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(54) **FORMULATION**

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(58) **Field of Search** 514/177, 178

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,822,316 A		2/1958	Richter et al.
2,983,649 A		5/1961	Ercoli et al.
3,541,209 A		11/1970	Neumann et al.
RE28,690 E	*	1/1976	Lehmann et al.
4,048,309 A		9/1977	Chen et al.
4,048,310 A		9/1977	Chen et al.
4,659,516 A		4/1987	Bowler et al.
4,888,331 A		12/1989	Elger et al.
5,095,129 A		3/1992	Ottow et al.
5,183,814 A		2/1993	Dukes
5,484,801 A		1/1996	Al-Razzak et al.
5,733,902 A		3/1998	Schneider
5,929,030 A		7/1999	Hamied et al.

FOREIGN PATENT DOCUMENTS

EP	0 138 504	4/1985
EP	0 346 014	12/1989
FR	6241	9/1968
GB	817241	7/1959
GB	1 126 892	9/1968
GB	1 207 571	10/1970
GB	1 569 286	6/1980
SU	549118	3/1977
SU	676284	7/1979
WO	WO 95/12383	5/1995
WO	WO 96/19997	7/1996
WO	WO 97/21440	6/1997
WO	WO 97/37653	10/1997
WO	WO 97/40823	11/1997
WO	WO 98/11902	3/1998
ZA	681014	2/1968
ZA	682530	4/1968

OTHER PUBLICATIONS

Remington's Pharmaceutical Sciences, 18th ed., 1990, p. 219.*

(List continued on next page.)

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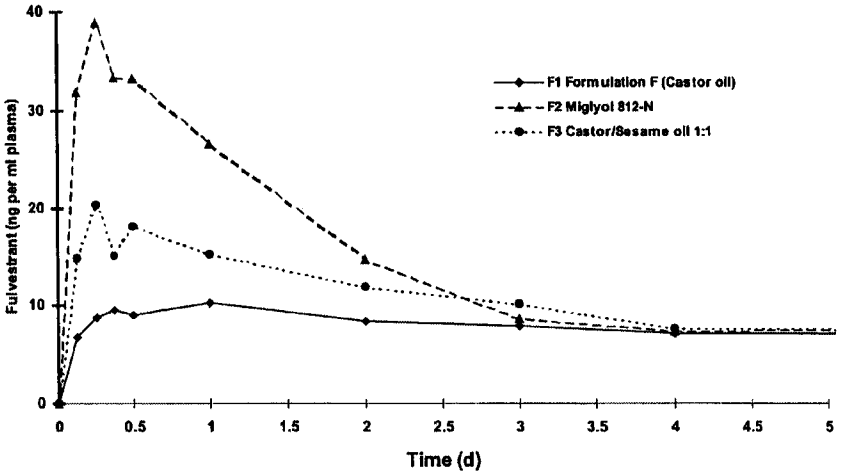
(57) **ABSTRACT**

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.

9 Claims, 1 Drawing Sheet



OTHER PUBLICATIONS

Davis et al., "17–Alpha–Hydroxyprogesterone–Caproate . . . with Chemically Pure Progesterone", J. Clin. Endocrinol. And Metabolism, 1955, vol. 15, pp. 923–930.

Dukes et al., "Antiuterotrophic effects of the pure antioestrogen ICI 182, 780 . . . quantitative magnetic resonance imaging"; J. Endocrinology, 1992, vol. 138, pp. 203–209.

Dukes et al., "Antiuterotrophic effects of pure antioestrogen. ICI 182,780 . . . the uterus in ovariectromized monkeys", J. Endocrinology, 1992, vol. 135, pp. 239–247.

Howell et al., "Pharmacokinetics, pharmacological and anti–tumour effects of the specific anti–oestrogen ICI 182780 in women with advanced breast cancer", British Journal of Cancer, 1996, vol. 74, pp. 300–308.

Martindale, 32nd Ed., "Alcohol", Pharmaceutical Press, 1999, pp. 1099–1101.

Martindale, 32nd Ed., "Benzoates" and "Benzyl Alcohol"; Pharmaceutical Press, 1999, pp. 1102–1104.

Martindale, 32nd Ed., "Caster Oil"; 32nd Ed., Pharmaceutical Press, 1999, p. 1560.

Migally, "Effect of Castor Oil and Benzyl Benzoate Used as a Vehicle for Antiandrogens on the Adrenal Cortex", Archives of Andrology 2, 1979 pp. 365–369.

Pellegrino, "Use of 17 α Hydroxyprogesterone Caproate in Threatened Abortion", Current Therapeutic Research, vol. 4, No. 6, Jun., 1962, pp. 301–305.

