PHARMACEUTICAL FORMULATION FOR THE INTRAMUSCULAR ADMINISTRATION OF FULVESTRANT

The invention relates to a sustained release pharmaceutical formulation adapted for administration by injection containing the compound fulvestrant, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, at concentration of at least 100mg/ml 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, Pharmacology & Therapeutics, 25:127-206, 1984; May and Westley, J Biol Chem 262:15894-15899, 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.

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.

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

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).

Our earlier application PCT/GB01/00049, WO 01/51056, describes certain fulvestrant formulations at a most preferred concentration of 50mg/ml. This application disclosed one formulation with a solubility up to 102 mg/ml – see the last formulation in Table 3 thereof with 15 % weight of ethanol per volume of formulation, 15 % weight of benzyl alcohol per volume of formulation, 15 % weight of benzyl benzoate per volume of formulation in a ricinoleate vehicle. However there is a need for further formulations of fulvestrant that contain high concentrations of fulvestrant to facilitate administration thereof at higher doses or less frequent intervals.

According to another aspect of the invention there is provided a pharmaceutical formulation adapted for intramuscular injection comprising 100 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 5 % weight of ethanol per volume of formulation vehicle and provided that the following formulation is excluded: fulvestrant up to 102 mg/ml, 15 % weight of ethanol per volume of formulation vehicle, 15 % weight of benzyl alcohol per volume of formulation vehicle, 15 % weight of benzyl benzoate per volume of formulation vehicle and 30 % or more weight of ricinoleate excipient per volume of formulation vehicle.

A preferred pharmaceutical formulation adapted for intramuscular injection is one comprising 105 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation comprises at least 5 % weight of ethanol per volume of formulation vehicle.

A more preferred pharmaceutical formulation adapted for intramuscular injection is one comprising 110 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 5 % weight of ethanol per volume of formulation vehicle.

A more preferred pharmaceutical formulation adapted for intramuscular injection is one comprising 115 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 5 % weight of ethanol per volume of formulation vehicle.

A more preferred pharmaceutical formulation adapted for intramuscular injection is one comprising 120 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 5 % weight of ethanol per volume of formulation vehicle.

A more preferred pharmaceutical formulation adapted for intramuscular injection is one comprising 130 mg/ml or more of fulvestrant, 15 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 5 % weight of ethanol per volume of formulation vehicle.

A more preferred pharmaceutical formulation adapted for intramuscular injection is one comprising 140 mg/ml or more of fulvestrant, 15 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 12.5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the

formulation vehicle comprises at least 10 % weight of ethanol per volume of formulation vehicle.

A more preferred pharmaceutical formulation adapted for intramuscular injection is one comprising 150 mg/ml or more of fulvestrant, 15 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 17.5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 10 % weight of ethanol per volume of formulation vehicle.

Another aspect of the invention provides any of the formulations described herein stated as having any minimum ethanol content removed. For example, the formulation described in the paragraph immediately above becomes: a pharmaceutical formulation adapted for intramuscular injection is one comprising 150 mg/ml or more of fulvestrant, 15 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 17.5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle.

According to another aspect of the invention there is provided a pharmaceutical formulation having a solubility for fulvestrant of at least Y mg/ml adapted for intramuscular injection comprising;

100 mg/ml or more of fulvestrant;

5% (w/v) or more castor oil per volume of formulation vehicle;

and at least the following amounts (% weight/volume of formulation vehicle) of ethanol (ETOH), benzyl alcohol (BA), benzyl benzoate (BB) determined by the algorithm:

$Y = -29.77 + 5.44 \times ETOH + 2.38 \times BA + 1.57 \times BB$

wherein x is at least 100, ETOH is at least 5, BA is at least 5 and BB is at least 5.

A preferred pharmaceutical formulation is one wherein Y is selected from the group consisting of 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 170, 180, 190, and 200.

A more preferred pharmaceutical formulation is one wherein Y is selected from the group consisting of 120, 125, 130, 135, 140, 145, 150, 155, 160, 170, 180, 190, and 200.

A more preferred pharmaceutical formulation is one wherein Y is selected from the group consisting of 150, 155, 160, 170, 180, 190 and 200.

A more preferred pharmaceutical formulation is one wherein Y is selected from 150, 155, 160, 170, 180, 190 and 200 and the formulation comprises at least 150mg/ml of fulvestrant.

A more preferred pharmaceutical formulation is one wherein Y is 200 and the formulation comprises at least 200mg/ml of fulvestrant.

According to another aspect of the present invention there is provided a pharmaceutical formulation having a solubility for fulvestrant of at least 100 mg/ml adapted for intramuscular injection comprising;

100 mg/ml or more of fulvestrant;

5% (w/v) or more castor oil per volume of formulation vehicle;

and at least the following amounts (% weight/volume of formulation vehicle) of ethanol (EtOH), benzyl alcohol (BA), benzyl benzoate (BB) determined by the algorithm:

$100 = -29.77 + 5.44 \times ETOH + 2.38 \times BA + 1.57 \times BB$; and

provided that the following formulation is excluded: fulvestrant up to 102 mg/ml, 15 % weight of ethanol per volume of formulation vehicle, 15 % weight of benzyl alcohol per volume of formulation vehicle, 15 % weight of benzyl benzoate per volume of formulation vehicle and 30 % or more weight of castor oil per volume of formulation vehicle.

According to another aspect of the invention there is provided a pharmaceutical formulation comprising fulvestrant at a concentration of at least 100 mg/ml 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 in a human for at least 2 months and provided that the following formulation is excluded: fulvestrant up to 102 mg/ml, 15 % weight of ethanol per volume of formulation vehicle, 15 % weight of benzyl alcohol per volume of formulation vehicle, 15 % weight of benzyl benzoate per volume of formulation vehicle and 30 % or more weight of ricinoleate excipient per volume of formulation vehicle.

According to another aspect of the invention there is provided 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 in a human for at least 2 months.

According to another aspect of the invention there is provided a pharmaceutical formulation comprising fulvestrant at a concentration of at least 100 mg/ml 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 in a human for at least 2 months.

According to another aspect of the invention there is provided a pharmaceutical formulation comprising fulvestrant at a concentration of at least 150 mg/ml 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 in a human for at least 2 months.

According to another aspect of the invention there is provided a pharmaceutical formulation comprising fulvestrant at a concentration of at least 200 mg/ml 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 in a human for at least 2 months.

According to another aspect of the invention there is provided a pharmaceutical formulation comprising fulvestrant at a concentration of at least 300 mg/ml 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 in a human for at least 2 months.

