was stirred with petroleum ether (b.p. 40-60°C.; 100 ml.) and there was thus obtained 17β-acetoxy-7α-cyano-oestr-4-ene-3-one, m.p. 183-186°C.

A solution of the above compound (3.38 g.) in acetonitrile (15 ml.) was added rapidly to a vigorously stirred suspension of cupric bromide (4.46 g.) and lithium bromide (0.85 g.) in acetonitrile (30 ml.) which was heated under reflux under an atmosphere of argon. The mixture was stirred and heated under reflux for 10 minutes and then cooled, and saturated aqueous sodium bicarbonate solution (50 ml.) was added. The mixture was extracted 3 times with ethyl acetate (50 ml. each time) and the combined extracts were washed with water (20 ml.), dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 17:3 v/v mixture of toluene and ethyl acetate as eluant, and there was thus obtained 17β-acetoxy-7α-cyanooestra-1,3,5(10)-trien-3-ol. Early fractions eluted from the column contained 17β-acetoxy-6-bromo-7α-cyano-oestra-1,3,5(10)-trien-3-ol which was used in Example 22.

A stirred mixture of the above compound (0.69 g.), benzyl bromide (0.29 ml.), potassium carbonate (0.325 g.) and acetone (20 ml.) was heated under reflux for 16 hours, cooled and filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 9:1 v/v mixture of toluene and ethyl acetate as eluant, and there was thus obtained 17β-acetoxy-3-benzyloxy-7α-cyano-oestra-1,3,5(10)-triene.

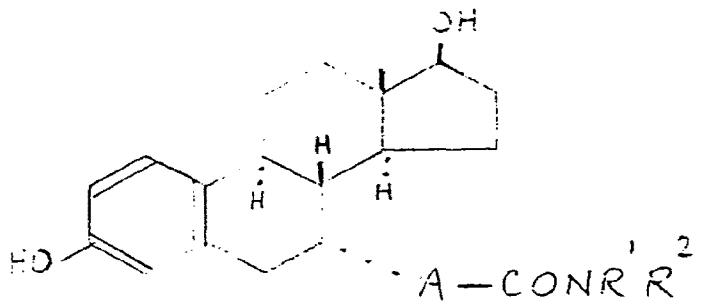
Diisobutyl aluminium hydride (3.1 ml. of a 1.5 molar solution in toluene) was added to a stirred solution of the above compound (0.68 g.) in toluene (10 ml.) and the mixture was stirred at laboratory temperature for 150 minutes. Methanol (2 ml.) and then aqueous 2N-hydrochloric acid (5 ml.) were added and the mixture was stirred for 15 minutes and then extracted three times with ethyl acetate (10 ml. each time). The combined extracts were washed with water (5 ml.), dried

and evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 4:1 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained 3-benzyloxy-17β-hydroxyoestra-1,3,5(10)-triene-7α-carboxaldehyde.

Dimsyl sodium (4 ml. of a 2-molar solution in dimethyl sulphoxide) was added dropwise to a solution of finely powdered (9-carboxynonyl)triphenylphosphonium bromide (1.94 g.) in dimethyl sulphoxide (10 ml.) which was maintained under an atmosphere of nitrogen, and a solution of the above aldehyde (0.3 g.) in a mixture of toluene (2 ml.) and dimethyl sulphoxide (2 ml.) was then added. The mixture was stirred at laboratory temperature for 1 hour and then evaporated to dryness under reduced pressure, and the residue was shaken with water (5 ml.) and diethyl ether (5 ml.). The aqueous solution was separated, acidified to pH 3 with aqueous 2N-oxalic acid solution and extracted three times with diethyl ether (10 ml. each time). The combined extracts were washed with water, dried and evaporated to dryness and the residue was purified by chromatography on a silica gel column using an 11:9 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained 11-(3-benzyloxy-17β-hydroxyoestra-1,3,5(10)-trien-7α-yl)undec-10-enoic acid.

Example 7

The process described in Example 6 was repeated using the appropriate ω-(3-benzyloxy-17β-hydroxyoestra-1,3,5(10-trien-7α-yl)alkenoic acid and the appropriate amine as starting materials. There were thus obtained the compounds described in the following table, all of which were oils the structures of which were confirmed by proton magnetic resonance and mass spectroscopy:-



A	R^1	R^2
$-(CH_2)_{11}-$	n-propyl	H
$-(CH_2)_{11}-$	n-butyl	methyl
$-(CH_2)_{11}-$	1-methylbutyl	methyl
$-(CH_2)_{10}-$	cyclopentyl	H
$-(CH_2)_{10}-$	1H,1H,heptafluorobutyl	methyl
$-(CH_2)_9-$	n-hexyl	methyl
$-(CH_2)_8-$	n-butyl	methyl
$-(CH_2)_8CH(CH_3)-$	n-heptyl	H
$-(CH_2)_6CH(CH_3)-$	$-CH_2(CF_2)_5CF_3$	H
$-(CH_2)_7-$	n-butyl	methyl*
$-(CH_2)_8CHFCH_2-$		

* In the starting material -A- is $-CH=CH-(CH_2)_6-CF=CH-$.

The steroidal starting materials were prepared as described in the second part of Example 6 except that the appropriate (ω-carboxyalkyl)triphenylphosphonium bromide was used as intermediate. The starting material for the last-mentioned compound, marked with an asterisk*, is unusual in that during the reaction of the steroidal-7α-carboxaldehyde with (9-carboxy-8,8-difluorononyl)triphenylphosphonium bromide a molecule of hydrogen fluoride is eliminated and the starting material is the steroidal-7α-yl-3-fluoroundeca-2,10-dienoic acid.

The (9-carboxy-8,8-difluorononyl)triphenylphosphonium bromide used as intermediate was obtained as follows:-

A solution of 8-bromooctanoyl chloride (1.2 g.) in methylene chloride (5 ml.) was added to a stirred solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (0.72 g.) and pyridine (0.8 ml.) in methylene chloride (20 ml.) which was kept at 5°C., and the mixture was stirred at that temperature for 1 hour and then at laboratory temperature for 90 minutes, washed successively with aqueous N-hydrochloric acid (20 ml.) and water (20 ml.), dried and evaporated to dryness. The residue was heated under reflux with methanol (20 ml.) for 16 hours, the excess of methanol was removed by evaporation and the residue was distilled under reduced pressure. There was thus obtained methyl 10-bromo-3-oxodecanoate, b.p. 135-144°C./1 mm.Hg.

A mixture of the above ester (4.4 g.) and sulphur tetrafluoride (10 g.) was heated at 60°C. for 6 hours in a sealed bomb (Hastelloy C) and the resulting tar was extracted with methylene chloride (150 ml.). The extract was washed with saturated aqueous sodium carbonate solution (50 ml.) and then with water (20 ml.), dried and evaporated to dryness. The residue was distilled under reduced pressure and there was thus obtained methyl 10-bromo-3,3-difluorodecanoate, b.p. 175°C./0.2 mm.Hg.

A mixture of the above ester (1.1 g.), acetic acid (1 ml.) and 48% aqueous hydrobromic acid (1 ml.) was heated under reflux for 2 hours and then poured into ice-water (20 ml.). The mixture was extracted three times with ethyl acetate (10 ml. each time) and the combined extracts were washed with water, dried and evaporated to dryness. The residue was distilled under reduced pressure and there was thus obtained 10-bromo-3,3-difluorodecanoic acid, b.p. 200°C./0.15 mm.Hg.

Triphenylphosphine (0.565 g.) was added to a solution of the above acid (0.61 g.) in acetonitrile (5 ml.) and the mixture ws heated under reflux for 18 hours and then evaporated to dryness. There was thus obtained as residual oil (9-carboxy-8,8-difluorononyl)-triphenylphosphonium bromide which was used without further purification.

Example 8

N-Methylmorpholine (0.107 ml.) and isobutyl chloroformate (0.133 ml.) were successively added to a stirred solution of p-[4-(17β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-7α-yl)but-1-enyl]cinnamic acid (0.17 g.) in methylene chloride (10 ml.) which was cooled to -30°C. under an atmosphere of argon, and the mixture was allowed to warm up to laboratory temperature. n-Hexylamine (0.06 ml.) was added, the mixture was stirred at laboratory temperature for 30 minutes, aqueous 2N-hydrochloric acid (10 ml.) was added and the mixture was extracted three times with diethyl ether (20 ml. each time). The combined extracts were washed with water, dried over magnesium sulphate and evaporated to dryness under reduced pressure. There was thus obtained, as an oil, N-n-hexyl-p-[4-(17β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-7α-yl)but-1-enyl]cinnamide, the structure of which was confirmed by proton magnetic resonance spectroscopy and mass spectroscopy.

Boron tribromide (0.5 ml.) was added to a stirred solution of the above amide (0.12 g.) in methylene chloride (10 ml.) which was cooled to -78°C. under an atmosphere of argon, and the mixture was allowed to warm up to -10°C. and was kept at that temperature for 4 hours. Saturated aqueous sodium bicarbonate solution (10 ml.) was added, the mixture was extracted three times with methylene chloride (15 ml. each time) and the combined extracts were washed with

water, dried over magnesium sulphate and evaporated to dryness. There was thus obtained, as an oil, p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)but-1-enyl]-N-n-hexyl-cinnamide, the structure of which was confirmed by nuclear magnetic resonance and mass spectroscopy.

The cinnamic acid used as starting material was obtained as follows:-

The process described in the first paragraph of Example 1 relating to the preparation of starting materials was repeated except that dimethyl-t-butylsilyl chloride was reacted with 3-bromopropanol instead of 11-bromoundecanol. The Grignard reagent from this was reacted with 6-dehydro-19-nortestosterone, and the sequence of reactions described in the succeeding two paragraphs of Example 1 was repeated. There was thus obtained 17β-acetoxy-7α-(3-acetoxypropyl)-oestra-1,3,5(10)-trien-3-ol.

Methyl iodide (6 ml.) and potassium carbonate (6g.) were added to a stirred solution of the above diacetate (5 g.) in acetone (80 ml.), and the mixture was stirred and heated under reflux for 16 hours, cooled and filtered and the filtrate was evaporated to dryness. A solution of the residual 17β-acetoxy-7α-(3-acetoxypropyl)-3-methoxyoestra-1,3,5(10)-triene (4.7 g.) in methanol (50 ml.) was cooled to 0°C., potassium carbonate (2.5 g.) was added and the mixture was stirred at 0°C. for 3 hours and then filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on a silica gel column (Merck 9385) using a 4:1 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained 17β-acetoxy-7α-(3-hydroxypropyl)-3-methoxyoestra-1,3,5(10)-triene as an oil.

Pyridinium chlorochromate (3.6 g.) was added to a stirred solution of this oestratriene (3.2 g.) in

methylene chloride (100 ml.) and the mixture was stirred for 2 hours and then filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on a silica gel column (Merck 9385) using a 9:1 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained 3-(17β-acetoxy-3-methoxyoestra-1,3,5(10)-trien-7α-yl)propionaldehyde.

n-Butyl-lithium (0.67 ml. of a 1.5 molar solution in hexane) was added to a stirred solution of diisopropylamine (0.14 ml.) in tetrahydrofuran (30 ml.) which was cooled to 0°C. under an atmosphere of argon. After 10 minutes the mixture was cooled to -78°C. and a solution of ethyl p-(diethylphosphonylmethyl)cinnamate (0.33 g.; b.p. 175°C./15 mm.Hg.; prepared by heating ethyl p-bromomethylcinnamate with triethylphosphite at 120°C. for 2 hours) in tetrahydrofuran (2 ml.) was added dropwise. A solution of the above propionaldehyde (0.19 g.) in tetrahydrofuran (1 ml.) was added and the mixture was allowed to warm up to laboratory temperature and was stirred at that temperature for 16 hours. Aqueous 2N-hydrochloric acid was added and the mixture was extracted three times with diethyl ether (15 ml. each time). The combined extracts were washed with water (20 ml.) and then with saturated aqueous sodium chloride solution (20 ml.), dried over magnesium sulphate and evaporated to dryness. The residue was purified by chromatography on a silica gel column (Merck 9385) using a 17:3 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained ethyl p-[4-(17β-acetoxy-3-methoxyoestra-1,3,5(10)-trien-7α-yl)but-1-enyl]cinnamate.

Aqueous 2N-sodium hydroxide solution (1 ml.) was added to a stirred solution of the above cinnamate (0.2 g.) in a mixture of methanol (1 ml.) and tetrahydrofuran (1 ml.), and the mixture was stirred at

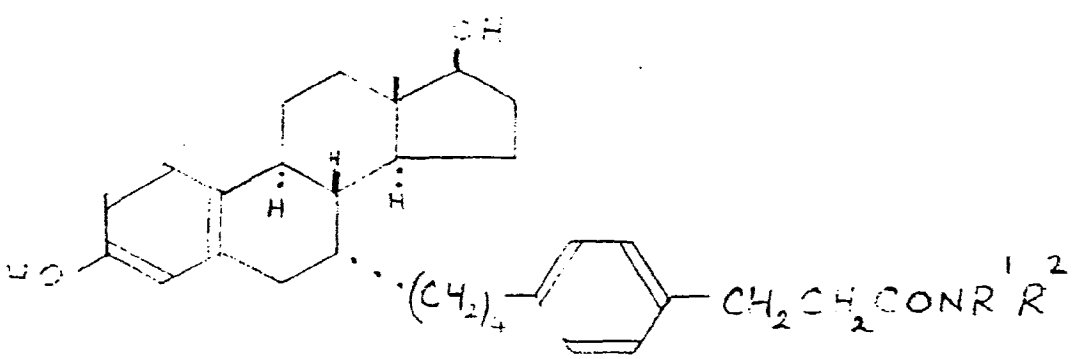
laboratory temperature for 3 hours, acidified with aqueous 2N-hydrochloric acid (2 ml.) and extracted three times with ethyl acetate (10 ml. each time). The combined extracts were washed with water, dried over magnesium sulphate and evaporated to dryness. There was thus obtained as residual gum p-[4-(17β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-7α-yl)but-1-enyl]cinnamic acid.

