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(54) Title: PHARMACEUTICAL FORMULATION FOR THE INTRAMUSCULAR ADMINISTRATION OF FULVESTRANT

(57) Abstract: The invention relates to a sustained release pharmaceutical formulation adapted for administration by injection containing the compound fulvestrant, 7 a-[9-(4,4,5,5,5-pentafluoropentylsulphiny1)nony1]oestra-1,3,5(10)-triene-3,17 ß-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.

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.

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