According to one aspect of the invention there is provided any one of the following pharmaceutical formulations comprising about:

i)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

15% weight per volume of benzyl benzoate

500-555mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

ii)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500-700mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

iii)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

500-750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

iv)

20% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500-1175mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

v)

15% weight per volume of ethanol

10% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

500-810 mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

vi)

15% weight per volume of ethanol

20% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

500 mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

vii)

15% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500-630mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

viii)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

ix)

20% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

x)

15% weight per volume of ethanol

10% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xi)

9% weight per volume of ethanol

19% weight per volume of benzyl alcohol

47% weight per volume of benzyl benzoate

700mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xii)

14% weight per volume of ethanol

19% weight per volume of benzyl alcohol

48% weight per volume of benzyl benzoate

700mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xiii)

15% weight per volume of ethanol

20% weight per volume of benzyl alcohol

45% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xiv)

9% weight per volume of ethanol

19% weight per volume of benzyl alcohol

47% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xv)

19% weight per volume of ethanol

19% weight per volume of benzyl alcohol

28% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xvi)

14% weight per volume of ethanol

9% weight per volume of benzyl alcohol

47% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xvii)

14% weight per volume of ethanol

19% weight per volume of benzyl alcohol

47% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xviii)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

45% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xix)

15% weight per volume of ethanol

10% weight per volume of benzyl alcohol

45% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xx)

20% weight per volume of ethanol

20% weight per volume of benzyl alcohol

25% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xxi)

10% weight per volume of ethanol

30% weight per volume of benzyl alcohol

25% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xxii)

10% weight per volume of ethanol

25% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xxiii)

10% weight per volume of ethanol

30% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xxiv)

15% weight per volume of ethanol

25% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xxv)

15% weight per volume of ethanol

25% weight per volume of benzyl alcohol

25% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil; and

xxvi)

15% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil.

The term "comprising about" in this context means that the numerical value assigned to each component of the formulation may be varied independently to accommodate manufacturing specifications encountered by a skilled person when making up the formulations. Typically this means plus or minus 5%, more preferably plus or minus 4%, more preferably plus or minus 3%, more preferably plus or minus 2%, more preferably plus or minus 1%. In a preferred embodiment, more variation in drug level is allowed compared with other components. For example:

Drug (+/- %)	Other components (+/- %)
5	4, 3, 2 or 1
4	3, 2 or 1
3	2 or 1
2	1

The individual formulations described herein may comprise further excipients commonly used in the formulation field including, for example, an antioxidant preservative, a colorant or a surfactant.

According to another aspect of the invention there is provided any one of the following pharmaceutical formulations:

i)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

15% weight per volume of benzyl benzoate

500-555mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

ii)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500-700mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

iii)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

500-750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

iv)

20% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500-1175mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

v)

15% weight per volume of ethanol

10% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

500-810 mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

vi)

15% weight per volume of ethanol

20% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

500 mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

vii)

15% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500-630mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

viii)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

ix)

20% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

x)

15% weight per volume of ethanol

10% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil.

A preferred pharmaceutical formulation described herein is one wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

A preferred pharmaceutical formulation described herein is one 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.

A preferred pharmaceutical formulation described herein is one wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

A preferred pharmaceutical formulation described herein is one wherein the ricinoleate excipient is castor oil.

According to one aspect of the present invention there is provided a pharmaceutical formulation adapted for intramuscular injection comprising 100 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of pharmaceutical formulation, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of pharmaceutical formulation and 5 % or more weight of ricinoleate excipient per volume of pharmaceutical formulation provided:

a) the pharmaceutical formulation comprises at least 5 % weight of ethanol per volume of pharmaceutical formulation;

b) if the pharmaceutically acceptable alcohol is less than or equal to 13%, then the pharmaceutical formulation must comprise at least 50 % non-aqueous ester solvent; and

c) if the pharmaceutically acceptable alcohol is greater than 20 % but less than or equal to 25 %, then the pharmaceutical formulation must comprise at least 30 % non-aqueous ester solvent;

and also provided that the following pharmaceutical formulation is excluded: fulvestrant up to 102 mg/ml, 15 % weight of ethanol per volume of formulation vehicle, 15 % weight of benzyl alcohol per volume of formulation vehicle, 15 % weight of benzyl benzoate per volume of formulation vehicle and 30 % or more weight of ricinoleate excipient per volume of formulation vehicle.

A preferred pharmaceutical formulation adapted for intramuscular injection is one comprising 100 mg/ml or more of fulvestrant, 20 % or more weight of a pharmaceutically acceptable alcohol per volume of pharmaceutical formulation, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of pharmaceutical formulation and 5 % or more weight of ricinoleate excipient per volume of pharmaceutical formulation provided:

a) the pharmaceutical formulation comprises at least 10 % weight of ethanol per volume of pharmaceutical formulation;

b) if the pharmaceutically acceptable alcohol is 20%, then the pharmaceutical formulation must comprise at least 22.5 % non-aqueous ester solvent; and

c) if the pharmaceutically acceptable alcohol is greater than 20 % but less than or equal to 25 %, then the pharmaceutical formulation must comprise at least 15 % non-aqueous ester solvent;

and also provided that the following pharmaceutical formulation is excluded: fulvestrant up to 102 mg/ml, 15 % weight of ethanol per volume of formulation vehicle, 15 % weight of benzyl

alcohol per volume of formulation vehicle, 15 % weight of benzyl benzoate per volume of formulation vehicle and 30 % or more weight of ricinoleate excipient per volume of formulation vehicle.

A more preferred pharmaceutical formulation adapted for intramuscular injection is one comprising 150 mg/ml or more of fulvestrant, 25 % or more weight of a pharmaceutically acceptable alcohol per volume of pharmaceutical formulation, 30 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of pharmaceutical formulation and 5 % or more weight of ricinoleate excipient per volume of pharmaceutical formulation provided:

a) the pharmaceutical formulation comprises at least 10 % weight of ethanol per volume of pharmaceutical formulation;

b) if the pharmaceutically acceptable alcohol is less than 30 %, then the pharmaceutical formulation must comprise at least 35 % non-aqueous ester solvent.

A particularly preferred pharmaceutical formulation is one which comprises 15% w/v or less of ethanol and in which the solubility of fulvestrant is at least 155mg/ml.

According to another aspect of the invention there is provided a unit dose of a pharmaceutical formulation as described herein wherein the total volume of the formulation is 6ml or less.

According to another aspect of the invention there is provided a pharmaceutical formulation adapted for intramuscular injection, as defined in any preceding claim for use in medical therapy.

According to another aspect of the invention there is provided use of fulvestrant in the preparation of a pharmaceutical formulation, as defined herein for the treatment of a benign or malignant disease of the breast or reproductive tract.

According to another aspect of the invention there is provided use of fulvestrant in the preparation of a pharmaceutical formulation, as defined in any preceding claim for the treatment of a benign or malignant disease of the breast or reproductive tract in a human with dosage intervals of at least 8 weeks.

According to another aspect of the invention there is provided a sterile syringe or vial comprising a pharmaceutical formulation as defined in any preceding claim.

The term "pharmaceutical formulation" as used herein means the combination of drug plus formulation vehicle. The terms "finished formulation" and "finished pharmaceutical formulation" mean the same as "pharmaceutical formulation".

The term "formulation vehicle" as used herein means the combination of all excipients used in the pharmaceutical formulation (and therefore excludes drug per se).

The distinction between pharmaceutical formulation and formulation vehicle is important for the following reason. For example, if the concentration (y % w/v) of an excipient "A" is measured by its concentration in formulation vehicle and then drug is added, the addition of drug will result in a concentration of excipient A that is lower than concentration y in the finished pharmaceutical formulation. To convert a concentration expressed in terms of "formulation vehicle" into a concentration of "finished pharmaceutical formulation" it is necessary to use a displacement value.