Example 9

A solution of p-[4-(4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)but-1-enyl]-N-n-hexylcinnamide (Example 8; 0.05 g.) in a mixture of ethyl acetate (10 ml.) and ethanol (2 ml.) was stirred with a 20% palladium-on-charcoal catalyst (0.01 g.) under an atmosphere of hydrogen at laboratory temperature and atmospheric pressure for 2 hours, and the mixture was then filtered and evaporated to dryness. There was thus obtained 3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)butyl]phenyl-N-n-hexylpropionamide, the structure of which was confined by proton magnetic resonance and mass spectroscopy.

Example 10

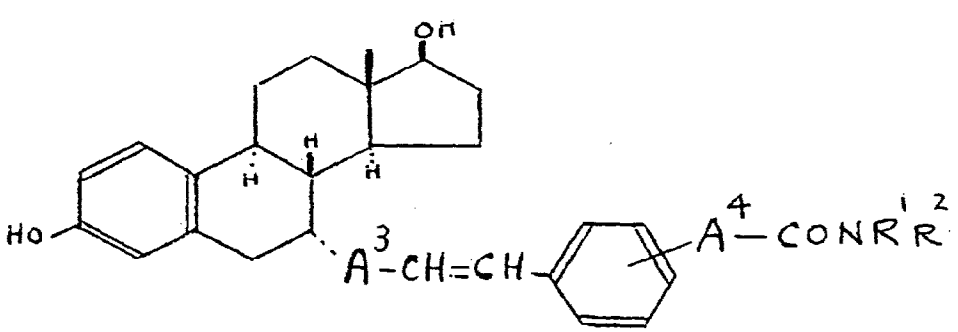
The processes described in Examples 8 and 9 were repeated using the appropriate amine in place of n-hexylamine as starting material in Example 8. There were thus obtained the compounds described in the following table, all of which were oils the structures of which were confirmed by proton magnetic resonance and mass spectroscopy:-



R^1	R^2
n-butyl	H
n-butyl	methyl
n-pentyl	H
n-hexyl	methyl
$-CH_2CF_2CF_2CF_3$	H
$-CH_2CF_2Cl$	H

Example 11

The process described in Example 8 was repeated using the appropriate amine and the appropriate ω-(17β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-7α-yl)alk-1-enylcinnamic acid or benzoic acid as starting materials. There were thus obtained the compounds described in the following table, all of which were oils the structures of which were confirmed by proton magnetic resonance and mass spectroscopy:-

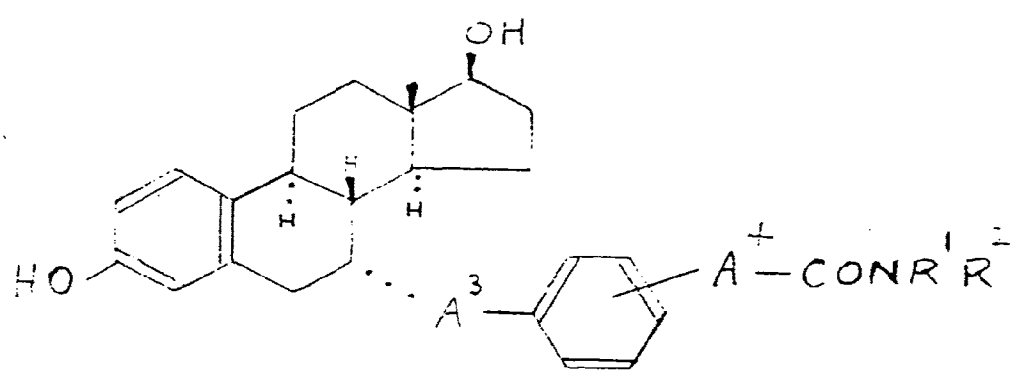


A^3	Position in benzene ring	A^4	R^1	R^2
$-(CH_2)_2-$	meta	-	n-hexyl	H
$-(CH_2)_2-$	meta	-CH=CH-	n-hexyl	H
$-(CH_2)_4-$	para	-CH=CH-	n-butyl	H
$-(CH_2)_4-$	para	-CH=CH-	n-butyl	methyl
$-(CH_2)_4-$	para	-	n-pentyl	H
$-(CH_2)_4-$	para	-	n-hexyl	H
$-(CH_2)_4-$	ortho	-	n-hexyl	H

The steroidal starting material wherein A^3 is $-(CH_2)_4-$ was prepared by a similar process to that described in Example 8 except that in the third paragraph thereof 5-bromopentanol was used in place of 3-bromopropanol. The phosphonate intermediates were prepared from the appropriate ethyl bromomethylcinnamate or ethyl bromomethylbenzoate and triethylphosphite.

Example 12

The hydrogenation described in Example 9 was repeated using the appropriate unsaturated compound, described in Example 11, as starting material. There were thus obtained the compounds described in the following table, all of which were oils the structures of which were confirmed by proton magnetic resonance and mass spectroscopy:-



A^3	Position in benzene ring	A^4	R^1	R^2
$-(CH_2)_4-$	meta	-	n-hexyl	H
$-(CH_2)_4-$	meta	$-CH_2CH_2-$	n-hexyl	H
$-(CH_2)_6-$	para	$-CH_2CH_2-$	n-butyl	H
$-(CH_2)_6-$	para	$-CH_2CH_2-$	n-butyl	methyl
$-(CH_2)_6-$	para	-	n-pentyl	H
$-(CH_2)_6-$	para	-	n-hexyl	H
$-(CH_2)_6-$	ortho	-	n-hexyl	H

Example 13

The process described in Example 8 was repeated using p-[2-(3-benzyloxy-17β-hydroxyoestra-1,3,5(10)-trien-7α-yl)ethenyl]cinnamic acid and n-octylamine as starting materials. There was thus obtained, as an oil p-[2-(3-benzyloxy-17β-hydroxyoestra-1,3,5(10)-trien-7α-yl)ethenyl]-N-n-octylcinnamide.

The hydrogenation process described in the second paragraph of Example 6 was repeated using the above compound as starting material, and there was thus obtained as an oil 3-p-[2-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)ethyl]phenyl-N-n-octylpropionamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The cinnamic acid used as starting material was obtained from 3-benzyloxy-17β-hydroxyoestra-

1,3,5(10)-trien-7α-carboxaldehyde (described in the sixth paragraph of Example 6) and ethyl p-(diethylphosphonylmethyl)cinnamate by a similar process to that described in the sixth and seventh paragraphs of Example 8.

Example 14

Aqueous N-sodium hydroxide solution (0.15 ml.) and benzoyl chloride (0.023 ml.) were successively added at 0°C. to a stirred solution of N-n-butyl-N-methyl-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide (Example 2; 0.06 g.) in acetone (1 ml.) and the mixture was stirred at 0°C. for 30 minutes and poured into saturated aqueous sodium bicarbonate solution (10 ml.). The mixture was extracted three times with diethyl ether (15 ml. each time) and the combined extracts were washed with water (3 ml.), dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 3:2 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained as an oil N-n-butyl-N-methyl-11-(3-benzoyloxy-17β-hydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 15

Sodium hydride (0.005 g. of a 50% dispersion in mineral oil) was added to a stirred solution of N-n-butyl-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)-N-ethylundecanamide (Example 2; 0.052 g.) in tetrahydrofuran (2 ml.) and the mixture was stirred at laboratory temperature for 3.5 hours. Butyryl chloride (0.014 ml.) was added and the mixture was stirred at laboratory temperature for 16 hours, diluted with ethyl acetate (30 ml.) and filtered. The filtrate was washed with water, dried and evaporated to dryness. The residue was purified by chromatography on a silica gel

column using a 1:1 v/v mixture of ethyl acetate and toluene as eluant. There was thus obtained as an oil N-n-butyl-11-(3-butyryloxy-17β-hydroxyoestra-1,3,5(10)-trien-7α-yl)-N-methylundecanamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The process described above was repeated using the appropriate acid chloride or acyl anhydride in place of butyryl chloride, and there were thus obtained the corresponding:

3-acetyl
3-propionyl
3-pivalyl
3-decanoyl
3-isopropoxycarbonyl

esters of N-n-butyl-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)-N-methylundecanamide.

Example 16

Acetic anhydride (0.2 ml.) was added to a stirred solution of N-n-butyl-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)-N-methylundecanamide (Example 2; 0.052 g.) in pyridine (0.5 ml.) and the mixture was stirred at laboratory temperature for 16 hours. Water (0.1 ml.) was added and then toluene was added and distilled off until the mixture was free of acetic acid. The residue was purified by chromatography on a silica gel column using a 4:1 v/v mixture of toluene and ethyl acetate as eluant, and there was thus obtained as an oil N-n-butyl-11-(3,17β-diacetoxyoestra-1,3,5(10)-trien-7α-yl)-N-methylundecanamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The process described above was repeated using succinic anhydride in place of acetic anhydride, and there were thus obtained as oils N-n-butyl-11-[3,17β-di-

(β-carboxypropionyl)oestra-1,3,5(10)-trien-7α-yl]-N-methylundecanamide and N-n-butyl-11-[17β-(β-carboxypropionyl)-3-hydroxyoestra-1,3,5(10)-trien-7α-yl]-N-methylundecanamide, which were separated one from the other during the chromatographic purification procedure, and the structures of which were confirmed as above.

Example 17

Jones' Reagent (8N-chromic acid solution; 0.15 ml.) was added to a stirred solution of N-n-butyl-N-methyl-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)-undecanamide (Example 2; 0.262 g.) in acetone (15 ml.) at 0°C., and after 15 minutes isopropanol (0.1 ml.) was added and the mixture was evaporated to dryness. Water (15 ml.) was added and the mixture was adjusted to pH 8 with aqueous sodium bicarbonate solution and then extracted three times with methylene chloride (30 ml. each time). The combined extracts were washed with water (15 ml.), dried and evaporated to dryness, and the residue was purified by chromatography on a silica gel column using a 7:3 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained N-n-butyl-N-methyl-11-(3-hydroxy-17-oxooestra-1,3,5(10)-trien-7α-yl)undecanamide as an oil, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 18

Lithium acetylide-ethylenediamine complex (0.097 g.) was added to a solution of N-n-butyl-N-methyl-11-(3-hydroxy-17-oxooestra-1,3,5(10)-trien-7α-yl)undecananamide (Example 17; 0.138 g.) in dimethyl sulphoxide and the mixture was kept at laboratory temperature for 4 hours. Water (0.1 ml.) was added, the mixture was evaporated to dryness and the residue was purified by chromatography on a silica gel column using a 7:3 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained N-n-butyl-N-methyl-11-(17α-ethynyl-3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide as an oil, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 19

The process described in Example 1 was repeated except that 11-(17α-ethynyl-3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanoic acid and N-methyl-1H,1H-heptafluorobutylamine were used as starting materials. There was thus obtained 11-(17α-ethynyl-3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)-N-(1H,1H-heptafluorobutyl)-N-methylundecanamide as an oil, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The undecanoic acid used as starting material was obtained as follows:-

The process described in Example 17 was repeated except that the corresponding undecanoic acid was used in place of the undecananamide, and that a 1:1 v/v mixture of toluene and ethyl acetate was used as eluant in the chromatographic purification. To a solution of the 11-(3-hydroxy-17-oxooestra-1,3,5(10)-trien-7α-yl)undecanoic acid thus obtained (0.075 g.) in dimethyl sulphoxide (1 ml.) was added a 2-molar solution of dimsyl sodium in dimethyl sulphoxide (2 ml.) which had been saturated with acetylene gas, and the mixture was kept at laboratory temperature fo 18 hours, diluted with water (15 ml.,) acidified to pH 1 with aqueous N-hydrochloric acid, and extracted three times with ethyl acetate (10 ml. each time). The combined extracts were washed with water, dried and evaporated to dryness and the residue was purified by chromatography on a silica gel column using a 1:1 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained the desired 11-(17α-ethynyl-3,17β-dihydroxyoestra-1,3,5(10)trien-7α-yl)undecanoic acid.

Example 20

A stirred mixture of cupric acetate (0.027 g.), iodine (0.038 g.), N-n-butyl-N-methyl-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide (Example 2; 0.052 g.) and acetic acid (2 ml.) was heated at 55°C. for 18 hours and then poured into a mixture of ice (10 ml.) and saturated aqueous sodium bicarbonate solution (5ml.). The mixture was extracted three times with ethyl acetate (15 ml. each time) and the combined extracts were washed with water, dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 3:2 v/v mixture of toluene and ethyl acetate as eluants and there were thus separately obtained N-n-butyl-N-methyl-11-(3,17β-dihydroxy-2-iodooestra-1,3,5(10)-trien-7α-yl)undecanamide (eluted first) and N-n-butyl-N-methyl-11-(3,17β-

dihydroxy-4-iodooestra-1,3,5(10)-trien-7α-yl)undecanamide (eluted second).