Piver et al., "Medroxyprogesterone Acetate (Depo–Provera) vs . . . Women with Metastatic Endometrial Adenocarcinoma", Cancer, vol. 45, American Cancer Society, 1980, pp. 268–272.

Riffkin et al., "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones", Journal of Pharmaceutical Sciences, vol. 53, No. 8, Aug. 1964, pp. 891–895.

Sawada et al., "Estrogen Receptor Antagonist ICII82,780 Exacerbates Ischemic Injury in Female Mouse", Journal of Cerebral Blood Flow and Metabolism, vol. 20. No. 1, 2000, pp. 112–118.

Vidal, Le Dictionnaire, "Benzo–Dynoestryl Retard", 1998 p. 201.

Vidal, Le Dictionnaire, "Gravibinan", 1995, pp 660–661.

Vidal, Le Dictionnaire, "Parabolan", 1997, p. 1245.

Vidal, Le Dictionnaire, "Trophobolene", 1997, pp. 1706–1707.

Wakeling et al., "A Potent Specific Pure Antiestrogen with Clinical Potential", Cancer Research, 1991, vol. 51, pp. 3867–3873.

Waterton et al., "A Case of Adenomyosis in a Pigtailed Monkey . . . Treated with the Novel Pure Antiestrogen, ICI 182,780"; Laboratory Animal Science, 1993, vol. 43, No. 3, 1993, pp. 247–251.

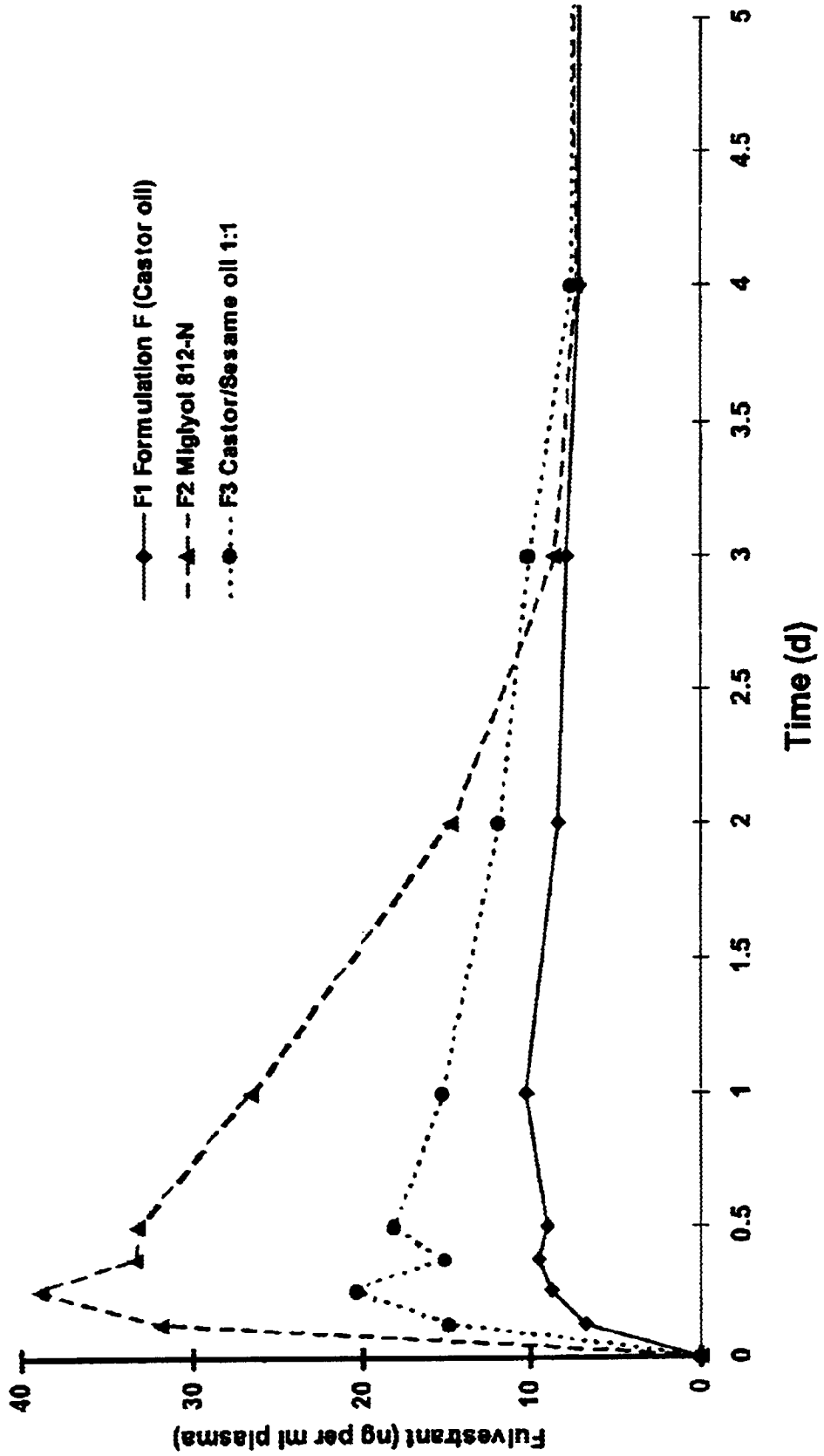
Howell et al., "Response to a specific antioestrogen (ICI 182780) in tamoxifen–resistant breast cancer", The Lancet, Jan. 7, 1995, pp. 29–30.