The "displacement value" is defined as the number of parts by weight of compound that displaces one part by weight of the formulation vehicle. The displacement value allows determination of the amount of formulation vehicle displaced by the compound. The displacement value is used to calculate the actual composition of the finished formulation in terms of proportions of excipients. The density of the compound affects the amount of formulation vehicle required to make the pharmaceutical formulation to the correct concentration. One part by weight of the compound with a density equal to the formulation vehicle will displace an equivalent volume of the formulation vehicle. A compound with twice the density of the formulation vehicle will displace half the volume. It is therefore necessary to make allowance for the compound in terms of the particular formulation vehicle, using the displacement value.

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

Where whole numbers are used for % weight per volume of formulation, these refer to rounded numbers where appropriate. For example, 4.6% would be rounded to 5%.

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.

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.

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.

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.

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:

By the use of the term ricinoleate excipient 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.

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 "extended release" we mean at least 4 weeks, at least 5 weeks, and, preferably at least 8 weeks of continuous release of fulvestrant is achieved. In a preferred feature extended release is achieved for at least 8 weeks or 2 months, more preferably for at least 12 weeks or 3 months.

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.

Preferably 5ml of the intramuscular injection is administered.

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, more preferably an antioxidant.

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.

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

References

1. Bowler J, Lilley TJ, Pittam JD, Wakeling AE. Novel steroidal pure antioestrogens. Steroids, 54: 71-100, 1989.

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

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The invention will now be illustrated by the following non-limiting Examples in which:

Figure 1 shows plasma profiles obtained following IM injection (data normalised for rabbit weight, based on 3.2 kg rabbit) in which the y-axis is conc (ng/ml) and the x-axis is time (days);

Figure 2 shows comparison of plasma profiles in which:

Figure 2A shows plasma profiles from group A in which the y-axis is conc (ng/ml) and the x-axis is time (days); and

Figure 2B shows plasma profiles from group B in which the y-axis is conc (ng/ml) and the x-axis is time (days);

Figure 3 shows plasma profiles from formulations 1, 5 and Control (normalised for rabbit weight, based on 3.2 kg rabbit in which the y-axis is conc (ng/ml) and the x-axis is time (days);

Figure 4 shows muscle residue data from 3 month PK study in which the y-axis is % fulvestrant remaining per injection site and the x-axis is formulation number. Each bar represents one injection site (2 sites per animal).

Figure 5 shows predicted versus actual solubility

Figure 6 shows a confidence interval for predicted solubility

Figure 7 shows plasma profiles obtained following IM injection (data normalised for rabbit weight, based on 3.2 kg rabbit) in which the y-axis is conc (ng/ml) and the x-axis is time (days);

Abbreviations

IM	intramuscular
PK	pharmacokinetic
AUC	area under curve
SD	standard deviation

Reference Example 1

Measurement of Solubility of Fulvestrant in Formulations

1. Materials and Apparatus

Balance

2 mL glass vials with screw caps

Magnetic stirrer bars

Temperature control reaction block with magnetic stirring facility

Positive displacement pipette (PDP) 20 - 25 µL with appropriate microsyringe tips

Polycarbonate ultracentrifuge tubes

Ultracentrifuge

Pipette 0.5 - 200 µL PDP with appropriate microsyringe tips

Pipette 200 µL - 1 mL with appropriate plastic tips

2 mL amber Snap Top glass HPLC vials

1 mm Snap Caps for HPLC vials

HPLC kit with diode array detector

Methanol (MeOH) HPLC Grade

Acetonitrile (ACN) Far UV HPLC Grade

Ultrapure de-ionised water

25 cm H5 ODS 5µ 4.6 mm i.d. HPLC column

Vortex mixer

Ultrasonic bath

20 - 200 µL pipette with appropriate plastic tips

Aluminium weigh pans 5 mL glass volumetric flasks

2. Experimental procedure

2.1 1ml formulation vehicles were made up in triplicate by adding the appropriate volumes of alcohols and benzyl benzoate, and then adding castor oil by weight

2.2 Fulvestrant was then added to excess, until no more drug was seen to visibly dissolve. The weight of fulvestrant added was noted.

2.3 A magnetic stirrer bar was placed in each vial.

2.4 All the samples were overlaid with nitrogen and the vials were capped placed in the reaction block and stirred at a speed of 1000 at a temperature of 4°C

2.5 Using the PDP 20 - 200 µL pipettor, 200 µL aliquots were removed from each vial after 6 days and transferred to ultracentrifuge tubes. These tubes were centrifuged at a speed of 80,000 r.p.m. for 30 minutes at 25°C.

2.6 HPLC eluent was prepared by adding 1400 mL methanol, 450 mL water and 150 mL acetonitrile to a 2 litre plastic-coated solvent bottle.

2.7 990 µL HPLC eluent was added to 60 amber glass HPLC vials using a 1mL Pipette.

2.8 3 x 10 µL of supernatant were removed from each ultracentrifuge tube using the Pipette PDP 0.5-25 µL pipette and added to the vials containing eluent.

2.9 The samples were diluted again 1 in 10. 100µl sample was added to 900µl HPLC eluent

2.10 The amber vials were capped, vortex mixed for 10 seconds, sonicated for 10 minutes and then placed in the HPLC autosampler tray.

3. Calibration preparation

3.1 Approximately 10 mg fulvestrant was accurately weighed into an aluminium weigh pan on the microbalance and placed in a 5 mL glass volumetric flask The actual weight was recorded.

3.2 Approximately 4.5 mL HPLC eluent was added to the flask using a plastic pasteur pipette. The flask was then sonicated for 5 minutes prior to making accurately to volume (to give a spiking solution of approximately 2 $mg.mL^{-1}$).

3.3 0 - 250 µL spiking solution was added to 2 mL amber HPLC vials using the appropriate Pipette and the volume made to 1 mL with HPLC eluent using a 1 mL Pipette as shown in the table below:

Volume Spiking Solution (µL)	Volume HPLC eluent (µL)	Theoretical fulvestrant Concentration ($\mu g.mL^{-1}$)
0	1000	0
5	995	10
25	975	50
50	950	100
100	900	200
150	850	300
200	800	400
250	750	500

3.4 The HPLC vials were capped, vortexed for 10 seconds and placed on the HPLC autosampler tray.

3.5 A calibration was prepared (as per 3.1 - 3.4) for both batches of ICI 182780.

4. HPLC Conditions

Eluent :	70% MeOH / 22.5% Water / 7.5% ACN
Column :	25 cm 5µ Hypersil ODS 4.6 mm i.d. with guard column
Detection wavelength :	280 nm
Flow rate :	1.2 $mL.min^{-1}$
Temperature :	Ambient
Injection volume :	50 µL
Retention time :	12 minutes approximately

Example 1

Pharmaceutical Formulations

Fulvestrant is mixed with ethanol 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. The process flow diagram below depicts the manufacturing process.