Example 21

The process described in the first two paragraphs of Example 1 was repeated except that 11-(17β-acetoxy-3-hydroxyoestra-1,3,5(10),6-tetraen-7-yl)undecanoic acid and N-methyl-N-butylamine were used as starting materials. There was thus obtained as an oil N-n-butyl-N-methyl-11-(3,17β-dihydroxyoestra-1,3,5(10),6-tetraen-7-yl)undecanamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The oestra-tetraene used as starting material was obtained as follows:-

A solution of bromine (0.114 ml.) in acetic acid (2 ml.) was added dropwise to a stirred solution of 11-(17β-acetoxy-3-oxo-oestra-4-en-7α-yl)undecanoic acid (Example 2; 0.5 g.) in a mixture of diethyl ether (5 ml.) and acetic acid (2 ml.) which was cooled to 15°C. and the mixture was stirred at that temperature for 30 minutes and then poured into water (50 ml.). The mixture was extracted three times with methylene chloride (30 ml. each time) and the combined extracts were washed with water, dried and rapidly evaporated to dryness under reduced pressure at a bath temperature below 20°C. A solution of the residue, which consisted of 11-(17β-acetoxy-2,6-dibromo-3-oxooestr-4-en-7α-yl)undecanoic acid in dimethylformamide (3 ml.) was immediately added to a stirred mixture of lithium bromide (1.0 g.), lithium carbonate (1.0 g.) and dimethylformamide (10 ml.) which was heated under reflux, and the mixture was stirred and heated under reflux for 30 minutes and then evaporated to dryness under reduced pressure. Water (20 ml.) was added to the residue and the mixture was acidified to pH 1 with

aqueous N-hydrochloric acid and extracted three times with methylene chloride (20 ml. each time). The combined extracts were washed with water, dried and evaporated to dryness and the residue was purified by chromatography on a silica gel column using a 7:3 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained as an oil 11-(17β-acetoxy-3-hydroxyoestra-1,3,5(10),6-tetraen-7-yl)undecanoic acid.

Example 22

Butyl-lithium (0.8 ml. of a 1.6 molar solution in hexane) was added dropwise to a stirred solution of [9-(N-n-butyl-N-methylcarbamoyl)nonyl]triphenyl-phosphonium bromide (1.2 g.) in a mixture of dimethyl sulphoxide (2 ml.) and tetrahydrofuran (18 ml.), a solution of 3-benzyloxy-17β-hydroxyoestra-1,3,5(10),6,8(9),14(15)-hexaene-7-carboxaldehyde (0.05 g.) in tetrahydrofuran (2 ml.) was then added and the mixture was stirred at laboratory temperature for 1 hour and then evaporated to dryness under reduced pressure. Water (15 ml.) was added and the mixture was extracted three times with ethyl acetate (10 ml. each time) and the combined extracts were washed with water, dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 3:1 v/v mixture of petroleum ether (b.p. 60-80°C.) and acetone as eluant. There was thus obtained as an oil 11-(3-benzyloxy-17β-hydroxyoestra-1,3,5(10),6,8(9),14(15)-hexaen-7-yl)-N-n-butyl-N-methylundec-10-enamide.

The above compound was hydrogenated by a similar process to that described in Example 4 and there was thus obtained as an oil N-n-butyl-N-methyl-11-(3,17β-dihydroxyoestra-1,3,5(10),6,8(9)-pentaen-7-yl)undecanamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The phosphonium bromide used as starting material was obtained as follows:-

Triethylamine (6.5 ml.) and N-methyl-N-n-butylamine (5.5. ml.) were successively added to a stirred solution of 10-bromodecanoyl chloride (13 g.) in diethyl ether (100 ml.) which was maintained at 0°C. and the mixture was stirred at that temperature for 2 hours. Water (20 ml.) was added and the ethereal layer was separated, dried and evaporated to dryness. Triphenylphosphine (10.95 g.) was added to a stirred solution of the 10-bromo-N-n-butyl-N-methyldecanamide thus obtained (12.2 g.) in acetonitrile (125 ml.) and the mixture was stirred and heated under reflux for 16 hours and then evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride (50 ml.), diethyl ether (200 ml.) was added and the solvent was decanted off. There was thus obtained as solid residue [9-(N-n-butyl-N-methylcarbamoyl)nonyl]-triphenylphosphonium bromide which was used without further purification.

The steroidal carboxaldehyde used as starting material was obtained as follows:-

17β-Acetoxy-6-bromo-7α-cyanooestra-1,3,5(10)-trien-3-ol (Example 6, paragraph 4) was converted to the 3-benzyloxy derivative thereof by a similar process to that described in paragraph 5 of Example 6, and this compound was purified by chromatography on a silica gel column using a 19:1 v/v mixture of toluene and ethyl acetate as eluant.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.03 g.) was added to a stirred solution of the above 3-benzyloxy compound (0.51 g.) in toluene (25 ml.) and the mixture was stirred and heated under reflux for 1 hour, cooled, diluted with diethyl ether (40 ml.) and washed three times with saturated aqueous sodium

bicarbonate solution and once with water (50 ml. each time). The organic layer was dried and evaporated to dryness and the residue was purified by chromatography on a silica gel column using a 19:1 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained 17β-acetoxy-3-benzyloxyoestra-1,3,5(10),6,8(9),14(15)-hexaene-7-carbonitrile, which was reduced to the corresponding 7-carboxaldehyde by a similar process to that described in paragraph 6 of Example 6.

Example 23

2,4-Bis-(p-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide (Lawesson's Reagent; 0.375 g.) was added to a stirred solution of N-n-butyl-11-(3-methoxy-17β-tetrahydropyranyloxyoestra-1,3,5(10)-trien-7α-yl)undecanamide (0.25 g.) in xylene (14 ml.) and the mixture was stirred and heated at 130°C. for 5 hours and then evaporated to dryness under reduced pressure. The residue was dissolved in a mixture of tetrahydrofuran (2 ml.), water (2 ml.) and acetic acid (4 ml.) and the solution was stirred at laboratory temperature for 16 hours and then evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column using a 4:1 v/v mixture of toluene and ethyl acetate as eluant, and there was thus obtained as an oil N-n-butyl-11-(17β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-7α-yl)thioundecanamide.

Boron tribromide (0.5 ml.) was added to a stirred solution of the above thioamide (0.061 g.)in methylene chloride (3 ml.) which was cooled to -20°C., and the mixture was stirred at that temperature for 4 hours and then poured into saturated aqueous sodium bicarbonate solution (2 ml.). The mixture was extracted three times with methylene chloride (2 ml. each time)

and the combined extracts were washed with water, dried and evaporated to dryness. The residue was purified by chromatography as decribed above and there was thus obtained as an oil N-n-butyl-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)thioundecanamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The tetrahydropyranyloxy-undecanamide used as starting material was obtained as follows:-

The procedure described in the third, fourth, fifth and sixth paragraphs of Example 6 was repeated except that methyl iodide was used in place of benzylbromide in the fifth paragraph. There was thus obtained 17β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-7α-carboxaldehyde. Dihydropyran (2.4 ml.) and p-toluene-sulphonic acid (4.46 ml. of an 0.1 molar solution in tetrahydrofuran) were successively added to a stirred solution of this aldehyde (2.8 g.) in methylene chloride (50 ml.) which was kept at 0°C., and after 5 minutes pyridine (0.2 ml.) was added and the mixture was washed with saturated aqueous sodium bicarbonate solution (5 ml.), dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 9:1 v/v mixture of toluene and ethyl acetate as eluant.

The 3-methoxy-17β-tetrahydropyranyloxyoestra-1,3,5(10)-trien-7α-carboxaldehyde thus obtained was then converted to the desired amide by a similar procedure to that described in the last paragraph of Example 6 [reaction with (9-carboxynonyl)triphenylphosphonium bromide] followed by that described in the first paragraph of Example 6, except that n-butylamine was used in place of N-methylisobutylamine.

Example 24

Triethylamine (0.053 g.) and methanesulphonyl chloride (0.044 g.) were successively added to a stirred

solution of 17β-acetoxy-3-benzoyloxy-7α-(11-hydroxyundecyl)oestra-1,3,5(10)-triene (penultimate paragraph of Example 1; 0.206 g.) in methylene chloride (3 ml.) at -10°C., and the mixture was stirred for 30 minutes and then shaken with diethyl ether (30 ml.) and saturated aqueous sodium bicarbonate solution. The layers were separated, the aqueous layer was extracted with diethyl ether (30 ml.) and the combined ethereal solutions were washed with water (5 ml.), dried and evaporated to dryness. A mixture of the 11-methanesulphonyloxyundecyl compound thus obtained (0.228 g.) and diethylamine (4 ml.) was heated under reflux for 16 hours and evaporated to dryness. The residue was purified by chromatography on a silica gel column (Kieselgel 60) using a 4% v/v solution of triethylamine in toluene as eluant. There was thus obtained as an oil 17β-acetoxy-3-benzoyloxy-7α-(11-diethylaminoundecyl)oestra-1,3,5(10)-triene, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The above compound was hydrolysed by a similar process to that described in the second part of Example 1. There was thus obtained as an oil 7α-(11-diethylaminoundecyl)oestra-1,3,5(10)-triene-3,17β-diol, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 25

A mixture of 17β-acetoxy-3-benzoyloxy-7α-(11-methanesulphonyloxyundecyl)oestra-1,3,5(10)-triene (Example 24; 0.1 g.) and saturated methanolic ammonia solution (10 ml.) was heated in a sealed tube at 100°C. for 16 hours and was then evaporated to dryness. Butyryl chloride (0.2 ml.) was added to a stirred solution of the residue in pyridine (1 ml.) and the mixture was stirred at laboratory temperature for 16

hours, and then poured into water (10 ml.). The mixture was extracted three times with diethyl ether (10 ml. each time) and the combined extracts were washed with water (2 ml.), dried and evaporated to dryness. Aqueous N-sodium hydroxide solution (1 ml.) was added to a solution of the residue in methanol (5 ml.) and the mixture was kept at laboratory temperature for 18 hours, neutralised with aqueous N-hydrochloric acid and extracted three times with ethyl acetate (10 ml. each time). The combined extracts were washed with water (5 ml.), dried and evaporated to dryness and the residue was purified by chromatography on a silica gel column using a 1:1 v.v mixture of toluene and ethyl acetate as eluant. There was thus obtained as an oil N-[N-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecyl]-butyramide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 26

The process described in the last paragraph of Example 6 was repeated except that (8-hexanamidooctyl)triphenylphosphonium bromide was used in place of (9-carboxynonyl)triphenylphosphonium bromide. The hydrogenation process described in the second paragraph of Example 6 was then repeated using the N-[9-(3-benzyloxy-17β-hydroxyoestra-1,3,5(10)-trien-7α-yl)non-8-enyl]hexanamide thus obtained as starting material, and there was thus obtained as an oil N-[9-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)nonyl]hexanamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The (8-hexanamidooctyl)triphenylphosphonium bromide used as starting material was obtained as follows:-

Triethylamine (0.35 ml.) and hexanoyl chloride (0.35 ml.) were successively added to a stirred solution of 8-bromooctylamine (0.5 g.) in diethyl ether (5 ml.) and the mixture was stirred at laboratory temperature for 1 hour. Saturated aqueous sodium bicarbonate solution (5 ml.) was added, the ethereal layer was separated and the aqueous layer was extracted three times with diethyl ether (5 ml. each time). The combined ethereal solutions were washed with water (2 ml.), dried and evaporated to dryness. Triphenylphosphine (0.331 g.) was added to a stirred solution of the above N-(8-bromoethyl)hexanamide (0.385 g.) in acetonitrile (10 ml.) and the mixture was stirred and heated under reflux for 16 hours and then evaporated to dryness. The residue was stirred with diethyl ether and the ethereal solution was decanted off. There was thus obtained as residual gum (8-hexanamidooctyl)triphenylphosphonium bromide which was used without further purification.

