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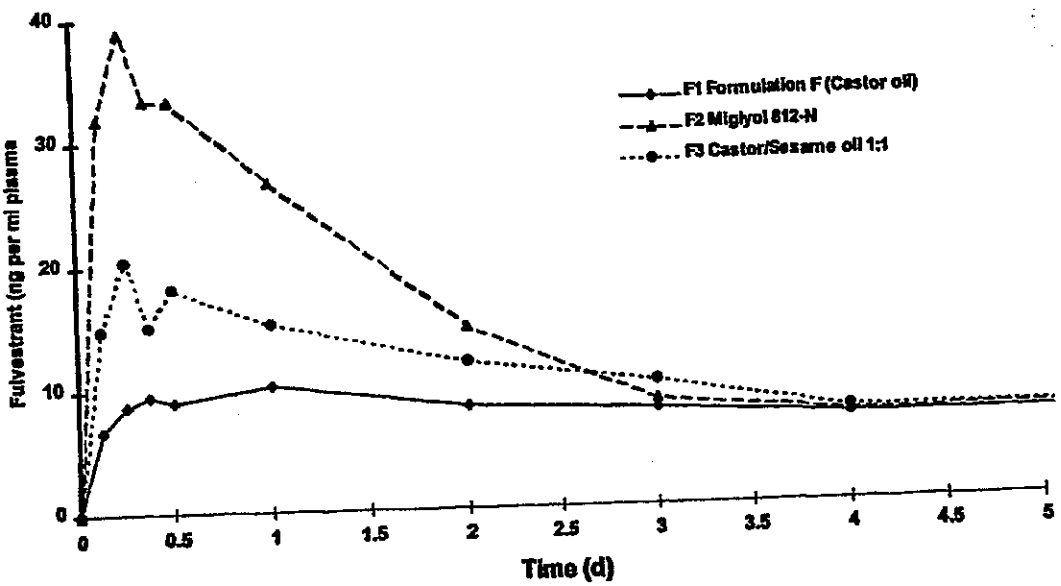
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(54) Title: FULVESTRANT FORMULATION



(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.

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FULVESTRANT 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

In US 5,183,814 Example 3 an oil based injection formulation of fulvestrant is described which comprises 50mg of fulvestrant, 400mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. Manufacture at a commercial scale of a formulation as described in US 5,183,814 will be complicated by the high alcohol concentration. Therefore, there is a need to lower the alcohol concentration in fulvestrant formulations whilst preventing precipitation of fulvestrant from the formulation.