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 the following formulations:

a)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

15% weight per volume of benzyl benzoate

500mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

b)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

c)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

500mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

d)

20% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

e)

15% weight per volume of ethanol

10% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

500mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

f)

15% weight per volume of ethanol

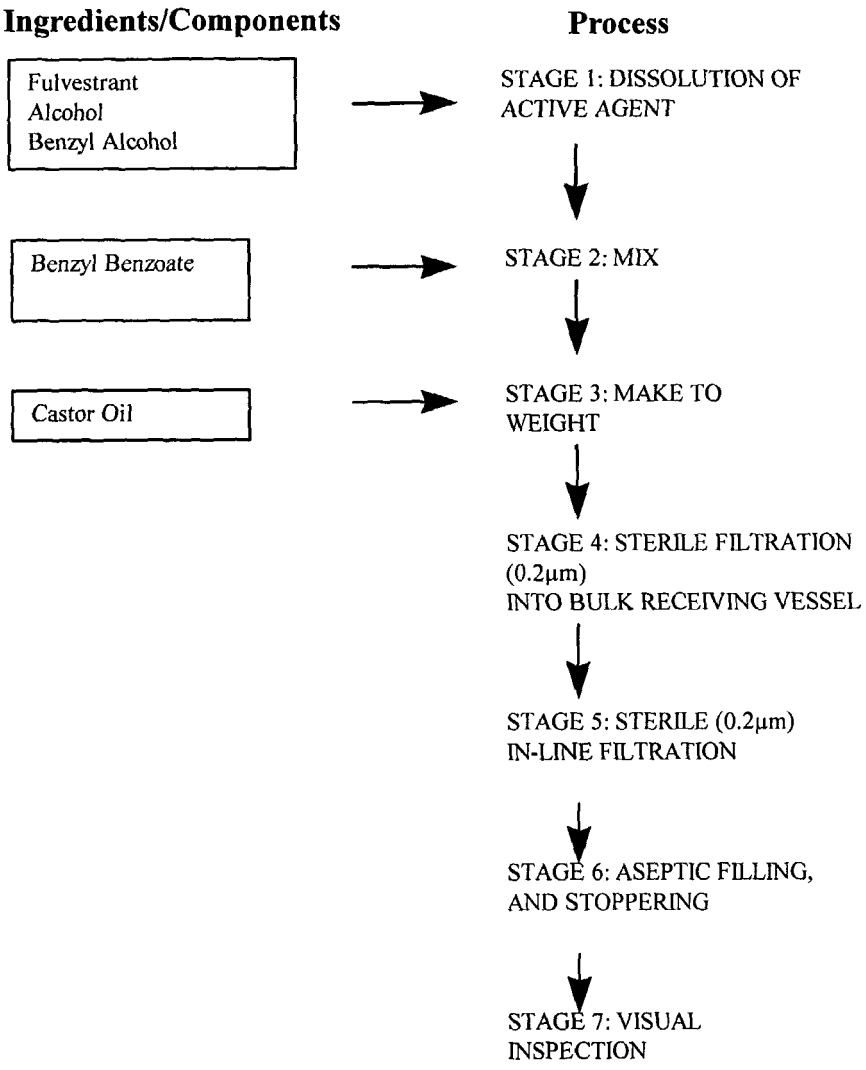
20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

FLOW DIAGRAM OF MANUFACTURING



Example 2

Stability studies to 4 months for selection of stable 100mg/ml Pharmaceutical formulations

Formulation No.	Fulvestrant	96% EtOH	Benzyl Alcohol	Benzyl Benzoate	Castor oil	Observations (visual)
	(mg/ml)	% w/v	% w/v	% w/v	% w/v	4 months
Sample 1	100	5	10	15	to 100%	Precipitated
Sample 2	100	5	10	30	to 100%	Precipitated
Sample 3	100	7.5	10	15	to 100%	Precipitated
Sample 4	100	7.5	10	30	to 100%	Precipitated
Sample 5	100	10	10	15	to 100%	Precipitated
Sample 6	100	10	10	17.5	to 100%	Precipitated
Sample 7	100	10	10	20	to 100%	Precipitated
Sample 8	100	10	10	22.5	to 100%	Solution
Sample 9	100	10	10	25	to 100%	Solution
Sample 10	100	10	10	27.5	to 100%	Solution
Sample 11	100	10	10	30	to 100%	Solution
Sample 12	100	10	10	40	to 100%	Solution
Sample 13	100	10	10	50	to 100%	Solution
Sample 14	100	10	15	15	to 100%	Solution
Sample 15	100	10	15	30	to 100%	Solution
Sample 16	100	10	15	40	to 100%	Solution
Sample 17	100	10	15	50	to 100%	Solution
Sample 18	100	10	20	15	to 100%	Solution
Sample 19	100	10	20	30	to 100%	Solution
Sample 20	100	10	20	40	to 100%	Solution
Sample 21	100	10	20	50	to 100%	Solution
Sample 22	100	15	10	15	to 100%	Solution
Sample 23	100	15	10	30	to 100%	Solution
Sample 24	100	15	10	40	to 100%	Solution
Sample 25	100	15	10	50	to 100%	Solution
Sample 26	100	20	5	15	to 100%	Solution
Sample 27	100	20	5	30	to 100%	Solution
Sample 28	100	20	10	15	to 100%	Solution
Sample 29	100	20	10	30	to 100%	Solution
Sample 30	100	20	10	40	to 100%	Solution
Sample 31	100	20	10	50	to 100%	Solution
Sample 32	100	15	15	15	to 100%	Solution
Sample 33	100	15	15	30	to 100%	Solution
Sample 34	100	15	15	40	to 100%	Solution
Sample 35	100	15	15	50	to 100%	Solution
Sample 36	100	15	20	15	to 100%	Solution
Sample 37	100	15	20	30	to 100%	Solution
Sample 38	100	15	20	50	to 100%	Solution
Sample 39	100	20	20	15	to 100%	Solution

Sample 40	100	20	20	30	to 100%	Solution
Control Sample	**52.16**	**10**	**10**	**15**	**60**	**Solution**

The Control Sample refers to the following Pharmaceutical formulation: fulvestrant 50mg/ml, ethanol 10% w/v, benzylalcohol 10% w/v, benzyl benzoate 15% w/v and made to volume with castor oil.

Example 3

Pharmaceutical formulations selected for *in vivo* deposition and *in vitro* precipitation studies

The pharmaceutical formulations below were selected from Example 2 for further study.

Formulation	Fulvestrant	95% ETOH	Benzyl Alcohol	Benzyl Benzoate	Castor oil
	% w/v	%w/v	%w/v	%w/v	% w/v
Sample 1	10	10	10	30	to 100%
Sample 2	10	10	10	50	to 100%
Sample 3	10	10	20	15	to 100%
Sample 4	10	10	20	30	to 100%
Sample 5	10	10	20	50	to 100%
Sample 6	10	20	5	15	to 100%
Sample 7	10	20	5	30	to 100%
Sample 8	10	20	20	15	to 100%
Sample 9	10	20	20	30	to 100%
Sample 10	10	15	10	15	to 100%
Sample 11	10	15	10	30	to 100%
Sample 12	10	15	10	50	to 100%
Sample 13	10	15	20	15	to 100%
Sample 14	10	15	20	50	to 100%
Sample 15	10	15	20	30	to 100%
Sample 16	5	10	10	15	to 100%

A matrix of 7 pharmaceutical formulations (samples 3, 4, 5, 9, 12, 14 and 16 – see Example 3 below) was identified for further evaluation from in vitro precipitation and deposition studies.