Example 27

The procedure described in the last paragraph of Example 6 was repeated except that (7-N-methylcarbamoylheptyl)triphenylphosphonium bromide (prepared from 8-bromo-N-methyloctanamide and triphenylphosphine by a similar process to that described in the last part of Example 22) was used in place of (9-carboxynonyl)triphenylphosphonium bromide. The hydrogenation process described in the second paragraph of Example 6 was then repeated using the 9-(3-benzyloxy-17β-hydroxyoestra-1,3,5(10)trien-7α-yl)-N-methylnon-8-enamide thus obtained as starting material, and there was thus obtained as an oil 9-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)-N-methylnonanamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 28

A mixture of 9-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)-N-methylnonanamide (Example 27; 0.047 g.) and a molar solution of borane in tetrahydrofuran (5 ml.) was heated under reflux for 2 hours, cooled and concentrated aqueous hydrochloric acid (2 ml.) was added. The tetrahydrofuran was removed by evaporation and the residue was basified with aqueous 5N-sodium hydroxide solution and extracted three times with ethyl acetate (10 ml. each time). The combined extracts were washed with water (2 ml.), dried and evaporated to dryness. There was thus obtained as an oil 7α-(9-methylaminononyl)oestra-1,3,5(10)-triene-3,17β-diol, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 29

Hexanoyl chloride (0.5 ml.) was added to a solution of 7α-(9-methylaminononyl)oestra-1,3,5(10)-trien-3,17β-diol (Example 28; 0.037 g.) in pyridine (5 ml.) and the mixture was kept at laboratory temperature for 16 hours and then extracted with ethyl acetate (20 ml.). The extract was washed successively with aqueous 2N-hydrochloric acid (5 ml.), saturated aqueous sodium bicarbonate solution (5 ml.) and water (2ml.), dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 9:1 v/v mixture of toluene and ethyl acetate as eluant, and there was thus obtained N-[9-(3,17β-dihexanoyloxyoestra-1,3,5(10)-trien-7α-yl)nonyl]-N-methylhexanamide. A solution of this compound (0.027 g.) in methanol (5 ml.) and aqueous 2N-sodium hydroxide solution (2 m.) were stirred at laboratory temperature for 16 hours and the mixture was then extracted three times with ethyl acetate (10 ml. each time). The combined extracts were washed with water,

dried and evaporated to dryness and there was thus obtained as residual oil N-[9-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)nonyl]-N-methylhexanamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 30

N-Methylmorpholine (0.028 ml.) and isobutyl chloroformate (0.038 ml.) were successively added to a stirred solution of 7α-(9-methylaminononyl)oestra-1,3,5(10)-trien-3,17β-diol (Example 28; 0.08 g.) in tetrahydrofuran (3 ml.) and the mixture was stirred at laboratory temperature for 150 minutes. Saturated aqueous sodium bicarbonate solution (2 ml.) was added and the mixture was extracted three times with methylene chloride (10 ml. each time). The combined extracts were washed with water (5 ml.), dried and evaporated to dryness and there was thus obtained as residual oil isobutyl N-[9-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)nonyl]-N-methylcarbamoate.

Example 31

The process described in Example 25 was repeated except that 17β-acetoxy -3-methoxy-7α-(9-methanesulphonyloxynonyl)oestra-1,3,5(10)-triene was reacted with ammonia, and that the resulting 9-aminononyl compound was reacted with n-butyl isocyanate. The 17β-acetoxy group was removed by hydrolysis with aqueous methanolic sodium hydroxide solution, and the 3-methoxy group was converted to a hydroxy group with boron tribromide by a similar process to that described in the second paragraph of Example 8. There was thus obtained N^1-n-butyl-N^3-[9-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)nonyl]urea, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The steroidal starting material was prepared by a similar process to that described in Examples 1 and

24, except that 9-bromononanol was used in place of 11-bromoundecanol in the third paragraph of Example 1, and that the benzoylation step described in the eighth paragraph of Example 1 was replaced by the methylation step described in the fourth paragraph of Example 8.

Example 32

A solution of sodium thiobutoxide [generated from butanethiol (0.045 g.) and a 60% dispersion of sodium hydride in mineral oil (0.02 g.)] in tetrahydrofuran (2 ml.) was added to a solution of 17β-acetoxy-3-benzoyloxy-7α-(11-methanesulphonyloxyundecyl)oestra-1,3,5(10)-triene (Example 24; 0.078 g.) in tetrahydrofuran (1 ml.) and the mixture was kept for 1 hour at laboratory temperature, neutralised with aqueous N-hydrochloric acid and extracted three times with ethyl acetate (10 ml. each time). The combined extracts were washed with water (3 ml.), dried and evaporated to dryness, and the residue was dissolved in methanol (3 ml.). Aqueous N-sodium hydroxide solution (1 ml.) was added and the mixture was kept at laboratory temperature for 18 hours, neutralised with aqueous N-hydrochloric acid and extracted three times with ethyl acetate (10 ml. each time). The combined extracts were washed with water (10 ml.), dried and evaporated to dryness and the residue was purified by chromatography on a silica gel column using a 4:1 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained as an oil 7α-(11-n-butylthioundecyl)oestra-1,3,5(10)-triene-3,17β-diol, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 33

A solution of sodium metaperiodate (0.016 g.) in water (0.5 ml.) was added to a solution of 7α-(11-n-butylthioundecyl)oestra-1,3,5(10)-triene-3,17β-diol

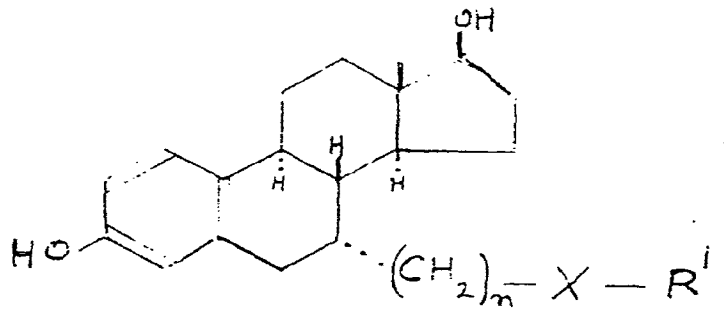
(Example 32; 0.035 g.) in methanol (1 ml.) and the mixture was stirred at laboratory temperature for 18 hours, evaporated to dryness and evaporated from toluene to remove the last traces of water. The residue was extracted three times with acetone and the combined extracts were evaporated to dryness. There was thus obtained as an oil 7α-(11-n-butylsulphinylundecyl)-oestra-1,3,5(10)-triene-3,17β-diol, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 34

m-Chloroperbenzoic acid (0.026 g.) was added to a solution of 7α-(11-n-butylthioundecyl)oestra-1,3,5(10)-triene-3,17β-diol (Example 32; 0.035 g.) in chloroform (1 ml.) and the mixture was kept for 2 hours at laboratory temperature and then evaporated to dryness. The residue was shaken with water (2 ml.) and the mixture extracted three times with ethyl acetate (10 ml. each time). The combined extracts were washed with saturated aqueous sodium bicarbonate solution and then with water, dried and evaporated to dryness. There was thus obtained as residual oil 7α-(11-n-butylsulphonylundecyl)oestra-1,3,5(10)-triene-3,17β-diol, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 35

The process described in Examples 32, 33 and 34 was repeated using the appropriate thiol and the appropriate 7α-(ω-methanesulphonyloxyalkyl)-steroidal derivative as initial starting materials in the process of Example 32. There were thus obtained as oils the compounds described in the following table:-



n	X	R^1
6	S	n-nonyl
9	S	n-hexyl
9	S	n-heptyl
9	S	4,4,5,5,5-pentafluoropentyl
9	S	p-chlorophenyl
9	S	p-chlorobenzyl
9	S	p-chlorophenethyl
10	S	n-pentyl
10	S	4,4,4-trifluorobutyl
10	S	4,4,5,5,5-pentafluoropentyl
10	S	1H,1H-heptafluorobutyl
10	S	m-chlorophenyl
10	S	p-chlorophenyl
10	S	p-fluorophenyl
10	S	p-bromophenyl
10	S	p-chlorobenzyl
10	S	p-chlorophenethyl
11	S	4,4,4-trifluorobutyl
6	SO	n-nonyl
9	SO	n-hexyl
9	SO	n-heptyl
9	SO	4,4,5,5,5-pentafluoropentyl
9	SO	p-chlorophenyl

n	X	R^1
9	SO	p-chlorobenzyl
9	SO	p-chlorophenethyl
10	SO	n-pentyl
10	SO	4,4,4-trifluorobutyl
10	SO	4,4,5,5,5-pentafluoropentyl
10	SO	1H,1H-heptafluorobutyl
10	SO	p-chlorophenyl
10	SO	p-fluorophenyl
10	SO	p-bromophenyl
10	SO	p-chlorobenzyl
10	SO	p-chlorophenethyl
11	SO	4,4,4-trifluorobutyl
9	SO_2	n-heptyl
10	SO_2	p-chlorobenzyl
10	SO_2	p-chlorophenethyl

The 7α-(ω-methanesulphonyloxyalkyl)-steroidal derivatives used as starting materials were obtained as described in Example 24 from the corresponding 7α-(ω-hydroxyalkyl)-steroidal derivatives which in turn were obtained as described in Example 1 using the appropriate ω-(dimethyl-t-butylsilyloxy)alkyl bromide in place of 11-(dimethyl-t-butylsilyloxy)undecyl bromide as intermediate.

Example 36

The process described in the penultimate paragraph of Example 3 was repeated except that [4-(N-heptylsulphamoyl)butyl]triphenylphosphonium bromide was used in place of (4-carboxybutyl)triphenylphosphonium bromide. There was thus obtained as an oil N-heptyl-7-

(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)hept-4-enesulphonamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy. Both the 3-benzoyl and 17-acetyl groups were removed during the reaction, by contrast with Example 3 wherein only the 3-benzoyl group was removed.

The phosphonium bromide used as starting material was obtained as follows:-

Sodium iodide (1.1 g.) was added to a solution of 1,4-butanesultone (1.0 g.) in acetone (10 ml.) and the mixture was heated under reflux for 1 hour, cooled and filtered. Dimethylformamide (0.05 ml.) and oxalyl chloride (0.475 ml.) were successively added to a stirred solution of the sodium 4-iodobutanesulphonate thus obtained (1.32 g.) in toluene (20 ml.) and the mixture was stirred at laboratory temperature for 3 hours, filtered and the filtrate was evaporated to dryness.

Triethylamine (0.65 ml.) and n-heptylamine (0.68 ml.) were successively added to a solution of the 4-iodobutanesulphonyl chloride thus obtained (1.3 g.) in diethyl ether (30 ml.) and the mixture was kept at laboratory temperature for 2 hours and then evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was washed twice with water (5 ml.each time), dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column using methylene chloride as eluant, and there was thus obtained N-heptyl-4-iodobutanesulphonamide.

A mixture of the above sulphonamide (0.25 g.), triphenylphosphine (0.18 g.) and toluene (10 ml.) was heated under reflux for 2 hours and then cooled, and the toluene solution was decanted off the oil which formed. The oil was washed with more toluene, and then used without further purification. It consisted of

4-(N-heptylsulphamoyl)butyl]triphenylphosphonium bromide.

Example 37

A solution of N-heptyl-7-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)hept-4-enesulphonamide (Example 36; 0.04 g.) in ethyl acetate (10 ml.) was stirred with a 10% palladium-on-charcoal catalyst (0.01 g.) at laboratory temperature for 90 minutes and then filtered, and the filtrate was evaporated to dryness. There was thus obtained as residual oil N-heptyl-7-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)-heptanesulphonamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 38

n-Butyl-lithium (0.27 ml. of a 1.5 molar solution in diethyl ether) was added to a stirred solution of 11-(17β-acetoxy-3-hydroxyoestra-1,3,5(10)-trien-7α-yl)undecanoic acid (Example 2; 0.046 g.) in tetrahydrofuran (1 ml.) and the mixture was stirred at laboratory temperature for 2 hours. Saturated aqueous sodium hydrogen tartrate solution (2 ml.) was added and the mixture was extracted three times with ethyl acetate (5 ml. each time). The combined extracts were washed with water, dried and evaporated to dryness and the residue was purified by chromatography on a silica gel column using a 17:3 v/v mixture of toluene and ethyl acetate as eluant. There was thus obtained as an oil 15-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)pentadecan-5-one, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

Example 39

n-Butyl-lithium (0.341 ml. of a 1.6 molar solution in hexane) was added to a stirred solution of

2-oxotridecylphosphonate (0.193 g.) in tetrahydrofuran (10 ml.) which was maintained at -70°C. and the mixture was stirred at that temperature for 40 minutes. A solution of 3-(17β-acetoxy-3-benzoyloxyoestra-1,3,5(10)-trien-7α-yl)propionaldehyde (Example 3; 0.2 g.) in tetrahydrofuran (10 ml.) was added and the mixture was allowed to warm up to laboratory temperature and was stirred at that temperature for 4.5 hours. Acetic acid was added until the mixture was acidic and the mixture was evaporated to dryness. Water (10 ml.) was added and the mixture was extracted three times with ethyl acetate (30 ml. each time). The combined extracts were washed with water, dried and evaporated to dryness and there was thus obtained as residual oil 1-(17β-acetoxy-3-benzoyloxyoestra-1,3,5(10)-trien-7α-yl)hexadec-3-en-5-one.

The above compound was hydrogenated by a similar process to that described in Example 4, and there was thus obtained as an oil 1-(17β-acetoxy-3-benzoyloxyoestra-1,3,5(10)-trien-7α-yl)hexadecan-5-one.

The above compound was hydrolysed by a similar process to that described in the second paragraph of Example 1, and there was thus obtained 1-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)hexadecan-5-one, which was purified by chromatography on a silica gel column using a 4:1 v/v mixture of toluene and ethyl acetate as eluant.

Example 40

The process described in Example 26 was repeated using [3-(5-N-n-butyl-N-methylcarbamoyl pentyloxy)propyl]triphenylphosphonium bromide and 3-benzyloxy-17β-hydroxyoestra-1,3,5(10)-triene-7α-carboxaldehyde (Example 6) as starting materials. There was thus obtained after simultaneous hydrogenolysis and hydrogenation, as an oil, 6-[4-(3,17β-dihydroxyoestra-

1,3,5(10)-triene-7α-yl)butoxy]-N-n-butyl-N-methylhexanamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The triphenylphosphonium bromide used as starting material was obtained from 6-bromohexanoic acid by reaction with oxalyl chloride and N-methyl-n-butylamine to form the amide, then with 1,3-trimethylene glycol and sodium hydride in dimethylformamide to form the 6-(3-hydroxypropoxy)hexanamide, followed by conversion of the 3-hydroxy group to a 3-bromo group with bromine and triphenylphosphine in dimethylformamide and finally reaction with triphenylphosphine in toluene.