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

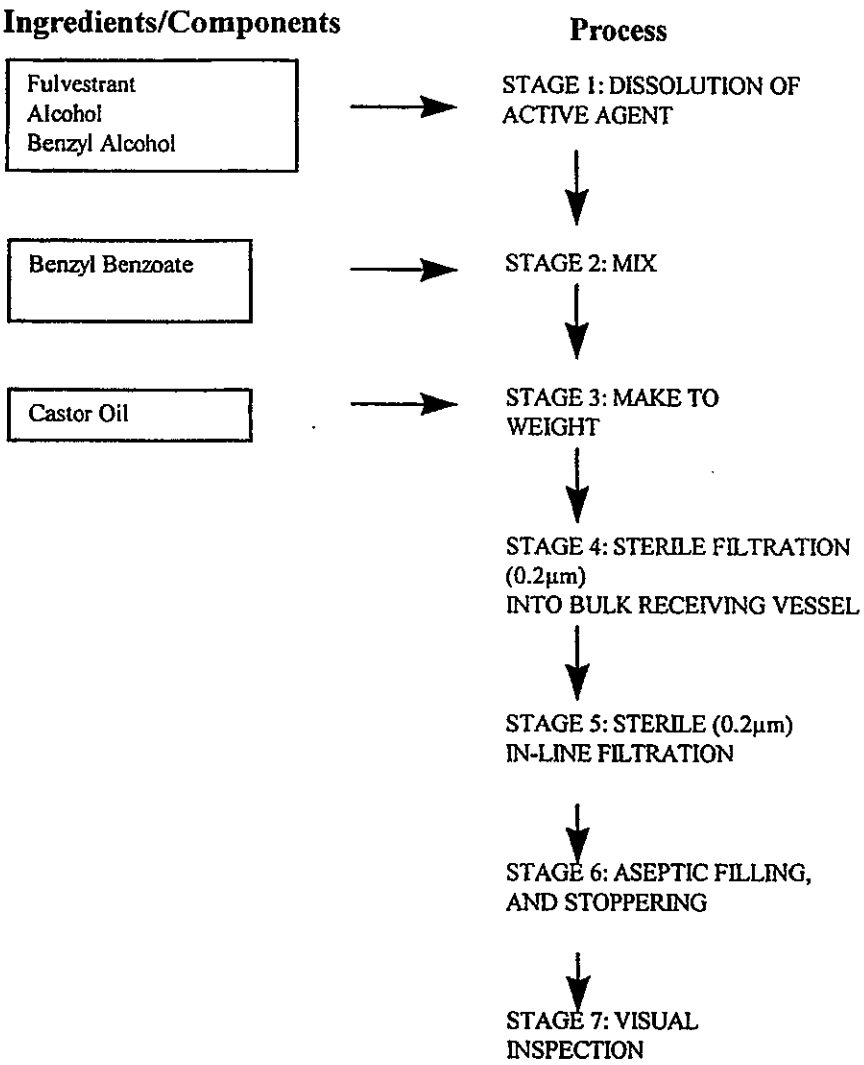
10% weight per volume of ethanol

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 comprising fulvestrant 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.

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

3. A pharmaceutical formulation as claimed in claim 1 or 2 wherein the blood plasma fulvestrant concentration attained is at least 2.5ngml^{-1} for at least 2 weeks..

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

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

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

7. A pharmaceutical formulation as claimed in 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. An pharmaceutical formulation adapted for intramuscular injection, as defined in any claim from 1 to 20, for use in medical therapy.

22. Use of fulvestrant in the preparation of a pharmaceutical formulation, as defined in any claim from 1 to 20, for the treatment of a benign or malignant disease of the breast or reproductive tract.

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

Claims

1. A pharmaceutical formulation comprising fulvestrant in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

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

3. A pharmaceutical formulation as claimed in claim 1 or 2 wherein the blood plasma fulvestrant concentration attained is at least $2.5ngml^{-1}$ for at least 2 weeks..

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

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

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

7 A pharmaceutical formulation as claimed in claim 5 which contains 15-25% w/v of a pharmaceutically acceptable alcohol.

8 A pharmaceutical formulation as claimed in claim 5 which contains 17-23% w/v of a pharmaceutically acceptable alcohol.

9. A pharmaceutical formulation as claimed in any claim from 1 to 8 which contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

10. A pharmaceutical formulation as claimed in claim 9 which contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent .

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

12. A pharmaceutical formulation as claimed in claim 9 which contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

13. A pharmaceutical formulation as claimed in claim 9 which contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

14. A pharmaceutical formulation as claimed in claim 9 which contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

15. A pharmaceutical formulation as claimed in claim 9 which contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

16 A pharmaceutical formulation as claimed in claim 9 which contains 10-25% w/v of a pharmaceutically acceptable non-aqueous ester solvent.

17 A pharmaceutical formulation as claimed in claim 9 which contains 12-18% w/v of a pharmaceutically acceptable non-aqueous ester solvent.

18 A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 15-25% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 10-25 % weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

27. A pharmaceutical formulation as claimed in any claim from 1 to 26 wherein the total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.

28. A pharmaceutical formulation as claimed in any claim from 1 to 27 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

29. A pharmaceutical formulation as claimed in claim 28 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5 to 5.25ml.

30. A pharmaceutical formulation as claimed in any of claims 1-29 wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation, and the formulation contains 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

31. A pharmaceutical formulation adapted for intramuscular injection, as defined in any claim from 1 to 30, for use in medical therapy.

32. Use of fulvestrant in the preparation of a pharmaceutical formulation, as defined in any claim from 1 to 30, for the treatment of a benign or malignant disease of the breast or reproductive tract.

33. A syringe or vial containing a pharmaceutical formulation as defined in claim 30.

INTERNATIONAL SEARCH REPORT

Inte .ional Application No
PCT/GB 01/00049

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/565 A61P35/00 A61K47/14 A61K47/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 96 19997 A (SCHERING) 4 July 1996 (1996-07-04) claims 1,5,6,8 page 16; example 5 ---	1-23
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 May 2001	18/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ventura Amat, A

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