Sample 16 was a control. The precipitation experiment involved visual inspection of each sample under conditions where evaporation of alcohols led to precipitation of drug.

Example 4

In vivo Studies

Pharmaceutical formulations identified for further *in vivo* evaluation

		Excipients (% w/v)			
No.	Fulvestrant (%w/v)	Ethanol 96%	Benzyl alcohol	Benzyl benzoate	Castor oil
F1	10	10	20	15	45
F2	10	10	20	30	30
F3	10	10	20	50	10
F4	10	20	20	30	20
F5	10	15	10	50	15
F6	10	15	20	50	5
F7	10	15	20	30	25
Control	5	10	10	15	60

(a) **An in vivo pharmacokinetic (PK) study on these 7 pharmaceutical formulations was performed over 3 months duration**; results are shown in Figures 1, 2 and 3.

Analysis of PK results

Plasma levels were more variable than Control over the first 30 days; variability was similar to control thereafter. After 2 months, drug levels were equivalent to Control at 1 month indicating a prolonged period of action over Control. This release profile was surprising because, compared with Control which does not precipitate drug locally, local precipitation at the site of injection of the tested formulations was expected to impair their release profile.

Some differences in profiles were noted over the first 30 days such that they were divided into 2 groups (with Formulation F7 showing intermediate behaviour).

Group A, rapid release early time points (50% Benzyl benzoate and low castor oil ≤ 15%) – see figure 2A

Group B, lower release, flatter profile (≤ 30% Benzyl benzoate and higher castor oil ≥ 20%) – see figure 2B

(b) **Histopathology**

Local tolerance was assessed to IM injection of the 7 pharmaceutical formulations and Control. Lesions were observed over a 51 day period. All pharmaceutical formulations caused tissue reactions greater than Control.

(c) **Plasma levels for 100mg dose at critical time points (ng/ml)**

Form.	Dose	Time point (days)		
	(mg)	28	56	84
1	100	8.7	4.6	3.5
2	100	8.0	3.6	2.6
3	100	9.4	3.5	2.0
4	100	7.7	5.0	3.4
5	100	9.1	4.5	2.6
6	100	9.9	3.3	1.9
7	100	9.9	5.5	3.2
Control	50	**3.3**	**1.7**	

Summary

Duration for 100mg dose = min 2 months.

Duration for 150mg dose = min 3 months.

(d) **Measurement of Fulvestrant solubility in 7 pharmaceutical formulations after 6 days**

Formulation	**Solubility (mg/ml)**
	6days
F1	111
F2	140
F3	175
F4	235
F5	162
F6	212
F7	126

Example 5

Model for Fulvestrant Solubility

Formulation vehicles for Fulvestrant - solubility

Formulation No.	96% ETOH % w/v	Benzyl Alcohol % w/v	Benzyl Benzoate % w/v	Castor oil % w/v	Measured Fulvestrant Solubility (mg/ml)	Predicted solubility (mg/ml)
Sample 1	5	5	0	to 100%	27	9.4
Sample 2	5	5	15	to 100%	36	32.8
Sample 3	10	5	0	to 100%	46	48.5
Sample 4	10	5	15	to 100%	54	36.6
Sample 5	10	10	0	to 100%	45	60.1
Sample 6	10	10	15	to 100%	65	72
Sample 7	15	15	0	to 100%	76	87.6
Sample 8	15	15	15	to 100%	102	111.1
Sample 9	11	22	17	to 100%	111	109.8
Sample 10	11	22	33	to 100%	140	166.1
Sample 11	11	22	56	to 100%	175	135.8
Sample 12	22	22	33	to 100%	235	174.4
Sample 13	17	11	56	to 100%	162	170.6
Sample 14	17	22	56	to 100%	212	200.9
Sample 15	17	22	33	to 100%	126	196.3

A linear regression model was fitted to solubility data from 15 samples using as independent variables the % ethanol, benzyl alcohol and benzyl benzoate levels in the formulations. The following model was obtained which had an R-Squared value of 93.2%:

SOLUBILITY = -29.77 + 5.44 x ETOH + 2.38 x BA + 1.57 x BB

Benzyl alcohol = BA, benzyl benzoate = BB, Ethanol = ETOH.

Solubility measured as mg/ml

See Figures 5 and 6 based on the following data

measured	lower C.L.	predicted	upper C.L.
27	0	9.4	31.1
36	10	32.8	55.7
45	31.6	48.5	65.4
46	17.1	36.6	56.1
54	40.9	60.1	79.2
65	59	72	85
76	64.7	87.6	110.6
102	95.6	111.1	126.7
111	85.4	109.8	134.1
126	149	166.1	183.1

140	114.2	135.8	157.5
162	142.5	174.4	206.3
175	143.4	170.6	197.9
212	179.6	200.9	222.2
235	168.7	196.3	224

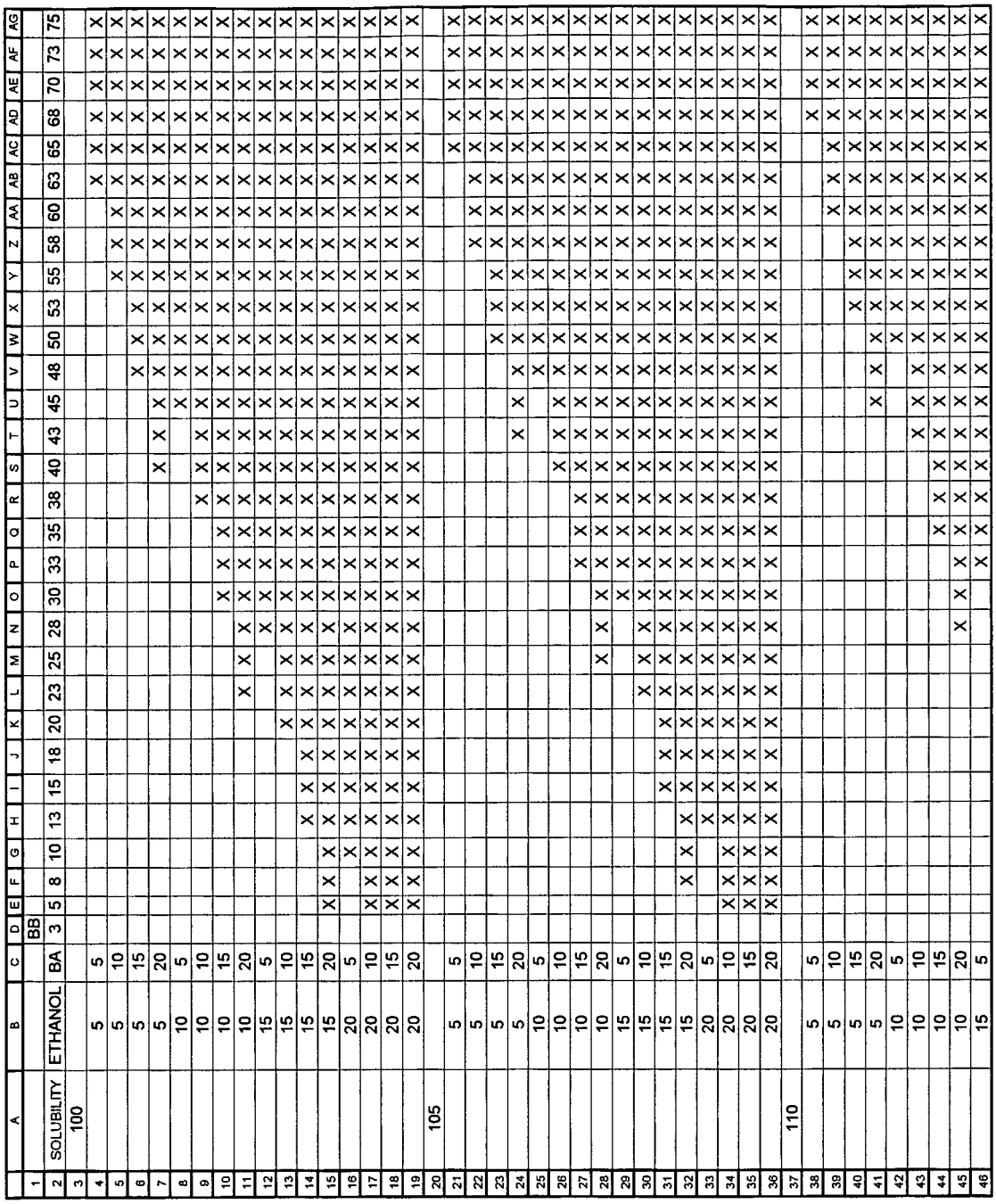
The table below shows predicted solubilities for a matrix of pharmaceutical formulations tested for stability. A good correlation was obtained with visual observations.