Example 41

A mixture of 7α-(10-mesyloxydecyl)oestra-1;3,5(10)-triene-3,17β-diol (0.07 g.) and N-methylhexylamine (0.5 ml.) was heated at 75°C. for 2 hours and the excess of N-methylhexylamine was removed by evaporation. The residue was purified by chromatography on a silica gel column using a 24:1 v/v mixture of ethyl acetate and triethylamine as eluant, and there was thus obtained as an oil 7α-(10-N-methylhexylaminodecyl)-oestra-1,3,5(10)-trien-3,17β-diol, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The process described above was repeated using N-methyl-4,4,5,5,6,6,6-heptafluorohexylamine or N-methyl-p-chlorophenethylamine in place of N-methylhexylamine, and there were thus obtained respectively 7α-[10-(N-methyl-4,4,5,5,6,6,6-heptafluorohexylamino)decyl)- and 7α-(10-N-methyl-p-chlorophenethylaminodecyl)-oestra-1,3,5(10)-trien-3,17β-diol.

The 7α-mesyloxydecyl-oestradiol used as starting material was obtained from 3-benzyloxy-17β-

hydroxyoestra-1,3,5(10)-triene-7α-carboxaldehyde (described in Example 6) by reaction with 9-(dimethyl-t-butylsilyloxynonyl)triphenylphosphonium bromide (prepared from 9-bromononanol, dimethyl-t-butylsilyl chloride and triphenylphosphine) by a similar process to that described in the last paragraph of Example 6, followed by acid hydrolysis of the silyl group, mesylation of the decenol thus obtained and simultaneous hydrogenation of the mesyloxydecene side-chain to a mesyloxydecane side-chain and hydrogenolysis of the 3-benzyloxy group.

Example 42

m-Chloroperbenzoic acid (0.02 g.) was added to a solution of 7α-(10-N-methylhexylaminodecyl)-oestra-1,3,5(10)-triene-3,17β-diol (Example 41; 0.047g.) in methylene chloride (8 ml.) and the mixture was kept at laboratory temperature for 2.5 hours. Methylene chloride (20 ml.) was added and the solution was washed successively with saturated aqueous sodium sulphite solution, saturated aqueous sodium bicarbonate solution and water (5 ml. each time), dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column using a 7:2:1 v/v/v mixture of ethyl acetate, methanol and triethylamine as eluant. There was thus obtained as an oil 7α-(10-N-methyl-N-hexylaminodecyl)oestra-1,3,5(10)-triene-3,17β-diol-N-oxide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The N-oxides of 7α-[10-(N-methyl-4,4,5,5,6,6,6-heptafluorohexylamino)decyl]- and 7α-(10-N-methyl-p-chlorophenethylaminodecyl)oestra-1,3,5(10)-triene-3,17β-diol (also described in Example 41) were similarly obtained by oxidation with m-chlorobenzoic acid.

Example 43

The process described in Example 32 was repeated using 7α-(7-mesyloxyheptyl)oestra-1,3,5(10)-triene-3,17β-diol (obtained as described in Example 41 using initially 6-(dimethyl-t-butylsilyloxy)hexyl-triphenylphosphonium bromide) and 2-n-pentylthio-ethanol (obtained from pentanethiol and 2-bromoethanol) as starting materials. There was thus obtained as an oil 7α-[7-(2-n-pentylthioethoxy)heptyl]oestra-1,3,5(10)-triene-3,17β-diol, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The above compound was oxidised with sodium metaperiodate by a similar process to that described in Example 33, and there was thus obtained 7α-[7-(2-n-pentylsulphinylethoxy)heptyl]oestra-1,3,5(10)-triene-3,17β-diol.

Example 44

The process described in Example 32 was repeated using 7α-(6-mesyloxyhexyl)oestra-1,3,5(10)-triene-3,17β-diol (obtained as described in Example 41 using initially 5-(dimethyl-t-butylsilyloxy)pentyl-triphenylphosphonium bromide and 3-n-pentylthiopropane-thiol (obtained from trimethylene-1,3-dithiol and pentyl bromide) as starting materials. There was thus obtained as an oil 7α-[6-(3-n-pentylthiopropylthio)hexyl]-oestra-1,3,5(10)triene-3,17β-diol, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The above compound was oxidised with sodium metaperiodate by a similar process to that described in Example 33, and there was thus obtained 7α-[6-(3-n-pentylsulphinylpropylsulphinyl)hexyl]oestra-1,3,5(10)-triene-3,17β-diol.

Example 45

The process described in Example 1 was repeated using N-methyl-n-butylamine and 3-[7-(3,17β-dihydroxyoestra-1,3,5(10)-triene-7α-yl)-heptylthio]propionic acid as starting materials. There was thus obtained as an oil 3-[7-(3,17β-dihydroxyoestra-1,3,5(10)-triene-7α-yl)heptylthio]-N-n-butyl-N-methylpropionamide, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

The propionic acid used as starting material was obtained by the reaction of 7α-(7-mesyloxyheptyl)oestra-1,3,5(10)-triene-3,17β-diol (obtained as described in Example 41 using initially 6-(dimethyl-t-butylsilyloxy)hexyltriphenylphosphonium bromide) with methyl 3-mercaptopropionate, followed by alkaline hydrolysis of the methyl ester.

Example 46

A mixture of 7α-(10-mesyloxydecyl)oestra-1,3,5(10)-triene-3,17β-diol (Example 41; 0.1 g.), sodium iodide (0.034 g.), butylmethylphenylphosphine (0.039 ml.) and acetonitrile (5 ml.) was heated under reflux for 16 hours, evaporated to dryness and the residue was dissolved in methylene chloride (20 ml.). The mixture was filtered and the filtrate was diluted with diethyl ether (100 ml.). The mixture was filtered and the solid residue, which consisted of butyl[10-(3,17β-dihydroxyoestra-1,3,5(10)-triene-7α-yl)decyl]methyl-phenylphosphonium iodide, was dissolved in a mixture of tetrahydrofuran (6 ml.) and dimethyl sulphoxide (1 ml.). n-Butyl-lithium (0.5 ml. of a 1.6M molar solution in hexane) was added and the mixture was stirred at laboratory temperature for 90 minutes. Water (10 ml.) was added and the mixture was extracted three times with ethyl acetate (10 ml. each time). The combined extracts

were washed with water, dried and evaporated to dryness and the residue was purified by chromatography on a silica gel column using a 97:3 v/v mixture of methylene chloride and methanol as eluant. There were thus obtained as oils a less polar substance 7α-(10-butylphenylphosphinyldecyl)oestra-1,3,5(10)-triene-3,17β-diol and a more polar substance 7α-(10-methylphenylphosphinyldecyl)oestra-1,3,5(10)-triene-3,17β-diol, the structures of both of which were confirmed by proton magnetic resonance and mass spectroscopy.

Example 47

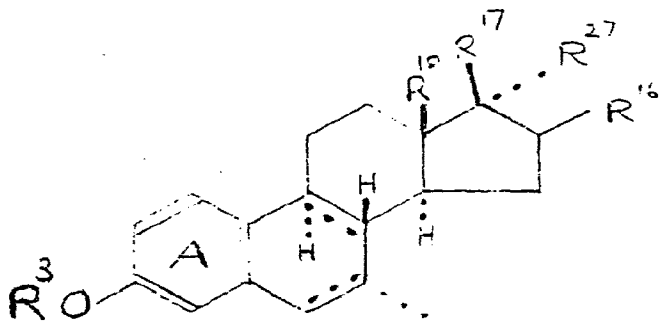
A mixture of butyl[10-(3,17β-dihydroxyoestra-1,3,5(10)-triene-7α-yl)decyl]methylphenylphosphonium iodide (Example 46; 0.05 g.), tetrahydrofuran (5 ml.) and aqueous 30% sodium hydroxide solution (2 ml.) was stirred at laboratory temperature for 18 hours, diluted with water (10 ml.) and extracted three times with ethyl acetate (10 ml. each time). The combined extracts were washed with water, dried and evaporated to dryness and the residue was purified by chromatography on a silica gel column using a 25:1 v/v mixture of methylene chloride and methanol as eluant. There was thus obtained as an oil 7α-(10-butylmethylphosphinyldecyl)-oestra-1,3,5(10)-triene-3,17β-diol, the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

What we claim is:-

1. A steroid derivative of the formula:-

$$ST\text{-}A\text{-}X\text{-}R^{1}$$

wherein ST is a 7α-linked steroid nucleus of the general formula:-



wherein the dotted lines between carbon atoms 6 and 7, and carbon atoms 8 and 9, of the steroid nucleus indicate that there is an optional double bond between carbon atoms 6 and 7, or that there are two optional double bonds between carbon atoms 6 and 7 and carbon atoms 8 and 9;

wherein the aromatic ring A may optionally bear one or two halogen or alkyl substituents;

wherein R^{3} is hydrogen or alkyl, alkanoyl, alkoxycarbonyl, carboxyalkanoyl or aroyl each of up to 10 carbon atoms;

wherein R^{16} is hydrogen, alkyl of up to 6 carbon atoms which is preferably in the β-configuration, or hydroxy which is preferably in the α-configuration;

wherein either R^{17} (in the β-configuration) is hydroxy or alkanoyloxy, carboxyalkanoyloxy or aroyloxy each of up to 10 carbon atoms; and R^{27} (in the α-configuration) is hydrogen or alkyl, alkenyl or alkynyl each of up to 6 carbon atoms ;
or R^{17} and R^{27} together form oxo (=0);
wherein R^{18} is alkyl of up to 6 carbon atoms;
wherein A is straight- or branched- chain alkylene, alkenylene or alkynylene each of from 3 to 14 carbon atoms, which may have one or more hydrogen atoms replaced by fluorine atoms, or has the formula

$$-A^{1}-Y-A^{11}-$$

wherein A^{1} and A^{11} are each alkylene or alkenylene, optionally fluorinated, having together a total of 2 to 13 carbon atoms and Y is -O-, -S-, -SO-, $-SO_2-$, -CO- or -NR- wherein R is hydrogen or alkyl of up to 3 carbon atoms;
or A^{1} is alkylene or alkenylene, optionally fluorinated, and A^{11} is a direct link or alkylene or alkenylene, optionally fluorinated, such that A^{1} and A^{11} together have a total of 1 to 12 carbon atoms, and Y is -NRCO-, -CONR-, -COO-, -OCO- or phenylene wherein R has the meaning stated above;
wherein R^{1} is hydrogen, or alkyl, alkenyl, cycloalkyl, halogenoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl or arylalkyl each of up to 10 carbon atoms, or dialkylaminoalkyl wherein each alkyl is of up to 6 carbon atoms, or R^{1} is joined to R^{2} as defined below;
and wherein X is $-CONR^{2}-$, $-CSNR^{2}-$, $-NR^{12}CO-$,

$-NR^{12}CS-$, $-NR^{12}CONR^{2}-$, $-NR^{12}-\overset{\overset{NR^{22}}{\|}}{C}-NR^{2}-$,

$-SO_2NR^{2}-$ or -CO-;

or, when R^1 is not hydrogen, is -O-, $-NR^2-$, $-(NO)R^2-$, $-(PO)R^2-$, $-NR^{12}-COO-$; $-NR^{12}-SO_2-$, -S-, -SO- or $-SO_2-$;

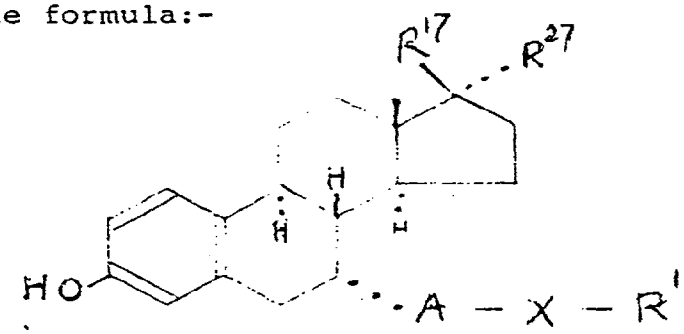
wherein R^2 is hydrogen or alkyl of up to 6 carbon atoms, or R^1 and R^2 together form alkylene or halogenoalkylene such that, with the adjacent nitrogen atom, they form a heterocyclic ring of 5 to 7 ring atoms, one of which atoms may be a second heterocyclic atom selected from oxygen, sulphur and nitrogen;

wherein R^{12} is hydrogen or alkyl of up to 6 carbon atoms;

and wherein R^{22} is hydrogen, cyano or nitro;

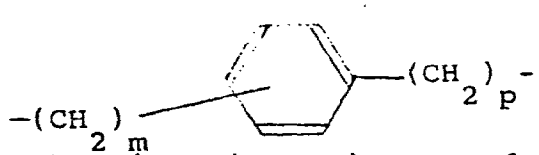
or a salt thereof when appropriate.

2. A steroid derivative as claimed in claim 1 which has the formula:-



wherein R^{17} is hydroxy and R^{27} is hydrogen or ethynyl, or R^{17} and R^{27} together form oxo;

wherein -A- is $-(CH_2)_n-$, wherein n is an integer from 3 to 14, or -A- is:-



wherein m is an integer from 2 to 9 and p is 0 to 2;

wherein R^1 is alkyl, fluoroalkyl or cycloalkyl each of up to 10 carbon atoms, or phenyl, chlorophenyl or benzyl, or is linked to R^2 as stated below;

wherein X is $-CONR^2-$, $-NR^{12}CO-$, -S-, -SO- or $-SO_2-$,

wherein R^2 is hydrogen or alkyl of up to 3 carbon atoms or together with R^1 forms alkylene of 5 or 6 carbon atoms, and wherein R^{12} is hydrogen or alkyl of up to 3 carbon atoms.