Osborne et al., "Comparison of the Effects of a Pure Steroidal Antiestrogen With Those of Tamoxifen in a Model of Human Breast Cancer", Journal of the National Cancer, May 1995, vol. 87, No. 10. pp. 746–750.

Robertson et al., "A Partially–Blind, Randomised, Multicentre Study Comparing The Anti–Tumor Effects of Single Doses (50, 125 and 250MG) of Long–Acting (LA) 'Faslodex' (ICI 182,780 With Tamoxifin in Postmenopausal Women with Primary Breast Cancer Prior to Surgery"; Abstract 28, 22nd Annual San Antonio Breast Cancer Symposium: Dec. 8–11, 1999, San Antonio, Breast Cancer Research and Treatment 1999; 57 (1; special issue); p. 31.

Mackey et al, "Tolerability of intramuscular injections of testosterone ester in oil vehicle", Human Reproduction, vol. 10, No. 4, pp., 869–865, 1995.

* cited by examiner



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'.
SUSTANON 100	Testosterone proprionate	30 mg	Androgen	Organon
	Testosterone phenylproprionate	60 mg		
	Testosterone isocaproate	60 mg		
	Testosterone decanoate	100 mg		
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250 $mgml^{-1}$	Progestogen	Schering HC
TOCOGESTAN	Hydroxy progesterone enantate	200 mg	Progestogen	Theramax
	Progesterone	50 mg		
	α-Tocopherol	250 mg		
TROPHOBOLENE	Estrapronicate	1.3 mg	Mixed	Theramax
	Nandrolone undecanoate	50 mg		
	Hydroxyprogesterone heptanoate	80 mg		
NORISTERAT	Norethisterone oenanthoate	200 mg	Contraceptive	Schering HC
BENZO-GYNOESTRYL	Estradiol hexahydrobenzoate	5 mg	Estradiol	Roussel
PROGESTERONE-RETARD	Hydroxy progesterone caproate	250 $mgml^{-1}$	Progestogen	Pharlon
GRAVIBINAN	Estradiol 17-β-valerate	5 $mgml^{-1}$	Mixed	Schering
	Hydroxyprogesterone caproate	250 $mgml^{-1}$		HC
PARABOLAN	Trenbolone	76 mg	Androgen	Negma
DELESTROGEN	Estradiol valerate	20 $mgml^{-1}$	Estradiol	BMS
		40 $mgml^{-1}$		
DELALUTIN	17-Hydroxy progesterone	250 $mgml^{-1}$	Progestrogen	DMS

PRODUCT NAME	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	DOSING
SUSTANON 100	ABPI Data Sheet Comp. 1999	Arachis		0.1 ml		1 ml	3 weeks
PROLUTON DEPOT	ABPI Data Sheet Comp. 1999	Castor	up to 46%			1 or 2 ml	1 week
TOCOGESTAN	Dict. Vidal 1999	Ethyl oleate	*40%			2 ml	<1 week
TROPHOBOLENE	Dict. Vidal 1997	Olive	45%			1 ml	15 to 30 days
NORISTERAT	ABPI Data Sheet Comp. 1999	Castor	YES			1 ml	8 weeks
BENZO-GYNOESTRYL	Dict. Vidal 1998	Arachis				1 ml	1 week
PROGESTERONE -RETARD	Dict. Vidal 1999	Castor	YES			1 or 2 ml	1 week
GRAVIBINAN	Dict. Vidal 1995	Castor	YES			1 or 2 ml	1–2 weeks
PARABOLAN	Dict. Vidal 1997	Arachis		75 mg	45 mg	1.5 ml	2 weeks
DELESTROGEN	J.Pharm Sci (1964) 53(8) 891	Castor	78% 58%	20% 40%	2% 2%		
DELALUTIN	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 50 mg of fulvestrant, 400 mg 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 U.S. Pat. No. 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

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