Formulation of Fulvestrant - stability

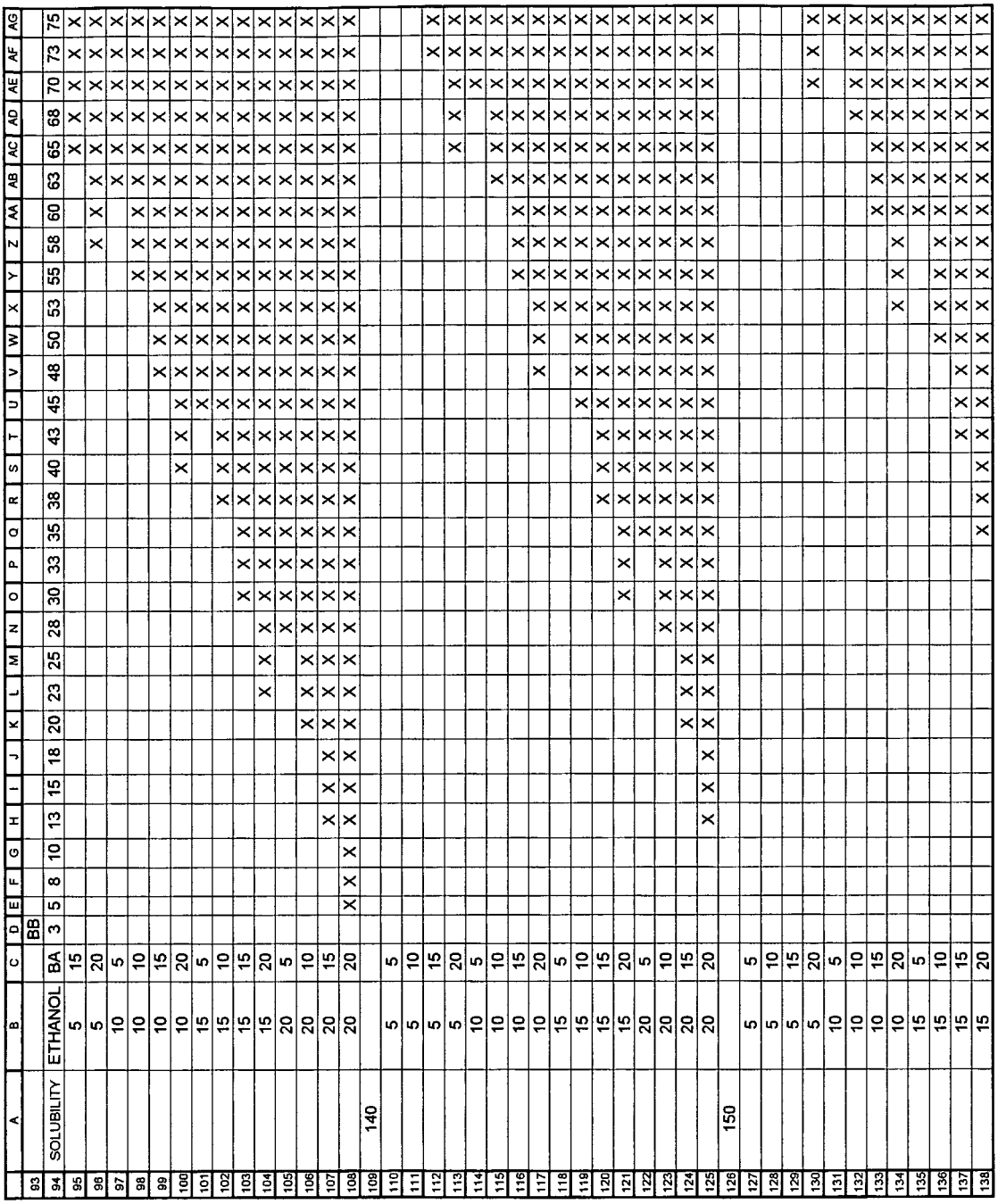
Formulation No.	Fulvestrant (mg/ml)	95% ETOH % w/v	Benzyl Alcohol % w/v	Benzyl Benzoate % w/v	Castor oil % w/v	Observations 4 months	**Predicted solubility (mg/ml)**
Sample 1	100	5	10	15	60	Precipitated	53.1
Sample 2	100	5	10	30	45	Precipitated	79.2
Sample 3	100	7.5	10	15	57.5	Precipitated	68.2
Sample 4	100	7.5	10	30	42.5	Precipitated	94.3
Sample 5	100	10	10	15	55	Precipitated	83.3
Sample 6	100	10	10	17.5	52.5	Precipitated	87.6
Sample 7	100	10	10	20	50	Precipitated	92.0
Sample 8	100	10	10	22.5	47.5	Solution	96.4
Sample 9	100	10	10	25	45	Solution	100.7
Sample 10	100	10	10	27.5	42.5	Solution	105.1
Sample 11	100	10	10	30	40	Solution	109.5
Sample 12	100	10	10	40	30	Solution	126.9
Sample 13	100	10	10	50	20	Solution	144.3
Sample 14	100	10	15	15	50	Solution	96.5
Sample 15	100	10	15	30	35	Solution	122.7
Sample 16	100	10	15	40	25	Solution	140.1
Sample 17	100	10	15	50	15	Solution	157.6
Sample 18	100	10	20	15	45	Solution	109.7
Sample 19	100	10	20	30	30	Solution	135.9
Sample 20	100	10	20	40	20	Solution	153.3
Sample 21	100	10	20	50	10	Solution	170.8
Sample 22	100	15	10	15	50	Solution	113.5
Sample 23	100	15	10	30	35	Solution	139.7
Sample 24	100	15	10	40	25	Solution	157.1
Sample 25	100	15	10	50	15	Solution	174.6
Sample 26	100	20	5	15	50	Solution	130.5
Sample 27	100	20	5	30	35	Solution	156.7
Sample 28	100	20	10	15	45	Solution	143.7
Sample 29	100	20	10	30	30	Solution	169.9
Sample 30	100	20	10	40	20	Solution	187.3
Sample 31	100	20	10	50	10	Solution	204.8
Sample 32	100	15	15	15	45	Solution	126.7
Sample 33	100	15	15	30	30	Solution	152.9
Sample 34	100	15	15	40	20	Solution	170.3
Sample 35	100	15	15	50	10	Solution	187.8
Sample 36	100	15	20	15	40	Solution	140.0
Sample 37	100	15	20	30	25	Solution	166.1
Sample 38	100	15	20	50	5	Solution	201.0