3. A steroid derivative as claimed in claim 2 wherein the number of carbon atoms in the two groups A and R^1 adds up to between 12 and 16 inclusive.

4. The compound N-n-butyl-N-methyl-, N-2,2,3,3,4,4,4-heptafluorobutyl-N-methyl- or N, N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecamide;

N-n-butyl- or N-2,2,3,3,4,4,4-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-pentafluorosulphonylnonyl]-, 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.

5. A process for the manufacture of a steroid derivative claimed in Claim 1, which comprises:

(a) when X has the formula $-CONR^2-$, $-CSNR^2-$ or $-SO_2NR^2-$, the reaction of a compound of the formula $ST^1—A-Z^1$, wherein A has the meaning stated in claim 1, wherein ST^1 either has the same meaning as stated in claim 1 for ST, or is an equivalent 7α-linked steroid nucleus which bears one or more protecting groups for functional derivatives, and wherein Z^1 is an activated group derived from a carboxylic, thiocarboxylic or sulphonic acid, with an amine of the formula HNR^1R^2, wherein R^1 and R^2 have the meanings stated in claim 1;

or (b) when X has the formula -CO-, the reaction of an acid of the formula ST^1-A-COOH, wherein ST^1 and A have the meanings stated above, with an organometallic compound of the formula R^1-M, wherein R^1 has the meaning stated above and M is a metal group;

or (c) when X has the formula -S-, -O-, $-NR^2-$ or $(PO)R^2$, the reaction of a compound of the formula ST^1-A-Z^2, wherein ST^1 and A have the meanings stated above and wherein Z^2 is a displaceable group, with a compound of the formula R^1SH, R^1OH, HNR^1R^2 or R^1R^2P-C_6H_5, wherein R^1 and R^2 have the meanings stated above, whereafter a phosphonium salt is hydrolysed to the phosphinyl compound;

or (d) when X has the formula $-NR^{12}CO-$, $-NR^{12}CS-$, $-NR^{12}CONR^2-$, $-NR^{12}-\overset{NR^{22}}{\overset{\|}{C}}-NR^2-$, $-NR^{12}COO-$ or $-NR^{12}SO_2-$, the reaction of a compound of the formula ST^1-A-NHR^{12}, wherein ST^1, A and R^{12} have the meanings stated above, with an acylating agent derived from an acid of the formula R^1COOH, R^1CSOH, R^1OCOOH or R^1SO_2OH; or, for the manufacture of a urea, with an isocyanate of the formula R^1NCO; or, for the manufacture of a guanidine, with a cyanamide of the formula R^1NR^2-CN;

or (e) when -A- is alkenylene of the formula $-A^3-CH=CH-A^4-$, the reaction of a compound of the formula:-

$$ST^1-A^3CHO$$

wherein ST^1 and A^3 have the meanings stated above, with a triphenylphosphonium salt of the formula:-

$$R^1X-A^4-CH_2-P^+(Ph)_3\ Q^-$$

wherein R^1, X and A^4 have the meanings stated above and wherein Q^- is an anion;

wherafter:

(i) any protecting group in ST^1 is removed by conventional means;

or (ii) a steroid derivative wherein ST is a 17-hydroxy-steroid derivative may be converted by conventional reactions into the corresponding 17- keto steroid derivative, and thence to the corresponding 17-hydroxy-17-hydrocarbyl steroid derivative (that is,a steroid derivative wherein R^{27} is alkyl, alkenyl or alkynyl);

or (iii) a steroid derivative wherein R^3 and/or R^{17} are other than hydrogen may be obtained from the corresponding compound wherein R^3 and/or R^{17} are hydrogen by a conventional etherification or esterification process;

or (iv) a steroid derivative wherein R^3 and/or R^{17} are hydrogen may be obtained by hydrolysis of the corresponding compound wherein R^3 and/or R^{17} are other than hydrogen;

or (v) a steroid derivative wherein A is alkenylene may be hydrogenated to provide the corresponding compound wherein A is alkylene;

or (vi) a steroid derivative wherein -X- is $-CH_2NR^2-$ or $-NR^2CH_2-$ may be obtained by the reduction of the corresponding compound wherein -X- is $-CONR^2-$ or $-NR^2CO-$;

or (vii) a steroid derivative wherein -X- is -CSNH- or -NHCS- may be obtained by the reaction of the corresponding compound wherein X is -CONH- or -NHCO- with 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide;

or (viii) a steroid derivative wherein X is $-(NO)R^2$, -SO- or $-SO_2-$ may be obtained by the oxidation of the

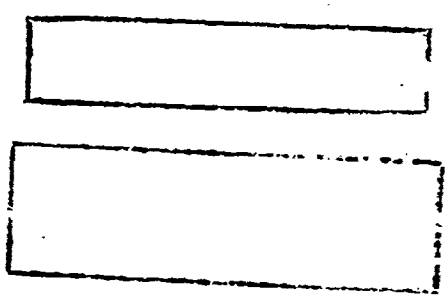
corresponding compound wherein X is $-NR^2-$ or -S-.

6. A pharmaceutical composition comprising a steroid derivative, claimed in claim 1, together with a pharmaceutical acceptable diluent or carrier.

7. A composition as claimed in claim 6 which contains, in addition to the steroid derivative, one or more antiandrogenic agents or antiprogestational agents.

8. A composition as claimed in claim 6 which is suitable for oral administration and which contains from 5 to 500 mg. of a steroid derivative.

9. A method for producing an antioestrogenic effect in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of at least one steroid derivative as claimed in claim 1.



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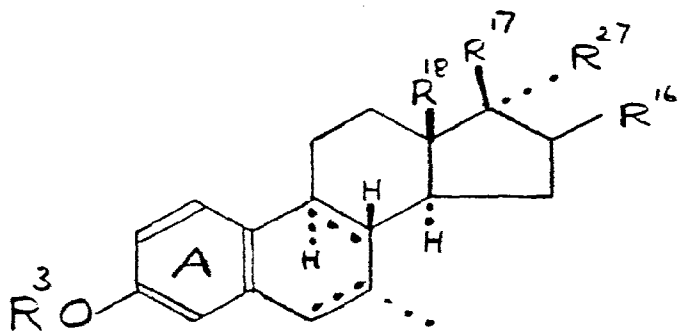
What we claim is:-

1. A process for the manufacture of a steroid derivative of the formula:-

$$ST\text{-}A\text{-}X\text{-}R^1$$

wherein ST is a 7α-linked steroid nucleus of the general formula:-



wherein the dotted lines between carbon atoms 6 and 7, and carbon atoms 8 and 9, of the steroid nucleus indicate that there is an optional double bond between carbon atoms 6 and 7, or that there are two optional double bonds between carbon atoms 6 and 7 and carbon atoms 8 and 9;

wherein the aromatic ring A may optionally bear one or two halogen or alkyl substituents;

wherein R^3 is hydrogen or alkyl, alkanoyl, alkoxycarbonyl, carboxyalkanoyl or aroyl each of up to 10 carbon atoms;

wherein R^{16} is hydrogen, alkyl of up to 6 carbon atoms which is preferably in the β-configuration, or hydroxy which is preferably in the α-configuration;

wherein either R^{17} (in the β-configuration) is hydroxy or alkanoyloxy, carboxyalkanoyloxy or aroyloxy each of up to 10 carbon atoms; and R^{27} (in the α-configuration) is hydrogen or alkyl, alkenyl or alkynyl each of up to 6 carbon atoms ;
or R^{17} and R^{27} together form oxo (=O);
wherein R^{18} is alkyl of up to 6 carbon atoms;
wherein A is straight- or branched- chain alkylene, alkenylene or alkynylene each of from 3 to 14 carbon atoms, which may have one or more hydrogen atoms replaced by fluorine atoms, or has the formula

$$-A^{1}-Y-A^{11}-$$

wherein A^{1} and A^{11} are each alkylene or alkenylene, optionally fluorinated, having together a total of 2 to 13 carbon atoms and Y is -O-, -S-, -SO-, $-SO_2-$, -CO- or -NR- wherein R is hydrogen or alkyl of up to 3 carbon atoms;
or A^{1} is alkylene or alkenylene, optionally fluorinated, and A^{11} is a direct link or alkylene or alkenylene, optionally fluorinated, such that A^{1} and A^{11} together have a total of 1 to 12 carbon atoms, and Y is -NRCO-, -CONR-, -COO-, -OCO- or phenylene wherein R has the meaning stated above;
wherein R^{1} is hydrogen, or alkyl, alkenyl, cycloalkyl, halogenoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl or arylalkyl each of up to 10 carbon atoms, or dialkylaminoalkyl wherein each alkyl is of up to 6 carbon atoms, or R^{1} is joined to R^{2} as defined below;
and wherein X is $-CONR^{2}-$, $-CSNR^{2}-$, $-NR^{12}CO-$,

$-NR^{12}CS-$, $-NR^{12}CONR^{2}-$, $-NR^{12}-\overset{\overset{NR^{22}}{\|}}{C}-NR^{2}-$,

$-SO_2NR^{2}-$ or -CO-;

or, when R^1 is not hydrogen, is -O-, $-NR^2-$, $-(NO)R^2-$, $-(PO)R^2-$, $-NR^{12}COO-$; $-NR^{12}SO_2-$, -S-, -SO- or $-SO_2-$;
wherein R^2 is hydrogen or alkyl of up to 6 carbon atoms, or R^1 and R^2 together form alkylene or halogenoalkylene such that, with the adjacent nitrogen atom, they form a heterocyclic ring of 5 to 7 ring atoms, one of which atoms may be a second heterocyclic atom selected from oxygen, sulphur and nitrogen;
wherein R^{12} is hydrogen or alkyl of up to 6 carbon atoms;
and wherein R^{22} is hydrogen, cyano or nitro;
or a salt thereof when appropriate, characterised by:-

(a) when X has the formula $-CONR^2-$, $-CSNR^2-$ or $-SO_2NR^2-$, the reaction of a compound of the formula ST^1-A-Z^1, wherein A has the meaning stated above, wherein ST^1 either has the same meaning as stated above for ST, or is an equivalent 7α-linked steroid nucleus which bears one or more protecting groups for functional derivatives, and wherein Z^1 is an activated group derived from a carboxylic, thiocarboxylic or sulphonic acid, with an amine of the formula HNR^1R^2, wherein R^1 and R^2 have the meanings stated above;
or (b) when X has the formula -CO-, the reaction of an acid of the formula $ST^1-A-COOH$, wherein ST^1 and A have the meanings stated above, with an organometallic compound of the formula R^1-M, wherein R^1 has the meaning stated above and M is a metal group;
or (c) when X has the formula -S-, -O-, $-NR^2-$ or $(PO)R^2$, the reaction of a compound of the formula ST^1-A-Z^2, wherein ST^1 and A have the meanings stated above and wherein Z^2 is a displaceable group,

with a compound of the formula R^1SH, R^1OH, HNR^1R^2 or $R^1R^2P\text{-}C_6H_5$, wherein R^1 and R^2 have the meanings stated above, whereafter a phosphonium salt is hydrolysed to the phosphinyl compound;

or (d) when X has the formula $-NR^{12}CO-$, $-NR^{12}CS-$, $-NR^{12}CONR^2-$, $-NR^{12}-\overset{\overset{NR^{22}}{\|}}{C}-NR^2-$, $-NR^{12}COO-$ or $-NR^{12}SO_2-$, the reaction of a compound of the formula $ST^1\text{-}A\text{-}NHR^{12}$, wherein ST^1, A and R^{12} have the meanings stated above, with an acylating agent derived from an acid of the formula R^1COOH, R^1CSOH, R^1OCOOH or R^1SO_2OH; or, for the manufacture of a urea, with an isocyanate of the formula R^1NCO; or, for the manufacture of a guanidine, with a cyanamide of the formula $R^1NR^2\text{-}CN$;

or (e) when -A- is alkenylene of the formula $-A^3\text{-}CH=CH\text{-}A^4-$, the reaction of a compound of the formula:-

$$ST^1\text{-}A^3CHO$$

wherein ST^1 and A^3 have the meanings stated above, with a triphenylphosphonium salt of the formula:-

$$R^1X\text{-}A^4\text{-}CH_2\text{-}P^+(Ph)_3\ Q^-$$

wherein R^1, X and A^4 have the meanings stated above and wherein Q^- is an anion;

wherafter:

(i) any protecting group in ST^1 is removed by conventional means;

or (ii) a steroid derivative wherein ST is a 17 -hydroxy-steroid derivative may be converted by conventional reactions into the corresponding 17- keto steroid derivative, and thence to the corresponding 17

-hydroxy-17 -hydrocarbyl steroid derivative (that is,a steroid derivative wherein R^{27} is alkyl, alkenyl or alkynyl);

or (iii) a steroid derivative wherein R^3 and/or R^{17} are other than hydrogen may be obtained from the corresponding compound wherein R^3 and/or R^{17} are hydrogen by a conventional etherification or esterification process;

or (iv) a steroid derivative wherein R^3 and/or R^{17} are hydrogen may be obtained by hydrolysis of the corresponding compound wherein R^3 and/or R^{17} are other than hydrogen;

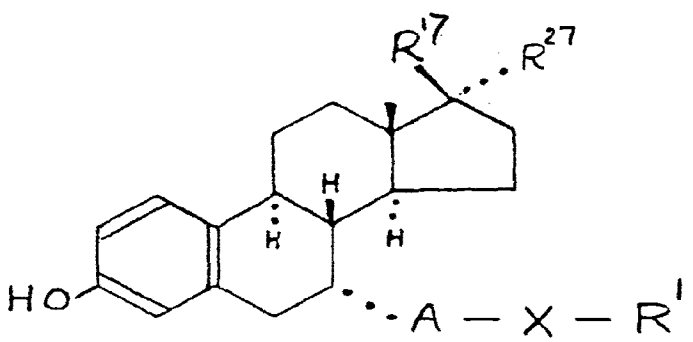
or (v) a steroid derivative wherein A is alkenylene may be hydrogenated to provide the corresponding compound wherein A is alkylene;

or (vi) a steroid derivative wherein -X- is $-CH_2NR^2-$ or $-NR^2CH_2-$ may be obtained by the reduction of the corresponding compound wherein -X- is $-CONR^2-$ or $-NR^2CO-$;

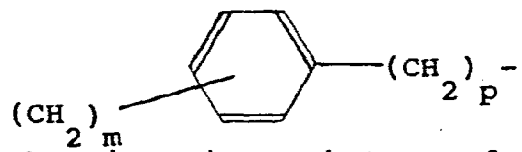
or (vii) a steroid derivative wherein -X- is -CSNH- or -NHCS- may be obtained by the reaction of the corresponding compound wherein X is -CONH- or -NHCO- with 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide;

or (viii) a steroid derivative wherein X is $-(NO)R^2$, -SO- or $-SO_2-$ may be obtained by the oxidation of the corresponding compound wherein X is $-NR^2-$ or -S-.