Sample 39	100	20	20	15	35	Solution	170.2
Sample 40	100	20	20	30	20	Solution	196.3
Control Sample [Faslodex]	**52.16**	**10**	**10**	**15**	**60**	**Solution**	72.0

The Tables below show predicted formulations for various solubilities of fulvestrant; where an "X" means in solution. Note that the Tables include some impractical formulations where the sum of components becomes greater than 100%. The principal purpose is to illustrate the wide combinations of ethanol/ benzyl alcohol / benzyl benzoate taught by the invention to achieve different solubilities of fulvestrant.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG
47				BB																													
48	SOLUBILITY	ETHANOL	BA	3	5	8	10	13	15	18	20	23	25	28	30	33	35	38	40	43	45	48	50	53	55	58	60	63	65	68	70	73	75
49		15	10										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
50		15	15							X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
51		15	20				X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
52		20	5						X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
53		20	10			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
54		20	15		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
55		20	20		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
56	115																																
57		5	5																												X	X	X
58		5	10																					X					X	X	X	X	X
59		5	15																					X	X	X	X	X	X	X	X	X	X
60		5	20																				X	X	X	X	X	X	X	X	X	X	X
61		10	5																						X	X	X	X	X	X	X	X	X
62		10	10																		X	X	X	X	X	X	X	X	X	X	X	X	X
63		10	15															X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
64		10	20												X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
65		15	5															X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
66		15	10												X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
67		15	15								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
68		15	20						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
69		20	5								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
70		20	10						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
71		20	15			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
72		20	20			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
73	120																																
74		5	5																													X	
75		5	10																											X	X	X	X
76		5	15																								X	X	X	X	X	X	X
77		5	20																					X	X	X	X	X	X	X	X	X	X
78		10	5																						X	X	X	X	X	X	X	X	X
79		10	10																				X	X	X	X	X	X	X	X	X	X	X
80		10	15																	X	X	X	X	X	X	X	X	X	X	X	X	X	X
81		10	20																X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
82		15	5																	X	X	X	X	X	X	X	X	X	X	X	X	X	X
83		15	10														X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
84		15	15												X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
85		15	20							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
86		20	5									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
87		20	10						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
88		20	15			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
89		20	20			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
90	130																																
91		5	5																														
92		5	10																													X	X



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG
139				BB																													
140	SOLUBILITY	ETHANOL	BA	3	5	8	10	13	15	18	20	23	25	28	30	33	35	38	40	43	45	48	50	53	55	58	60	63	65	68	70	73	75
141		20	5																	X	X	X	X	X	X	X	X	X	X	X	X	X	X
142		20	10														X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
143		20	15										X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
144		20	20							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
145	200																																
146		5	5																														
147		5	10																														
148		5	15																														
149		5	20																														
150		10	5																														
151		10	10																														
152		10	15																														
153		10	20																														
154		15	5																														
155		15	10																														
156		15	15																														X
157		15	20																											X	X	X	X
158		20	5																													X	X
159		20	10																										X	X	X	X	X
160		20	15																							X	X	X	X	X	X	X	X
161		20	20																				X	X	X	X	X	X	X	X	X	X	X

Example 6

In-vivo Pharmacokinetic study using compositions at 140mg/ml of fulvestrant

Formulations F3 and F6 as described in Example 4 were modified to contain an increased level of fulvestrant to 140mg/ml. The modified formulations were named F8 and F9 as described below.

Formulation Composition

The compositions of the formulations dosed in the PK study are shown in the table below.

Formulation No.	Fulvestrant (%w/v)	Ethanol 96% (%w/v)	Benzyl alcohol (%w/v)	Benzyl Benzoate (%w/v)	Castor Oil (%w/v)
F8	14	9	19	47	To 100%
F9	14	14	19	48	To 100%

PK Profile

The results are set out in Figure 7. The composition of the Control is the same as described in Example 4. Compositions F8 and F9 gave similar profiles with improved performance in terms of extended release of higher levels fulvestrant compared with Control.

Example 7

Compositions at 150mg/ml fulvestrant

Compositions analogous or similar to F3, F4, F5 and F6 (see Example 4) but comprising 150mg/ml of fulvestrant are prepared as follows.

Formulation No.	Fulvestrant (%w/v)	Ethanol 96% (%w/v)	Benzyl alcohol (%w/v)	Benzyl Benzoate (%w/v)	Castor Oil (%w/v)
F10	15	10	20	50	To 100%
F11	15	20	20	30	To 100%
F12	15	15	10	50	To 100%
F13	15	15	20	45	To 100%
F14	15	9	19	47	To 100%
F15	15	19	19	28	To 100%

F16	15	14	9	47	To 100%
F17	15	14	19	47	To 100%
F18	15	10	20	45	To 100%
F19	15	15	10	45	To 100%
F20	15	20	20	25	To 100%
F21	15	10	30	25	To 100%
F22	15	10	25	30	To 100%
F23	15	10	30	30	To 100%
F24	15	15	25	30	To 100%
F25	15	15	25	25	To 100%
F26	15	15	20	30	To 100%

Claims

1. A pharmaceutical formulation adapted for intramuscular injection comprising 100 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 5 % weight of ethanol per volume of formulation vehicle and provided that the following formulation is excluded: fulvestrant up to 102 mg/ml, 15 % weight of ethanol per volume of formulation vehicle, 15 % weight of benzyl alcohol per volume of formulation vehicle, 15 % weight of benzyl benzoate per volume of formulation vehicle and 30 % or more weight of ricinoleate excipient per volume of formulation vehicle.

2. A pharmaceutical formulation adapted for intramuscular injection according to claim 2 comprising 105 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation comprises at least 5 % weight of ethanol per volume of formulation vehicle.

3. A pharmaceutical formulation adapted for intramuscular injection according to claim 1 comprising 110 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 5 % weight of ethanol per volume of formulation vehicle.

4. A pharmaceutical formulation adapted for intramuscular injection according to claim 1 comprising 115 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the

formulation vehicle comprises at least 5 % weight of ethanol per volume of formulation vehicle.

5. A pharmaceutical formulation adapted for intramuscular injection according to claim 1 comprising 120 mg/ml or more of fulvestrant, 10 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 5 % weight of ethanol per volume of formulation vehicle.

6. A pharmaceutical formulation adapted for intramuscular injection according to claim 1 comprising 130 mg/ml or more of fulvestrant, 15 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 5 % weight of ethanol per volume of formulation vehicle.

7. A pharmaceutical formulation adapted for intramuscular injection according to claim 1 comprising 140 mg/ml or more of fulvestrant, 15 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 12.5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the formulation vehicle comprises at least 10 % weight of ethanol per volume of formulation vehicle.

8. A pharmaceutical formulation adapted for intramuscular injection according to claim 1 comprising 150 mg/ml or more of fulvestrant, 15 % or more weight of a pharmaceutically acceptable alcohol per volume of formulation vehicle, 17.5 % or more weight of a pharmaceutically acceptable non-aqueous ester solvent per volume of formulation vehicle and 5 % or more weight of ricinoleate excipient per volume of formulation vehicle provided the

formulation vehicle comprises at least 10 % weight of ethanol per volume of formulation vehicle.

9. A pharmaceutical formulation having a solubility for fulvestrant of at least Y mg/ml adapted for intramuscular injection comprising;
100 mg/ml or more of fulvestrant;
5% (w/v) or more castor oil per volume of formulation vehicle;
and at least the following amounts (% weight/volume of formulation vehicle) of ethanol (ETOH), benzyl alcohol (BA), benzyl benzoate (BB) determined by the algorithm:
$Y = -29.77 + 5.44ETOH + 2.38BA + 1.57BB$
wherein Y is at least 100, ETOH is at least 5, BA is at least 5 and BB is at least 5.

10. A pharmaceutical formulation according to claim 9 wherein Y is selected from the group consisting of 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 170, 180, 190, and 200.

11. A pharmaceutical formulation according to claim 9 wherein Y is selected from the group consisting of 120, 125, 130, 135, 140, 145, 150, 155, 160, 170, 180, 190, and 200.

12. A pharmaceutical formulation according to claim 9 wherein Y is selected from the group consisting of 150, 155, 160, 170, 180, 190 and 200.

13. A pharmaceutical formulation according to claim 9 wherein Y is selected from 150, 155, 160, 170, 180, 190 and 200 and the formulation comprises at least 150mg/ml of fulvestrant.

14. A pharmaceutical formulation according to claim 9 wherein Y is 200 and the formulation comprises at least 200mg/ml of fulvestrant.

15. A pharmaceutical formulation comprising fulvestrant at a concentration of at least 100 mg/ml 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 in a human for at least 2 months and provided that the following

formulation is excluded: fulvestrant up to 102 mg/ml, 15 % weight of ethanol per volume of formulation vehicle, 15 % weight of benzyl alcohol per volume of formulation vehicle, 15 % weight of benzyl benzoate per volume of formulation vehicle and 30 % or more weight of ricinoleate excipient per volume of formulation vehicle.

16. A pharmaceutical formulation comprising fulvestrant at a concentration of at least 150 mg/ml 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 in a human for at least 2 months.

17. Any one of the following pharmaceutical formulations comprising about:

i)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

15% weight per volume of benzyl benzoate

500-555mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

ii)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500-700mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

iii)

10% weight per volume of ethanol

20% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

500-750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

iv)

20% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

500-1175mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

v)

15% weight per volume of ethanol
10% weight per volume of benzyl alcohol
50% weight per volume of benzyl benzoate
500-810 mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

vi)

15% weight per volume of ethanol
20% weight per volume of benzyl alcohol
50% weight per volume of benzyl benzoate
500 mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

vii)

15% weight per volume of ethanol
20% weight per volume of benzyl alcohol
30% weight per volume of benzyl benzoate
500-630mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

viii)

10% weight per volume of ethanol
20% weight per volume of benzyl alcohol
50% weight per volume of benzyl benzoate
750mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

ix)

20% weight per volume of ethanol
20% weight per volume of benzyl alcohol
30% weight per volume of benzyl benzoate
750mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

x)

15% weight per volume of ethanol

10% weight per volume of benzyl alcohol

50% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xi)

9% weight per volume of ethanol

19% weight per volume of benzyl alcohol

47% weight per volume of benzyl benzoate

700mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xii)

14% weight per volume of ethanol

19% weight per volume of benzyl alcohol

48% weight per volume of benzyl benzoate

700mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xiii)

15% weight per volume of ethanol

20% weight per volume of benzyl alcohol

45% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xiv)

9% weight per volume of ethanol

19% weight per volume of benzyl alcohol

47% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xv)

19% weight per volume of ethanol

19% weight per volume of benzyl alcohol

28% weight per volume of benzyl benzoate
750mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

xvi)

14% weight per volume of ethanol
9% weight per volume of benzyl alcohol
47% weight per volume of benzyl benzoate
750mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

xvii)

14% weight per volume of ethanol
19% weight per volume of benzyl alcohol
47% weight per volume of benzyl benzoate
750mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

xviii)

10% weight per volume of ethanol
20% weight per volume of benzyl alcohol
45% weight per volume of benzyl benzoate
750mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

xix)

15% weight per volume of ethanol
10% weight per volume of benzyl alcohol
45% weight per volume of benzyl benzoate
750mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

xx)

20% weight per volume of ethanol
20% weight per volume of benzyl alcohol
25% weight per volume of benzyl benzoate
750mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil;

xxi)

10% weight per volume of ethanol

30% weight per volume of benzyl alcohol

25% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xxii)

10% weight per volume of ethanol

25% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xxiii)

10% weight per volume of ethanol

30% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xxiv)

15% weight per volume of ethanol

25% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil;

xxv)

15% weight per volume of ethanol

25% weight per volume of benzyl alcohol

25% weight per volume of benzyl benzoate

750mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil; and

xxvi)

15% weight per volume of ethanol

20% weight per volume of benzyl alcohol

30% weight per volume of benzyl benzoate
750mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil.

18. A pharmaceutical formulation as claimed in any preceding claim wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

19. A pharmaceutical formulation as claimed in any preceding claim 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.

20. A pharmaceutical formulation as claimed in any preceding claim wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

21. A pharmaceutical formulation as claimed in any preceding claim wherein the ricinoleate excipient is castor oil.

22. A unit dose of a pharmaceutical formulation as claimed in any preceding claim wherein the total volume of the formulation is 6ml or less.

23. A pharmaceutical formulation adapted for intramuscular injection, as defined in any preceding claim for use in medical therapy.

24. Use of fulvestrant in the preparation of a pharmaceutical formulation, as defined in any preceding claim for the treatment of a benign or malignant disease of the breast or reproductive tract.

25. Use of fulvestrant in the preparation of a pharmaceutical formulation, as defined in any preceding claim for the treatment of a benign or malignant disease of the breast or reproductive tract in a human with dosage intervals of at least 8 weeks.

26. A sterile syringe or vial comprising a pharmaceutical formulation as defined in any preceding claim.