2. A process as claimed in claim 1 for the manufacture of a steroid derivative of the formula $ST-A-X-R^1$ wherein ST has the formula:-



wherein R^{17} is hydroxy and R^{27} is hydrogen or ethynyl, or R^{17} and R^{27} together form oxo;
wherein -A- is $-(CH_2)_n-$, wherein n is an integer from 3 to 14, or -A- is:-



wherein m is an integer from 2 to 9 and p is 0 to 2;
wherein R^1 is alkyl, fluoroalkyl or cycloalkyl each of up to 10 carbon atoms, or phenyl, chlorophenyl or benzyl, or is linked to R^2 as stated below;
wherein X is $-CONR^2-$, $-NR^{12}CO-$, -S-, -SO- or $-SO_2-$,
wherein R^2 is hydrogen or alkyl of up to 3 carbon atoms or together with R^1 forms alkylene of 5 or 6 carbon atoms, and wherein R^{12} is hydrogen or alkyl of up to 3 carbon atoms, characterised by:-
(a) when X has the formula $-CONR^2-$,
the reaction of a compound of the formula ST^1-A-Z^1, wherein A has the meaning stated above, wherein ST^1 either has the same meaning as stated above for ST, or is an equivalent 7α-linked steroid nucleus which bears one or more protecting groups for functional derivatives, and wherein Z^1 is an activated group derived from a carboxylic acid, with an amine of the formula HNR^1R^2, wherein R^1 and R^2 have the meanings stated above;
or (b) when X has the formula -S-,
the reaction of a compound of the formula ST^1-A-Z^2, wherein ST^1 and A have the meanings stated above and wherein Z^2 is a displaceable group, with a compound of the formula R^1SH,
wherein R^1 has the meaning stated above;

or (c) when X has the formula $-NR^{12}CO-$, the reaction of a compound of the formula $ST^{1}-A-NHR^{12}$, wherein ST^{1}, A and R^{12} have the meanings stated above, with an acylating agent derived from an acid of the formula $R^{1}COOH$;

or (d) when -A- is alkylene of the formula $-A^{3}-CH_2-CH_2-A^{4}-$, the reaction of a compound of the formula:-

$$ST^{1}-A^{3}CHO$$

wherein ST^{1} and A^{3} have the meanings stated above, with a triphenylphosphonium salt of the formula:-

$$R^{1}X-A^{4}-CH_2-P^{+}(Ph)_3 \quad Q^{-}$$

wherein R^{1}, X and A^{4} have the meanings stated above and wherein Q^{-} is an anion. followed by the hydrogenation of the alkenylene group $-A^{3}-CH=CH-A^{4}-$ thus formed;

whereafter:

(i) any protecting group in ST^{1} is removed by conventional means;

or (ii) a steroid derivative wherein ST is a 17 -hydroxy-steroid derivative may be converted by conventional reactions into the corresponding 17- keto steroid derivative, and thence to the corresponding 17 -hydroxy-17 -ethynyl steroid derivative;

or (iii) a steroid derivative wherein X is -SO- or $-SO_2-$ may be obtained by the oxidation of the corresponding compound wherein X is -S-.

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(54) Title: AN INJECTABLE SOLUTION OF TESTOSTERONE UNDECANOATE

(54) 发明名称: 十一酸睾丸素注射液

(57) Abstract

The invention relates to an injectable solution of testosterone undecanoate, which contains testosterone undecanoate as the active component, injectable plant oil and/or benzyl benzoate. The injectable solution can be used to treat the diseases which need androgen therapy and need androgens for long-term therapy or replacement therapy. The injectable solution according to the invention also can be used alone or together with progestins or estrogens for long-effect male contraception.

(57) 摘要

本发明涉及十一酸睾丸素注射液, 它包括作为活性成份的十一酸睾丸素、注射用植物油和/或苯甲酸苄酯。该注射液用于治疗需雄激素治疗的疾病和需雄激素作长程或终身取代治疗的疾病;本发明的注射液单独或与少量孕激素或雌激素合用, 用于长效男性避孕。

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十一酸睾丸素注射液

本发明涉及长效十一酸睾丸素注射液，本发明还涉及将十一酸睾丸素注射液用于治疗需雄激素类药作长程治疗或终生取代治疗的疾病，及以十一酸睾丸素注射液与少量孕激素或雌激素联合用药，用于长效男性避孕。

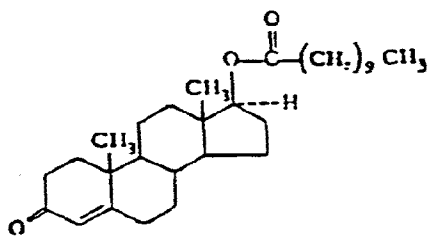
本发明作出之前，临床上对于需雄激素作长短程治疗或终生取代性治疗的疾病，如男子性功能低下症(包括克兰菲特综合症)、慢性再生障碍性贫血、转移性乳腺癌等症，国内常用的有丙酸睾丸素注射液，由于此药不能维持长效，故需每周肌注 2—3 次，由于吸收较差，长期应用致使注射部位大片皮肤硬结，病人痛苦不堪，以至无法注射；还常用口服雄激素剂如甲基睾丸素或康力龙，因为这些药品可损害肝功能，则不能长期使用。国外应用长效睾丸素制剂有庚酸睾丸素注射液、环戊丙酸睾丸素注射液，其长效维持时间为 2—4 周，一般需每 2 周肌注 1 次；国外口服雄激素制剂有十一酸睾丸素胶囊，此药对肝功能无损害，但口服给药经肠道及肝脏大部分被代谢失效，(即首过消除)，仅小部分经淋巴吸收故生物利用度低，需每日服用较大剂量，始能获效。上述进口雄激素类制剂价格昂贵，且需化费大量外汇，增加国家和人民医药费负担。另一方面，国内外尚无解决安全有效的男用避孕药，在过去二十年中，我国在研究棉酚作为男用避孕药取得很大成绩，但终因棉酚可引起低血钾等不良反应而不能推广。

本发明的目的在于寻找一种克服已有雄激素制剂存在的缺陷，开发能使雄激素活性维持更长时间的新型长效雄激素类制剂。

本发明人经多种动物实验研究证实将十一酸睾丸素制成油剂注射液，肌肉注射一次，可使雄激素(十一酸睾丸素)活性持续 70 以上并对需雄激素类药作长程治疗或终生取代性治疗的疾病显示出优良疗效。另外当其与少量孕激素或雌激素联合用药时，还可作为长效男性避孕药。该注射液不损害肝脏，不良反应少，使用安全，生

产成本低。本发明基于上述研究得以完成。

本发明的十一酸睾丸素注射液，由十一酸睾丸素、注射用植物油及药用规格的苯甲酸苄酯组成，其中以含有或不含苯甲酸苄酯的注射用植物油为混合溶媒，制剂规格为每1—2ml注射液含125—250mg十一酸睾丸素。所用的十一酸睾丸素的化学名为17β—羟基雄甾—4烯—3—酮—十一烷酸酯，结构式为



分子式为$C_{30}H_{48}O_3$，分子量为456.71，本品为白色结晶，或结晶性粉末，按干燥器计算，含$C_{30}H_{48}O_3$应为97.0—103.0%，比旋度〔d〕$_D^{25}$68℃～+72°，不溶于水和二甲基亚砜，能溶于丙酮和乙酸乙酯，紫外光谱(PE565型分光光度计)$\lambda_{max}^{C_2H_5OH}$ 239—240nm，红外光谱(Perkin—Klmer577型)ν_{max}^{KBr} cm^{-1}2910，1735(酯基Vc=o)，1670(C3酮基Vc=o)，1608(Vc4=C5)，1170及1270(酯Vc=o)。苯甲酸苄酯为药用规格，符合中国药典63年版规定，注射用植物油的质量标准符合中国药典85年版二部附录P4规定。注射用植物油可以是花生油、豆油、麻油、茶油、橄榄油等。

本发明内容通过以下实施例作进一步说明。

实施例1

本发明注射液的制备：取注射用植物油置烘箱中，150℃灭菌1小时，并放冷，然后按配比量与药用苯甲酸苄酯混匀成含5—15%的注射用植物油混合溶媒，取出部分溶媒加入十一酸睾丸素，搅拌使溶，再加适量溶媒至全量，过滤，灌封于干燥安瓿中，100℃流通蒸汽灭菌30分钟即得本发明注射液，制剂规格为每1—2ml含125—250mg十一酸睾丸素。

实施例2

2—1. 药理作用：(1)雄激素活性比较：给去势雄性大鼠及去

势雄鸡肌内注射十一酸睾丸素 13.7mg/kg(3×10^{-5}mol/kg)，产生典型的雄激素作用，持续时间为 70 天左右，同时以此剂量的庚酸睾丸素肌肉注射及丙酸睾丸素 1.5×10^{-5}mol/kg 分 7 天肌肉注射于去势雄大鼠与去势雄鸡，也有相似作用，但持续时间分别为 50 天与 20 天。见表 1、2，图 1，其中 TP 组为用丙酸睾丸酮注射液(分子量 344.48)、TE 组为用庚酸睾酮注射液(分子量为 400.60)，TU 组为用十一酸睾丸素注射液 。

表 1

十一酸睾丸素与其他两种睾酮制剂对去势大鼠性器官发育的影响

睾酮制剂及给药量	动物数	剖杀时间（给药后天数）	器官重 $\bar{X}$±SD(mg/100gwb)		
			前列腺	储精囊	提肛肌
十一酸睾丸素 3.0×10^{-5} mol/kg 单次肌注	6	10	22.1±6.4	55.0±19.2	95.2±16.4
	6	25	17.8±9.8	59.5±28.2	77.2±22.7
	6	40	11.8±6.3	31.1±14.5	70.0±27.2
	6	55	10.4±3.7	26.4±5.3	83.6±6.1
	6	70	7.4±3.1	22.2±6.3	79.5±14.4
庚酸睾酮 3.0×10^{-5} mol/kg 单次肌注	6	10	43.7±11.2	73.0±19.2	127.0±18.9
	6	25	27.4±10.7	68.3±19.8	112.4±17.0
	6	40	16.5±8.2	35.2±9.6	78.6±15.7
	6	55	7.5±2.8	15.6±3.7	57.8±7.0
	6	70	6.3±1.2	16.3±1.7	53.2±9.5
丙酸睾酮 1.5×10^{-5} mol/kg 分 7 天肌注	6	10	33.3±7.0	72.3±25.0	119.0±23.0
	6	25	5.3±2.2	14.3±3.4	39.4±5.2
	6	40	5.9±2.1	18.4±5.6	38.4±5.8
	6	55	3.6±1.8	10.3±2.2	32.2±3.4
	6	70	3.0±1.2	8.2±2.4	26.3±4.2
对照组 适量精制茶油 单次肌注	6	10	1.8±0.9	5.0±0.9	21.2±5.5
	6	25	2.5±1.0	3.9±1.4	27.9±4.1
	6	40	2.4±0.2	6.8±1.1	23.6±4.0
	6	55	1.5±0.7	4.8±1.5	21.9±4.0
	6	70	2.2±0.8	6.1±1.8	19.3±4.0

替换页(细则第 26 条)

表 2

十一酸睾丸素与其他两种睾酮制剂对去势雄鸡鸡冠发育的影响

睾酮制剂	剂量 mol/kg	动物数	鸡冠高度 $\bar{X}$±SD(mm/kgwb)							
			给药前	给药后时间(周)						
				1	2	3	4	5	6	9	11
十一酸睾丸素	3.0×10^{-5} 单次肌注	5	21.1±4.4	26.3±6.0	30.3±5.9	29.9±6.4	26.4±6.1	26.2±6.0	24.7±5.3	23.2±4.8	19.9±4.5
庚酸睾酮	3.0×10^{-5} 单次肌注	5	21.8±3.6	28.1±6.1	29.4±7.6	26.1±5.0	23.9±6.1	20.7±5.1	18.5±4.1	16.51±6.1	5.5±5.9
丙酸睾酮	1.5×10^{-5} 分7天肌注	5	19.4±4.0	29.5±5.0	25.2±3.3	21.6±3.0	20.0±4.3	18.5±2.2	17.4±2.7	14.6±2.4	13.8±2.4
对照	适量精制茶油 单次肌注	5	18.9±3.0	15.8±4.4	16.4±3.0	14.1±2.8	12.7±2.4	11.8±1.7	11.4±1.7	9.6±1.5	9.2±1.2

替换页(细则第26条)

TU 的剂量为 3.0×10^{-5}mol/kg，单次肌注。
TE 的剂量为 3.0×10^{-5}mol/kg，单次肌注。
TP 的剂量为 1.5×10^{-5}mol/kg，7 天分肌注。
对照组用精制茶油适量，单次肌注。

图 1 说明：十一酸睾丸素与其他两种睾丸酮制剂对去势雄鸡鸡冠发育影响比较(4 只典型动物的鸡冠大小变化)。

十一酸睾丸素肌肉注射与口服给药的雄激素活性比较：

去势雄大鼠的性器官为指标，口服级在剂量 9.0×10^{-5}mol/kg 时作用微弱，剂量高达 18.0×10^{-5}mol/kg 时，10 天后始与肌注 3.0×10^{-5}mol/kg 相仿的药效，25 天后药效明显消退。说明 TU 肌注给药时的药效约为口服给药时的 6 倍，且作用维持时间也显著延长。结果见表 3。

表 3

十一酸睾丸素对去势大白鼠肌注与经口给药的药效

TU 的剂量与给药途径	动物数	剖杀时间(给药后天数)	器官重 $\bar{X}$±SD(mg/100gwb)		
			前列腺	储精囊	提肛肌
十一酸睾丸素 3.0×10^{-5} mol/kg 单次肌注	5	10	26.9±6.8	48.8±16.1	101.3±17.1
	5	25	17.5±5.3	45.9±21.0	81.9±11.5
十一酸睾丸素 9.0×10^{-5} mol/kg 分 7 天口服	5	10	3.1±0.4	4.9±1.1	39.4±1.8
	5	25	2.2±0.2	9.0±2.5	30.9±2.4
十一酸睾丸素 18.0×10^{-5} mol/kg 分 7 天口服	5	10	23.4±1.8	40.7±6.5	99.7±13.5
	5	25	6.1±1.1	14.9±5.0	48.1±8.8
对照适量纯茶油 分 7 天口服	5	10	1.5±0.8	5.6±0.9	22.0±4.2
	5	25	2.5±0.8	4.1±1.5	30.2±4.0

替换页(细则第 26 条)

(2) 对实验性贫血的治疗作用：给去势大鼠皮下注射能破坏周围红细胞的苯肼，每天 25mg/kg，连续 3 天，血色素(Hb)、红细胞(RBC)显著减少，而网织红细胞(Rtc)比例增加，以后继续皮下注射苯肼 40mg/kg/周，连续 11 周，以造成贫血，从给予苯肼后第 4 天开始肌肉注射十一酸睾丸素 3.0×10^{-4}mol/kg (12 周内分 4 次给药)，同时设丙酸睾丸素组，4.3×10^{-4}mol/kg 总量，每周肌肉注射 2 次，共治疗 12 周，对照组给予适量茶油。开始治疗时，丙酸睾丸素与十一酸睾丸素疗效相近，随着疗程的延长，十一酸睾丸素在 Hb、RBC 及 Rtc 三项指标均明显优于丙酸睾丸素。结果见附表 4。所得数据显示十一酸睾丸素对苯肼所致实验性贫血有确切的疗效。

(3) 十一酸睾丸素合并孕激素或雌激素对雄性大鼠的抗生育作用：取具有生育力的雄性大鼠，第 1 个月肌肉注射十一酸睾丸素(TU)2 次，第 2 次及第 3 个月各给药 1 次，每次 12mg/kg，每次分别配伍醋酸甲孕酮 (MDP) 7mg/kg 或戊酸雌二醇(EDV)0.7mg/kg，肌肉注射，连续给 3 个月后停药，在给药期间与停药后 3 个月内，每月与雌鼠合笼 10 天，经阴道涂片检查，确证已交配的雌鼠，于交配后 15 天剖杀，按雌鼠怀孕率作为判断雄鼠生育力的指标。结果 TU+EDV 组的第 2 个月开始至五个月(停药后 2 个月)，雄鼠完全丧失其生育力。TU+MDP 组从第 3 个月至第 5 个月，雄鼠亦完全丧失生育力，均停药 3 个月开始恢复生育力。结果见表 5。

表 4

十一酸睾丸素与丙酸睾丸素对苯肼所致去势大鼠实验性贫血的作用

项目	组别	动物数	实验数据 ($\bar{X}$±SD)					
			注射苯肼前	注射苯肼后	开始治疗后周数			
					2	4	8	12
Hb (g/dL)	A	13	12.2±0.5	8.8±0.5	9.9±0.4	11.1±0.3*	10.2±0.3	13.1±0.3**
	B	13	11.8±0.8	8.4±0.6	9.9±0.5	11.0±0.4*	9.8±0.3*	12.2±0.4*
	C	13	12.2±0.7	8.8±0.6	8.6±0.6	8.9±0.6	8.4±0.5	10.7±0.7
RBC (百万/mm³)	A	13	7.6±1.3	5.1±0.6	4.3±0.9	4.8±0.5*	5.2±0.6**	7.3±0.7**
	B	13	7.5±0.6	4.6±1.0	3.9±0.5	4.9±0.6**	4.6±0.7*	6.7±0.7*
	C	13	8.3±1.9	4.3±0.8	3.2±1.4	3.5±1.1	3.3±0.6	5.3±0.6
Rto (Z)	A	13	0.4±0.7	39.3±9.8	72.0±6.1*	54.0±7.2*	38.5±2.7	15.2±3.4**
	B	13	0.3±0.5	39.8±5.9	73.2±5.0*	47.8±4.6	41.6±3.6	23.8±3.6*
	C	13	0.5±0.7	39.2±7.9	51.9±6.7	41.6±7.0	49.8±6.1	33.1±3.0
WBC (千/mm³)	A	13	14.8±3.5	20.5±4.6	13.2±2.1	17.9±3.5	11.4±3.3	10.3±1.7
	B	13	16.0±4.3	20.1±4.3	12.5±4.2	16.3±7.0	10.5±1.9	10.1±2.2
	C	13	15.0±3.2	18.6±5.3	12.9±2.7	16.1±3.8	12.1±2.4	10.7±1.2
体重 (kg)	A	13	0.34±0.03	0.33±0.03	0.39±0.03	0.41±0.03	0.46±0.03*	0.47±0.04**
	B	13	0.32±0.04	0.30±0.04	0.35±0.04	0.37±0.05	0.40±0.06	0.42±0.06
	C	13	0.32±0.02	0.31±0.02	0.33±0.02	0.35±0.02	0.38±0.03	0.38±0.03

注：1 A 组给予十一酸睾丸素，B 组给予丙酸睾丸素，C 组给予精制茶油，剂量与给药法详见正文。

2 * $P<0.05$，** $P<0.01$，均指 A 或 B 组分别与 C 组比较(t 测验)

替换页(细则第 26 条)

表 5

十一酸睾丸素配伍甲孕酮或戊酸雌二醇对雄性大鼠抗生育作用

药物与剂量 (mg/kg im)	有生育力雄鼠比率						
	给药前	给药期间(月)			停药期间(月)*		
		1#	2	3	4	5	6
TU 12.0 EDV 0.7	6/6	1/6	0/6	0/6	0/6	0/6	1/6
TU 12.0 MDP 7.0	6/6	5/6	3/6	0/6	0/6	0/6	6/6
对照组	6/6	6/6	4/6	5/6	5/6	5/6	5/6

第 1 个月给药 2 次，第 2,3 个月各给药 1 次，

* 按第 1 次给药计算

2—2 体内吸收、分布与消除：大鼠肌肉注射〔^{3}H〕十一酸睾丸素，2 天后出现血浆放射性高峰，32 天和 60 天后的血浆放射性分别为峰值的 13.3%和 9.9%，放射活性 t1/2β 为 15.4 天。体内分布以肝、肾、脂肪为高，提肛肌、附睾、前列腺等次之。药后 60 天，肌注部位残留放射性为给药量的 19.9%；尿和粪中放射性累积排泄量分别为给药量的 41.9%与 9.3%。在尿中排出原型药占 7.2%。结果见图 2，表 6。

图 2 说明：图 2 表示 4 只鼠肌注〔^{3}H〕TU12mg(14.76MBq)/kg 后血浆放射性—时间曲线($\bar{X}$±SD)

表 6

大鼠肌注[^{3}H]TU 12 mg(14.76 MBq)/kg

后组织中放射性分布(dpm×10^{-3}, $\bar{X}$±SD)

组　织	2 天	30 天	60 天
肝　脏	15.40±2.10	2.20±0.80	0.50±0.20
肾　脏	10.00±2.70	3.40±2.30	1.10±0.80
睾　丸	4.50±1.30	1.50±0.90	0.13±0.07
附　睾	6.70±1.70	1.30±0.60	0.33±0.07
前　列　腺	3.30±0.50	0.80±0.50	0.16±0.09
储精囊	3.90±0.50	0.90±0.50	0.08±0.04
提肛肌	3.50±0.60	2.50±1.00	2.30±0.40
脂　肪	14.10±7.60	1.60±0.80	0.90±0.50

注：4 只大鼠的均数

实施例 3

急性毒性，长期毒性及致突变试验

3—1 急性毒性试验 小鼠皮下注射十一酸睾丸素 3.75mg/kg（为大鼠有效量的 270 倍），观察 14 天未发现死亡或异常反应。

NIH 小鼠，体重 17—20g，雌雄各半，皮下注射 十一酸睾丸素注射液，观察给药后 14 天内毒性反应与死亡数，结果见表 7。

表 7 十一酸睾丸素的急性毒性试验

剂 量 (g/kg sc)	动物数	死亡数	异常反应
2.5	12	0	无
3.75	12	0	无

3—2 长期毒性试验 (1)大鼠试验：4 周龄 Wistar 大鼠 75 只，分为三组，A 组 8♀17♂，B 组 10♀15♂，对照 C 组 10♀15♂。每月肌注药物 1 次。A 组给注射用茶油作为对照，B 组给 TU42mg/kg，C 组给 TU14mg/kg，连续 6 个月。试验期间 A、B、C 三组分别有 3、4、2 只鼠死亡，似与给药无关。试验结果表明 TU 对肝、肾功能无不良影响，能使♀鼠红细胞及血红蛋白增加，体重增加加快。除 TU 高剂量组使个别鼠的曲细精管生精细胞层次减少外，未见其他明显病理变化。

(2) 狗试验结果：10—12 月龄犬 14 只，分为 3 组，A 组 4♀2♂，B 组 2♀2♂，C 组 2♀2♂。每月 im 药物 1 次，A 组给注射用植物油作为对照，B 组给 TU100mg/kg，C 组给 TU20mg/kg，连续 6 个月。

结果表明：

a. 一般体征等变化 在给药 3 个月内，各组狗食欲均佳，体重增加 1.4—1.5 倍。在用药 6 个月后，高剂量组食量比其余组减少，

体重增长相对缓慢，比用药前增长 1.7—1.9 倍；而低剂量组与对照组体重增长接近，平均 2.3—2.4 倍于用药前。高剂量组与对照组比较，体重增长显著减慢。

b. 血常规及血液生化项目观察　用药前后 WBC、Hgb 及 Pt 值各组均无明显改变。在给药 6 个月后，各组 RBC 计数明显升高，但给药组高、低剂量与对照组比较，RBC 升高无显著差别。

肝、肾功能测定结果表明：高、低剂量用药组与对照组在用药 6 个月内 SGPT 与 BUN 值与用药前比较无明显差别，均在正常范围内。

c. 心电图检查　各组动物心率、P—R 间期、QRS 波群及 Q—T 间期均在正常范围，用药前后无明显改变，也未出现异位节律。在给药 6 个月后，高剂量与对照组中各有 1 只狗出现 ST 段压低 0.5mv，此改变尚属正常范围。

d. 病理学检查　用药 6 个月并在停药 7 天后，每组各杀狗 2 只（雌、雄各 1 只），对重要脏器心、肝、肾、肺、脑垂体、胃、肠等作肉眼观察，未发现明显病变。经对肝、肾、睾丸及附睾切片镜检，结果显示：各组 2 只狗的肝实质细胞无明显改变，给药高、低剂量狗的肾皮质组织结构正常。高剂量组雄狗睾丸曲细精管径缩小，精子细胞受抑，精子显著减少，精原细胞无改变，低剂量相雄狗睾丸曲细精管组织结构基本正常。高剂量组雄狗附睾管腔少精或无精，而低剂量组狗附睾管腔精子数量稍有减少。

(3)致突变试验　将十一酸睾丸素纯品配制成不同浓度的系列溶液，测试菌株为组氨酸缺陷型鼠伤寒沙门氏菌，结果见表 8。