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(54) Title: A SOLUTION FOR ORAL ADMINISTRATION CONTAINING ICI 182,780

(57) Abstract

The invention concerns a pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises ICI 182,780, a pharmaceutically-acceptable oil, a pharmaceutically-acceptable lipophilic surfactant, a pharmaceutically-acceptable hydrophilic surfactant, and a pharmaceutically-acceptable water-miscible solvent, and the use of the composition on oral administration to a warm-blooded animal to produce an antioestrogenic effect.

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A SOLUTION FOR ORAL ADMINISTRATION CONTAINING ICI 182,780

The invention relates to a novel pharmaceutical composition, particularly to a pharmaceutical composition adapted for oral administration containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, and more particularly to a solution formulation containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol. The invention also relates to the use of the pharmaceutical composition of the invention for oral administration to a warm blooded animal to produce an antioestrogenic effect and to a method of producing an antioestrogenic effect by the oral administration of an effective amount of the pharmaceutical composition of the invention.

It is disclosed in European Patent Application No. 0 138 504 that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives of that invention. 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. For oral administration it is stated that a tablet or capsule containing the steroid derivative of the invention is particularly convenient. It is further stated therein that the tablet formulation can contain diluents, for example mannitol or maize starch, disintegrating agents, for example alginic acid, binding agents, for example methyl-cellulose, and lubricating agents, for example magnesium stearate. No pharmaceutically-acceptable diluent or carrier for a capsule formulation is specifically disclosed therein.

Subsequently the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol has been identified by the code number ICI 182,780 and that number shall be utilised for the compound hereinafter.

It is further disclosed in Cancer Research, 1991, 51, 3867-3873 and J. Endocrinology, 1992, 135. 239-247 that the antioestrogenic effect of ICI 182,780 in immature rats, mature rats or monkeys can be assessed by the administration of a suspension of the compound in arachis oil. This formulation was dosed either orally or by subcutaneous injection. The studies in rats demonstrated that the potency of the compound when dosed in arachis oil suspension was at least ten fold poorer when administration was by the oral route than when administration was by the subcutaneous route suggesting that the oral bioavailability of the compound from that formulation was low. A prolonged antioestrogenic effect was demonstrated when a dispersion of the compound in arachis oil was administered subcutaneously.

It is further disclosed in, for example, Laboratory Animal Science, 1993, 43, 247-251 that ICI 182,780 may be formulated for administration by intramuscular injection in a castor oil-based depot formulation. That formulation when given to laboratory animals at a dose of 4 milligrams per kilogram was found to inhibit the effects of endogenous oestrogen for three to four weeks.

Furthermore it is disclosed in J. Endocrinology, 1992, 135, 239-247, J. Endocrinology, 1993, 138, 203-209 and Cancer Research, 1994, 54, 408 that ICI 182,780 may be provided for administration by daily intramuscular injection in a 'short-acting' liquid formulation comprising ICI 182,780 in a propylene glycol-based solution.

It is an object of the present invention to provide a solution formulation containing the hydrophobic drug ICI 182,780 which does not exhibit, or which exhibits to a lesser degree, the problem of low oral bioavailability.

Many pharmaceutical compositions have been disclosed which are stated to be suitable for the dosing of hydrophobic drugs. Many of these formulations contain an oil such as arachis oil in which the hydrophobic drug is dissolved or dispersed. However the lack of miscibility of the oil with the aqueous environment of the gastrointestinal tract can lead to variable rates of absorption of the drug. To try to overcome the problem, it is common practice for a surfactant to be added to the pharmaceutical composition, particularly a hydrophilic surfactant such as a surfactant with a hydrophilic-lipophilic balance (HLB) of greater than about 8 and less than about 30. Such a surfactant may

produce an emulsion which, if the particle size is small, may lead to more complete absorption of the hydrophobic drug. However the use of hydrophilic surfactants may give a formulation of poor homogeneity as the surfactant may not be sufficiently miscible with the oil in which the hydrophobic drug is dissolved or dispersed. In a further refinement of such hydrophilic surfactant formulations, it is known that a lipophilic surfactant may be added to try to obtain the desired balance of hydrophilic and hydrophobic components to provide a stable emulsion when the formulation is added to an aqueous environment. The problem with this approach is that for each hydrophobic drug more than routine skill and knowledge is required to identify the exquisite balance of lipophilic and hydrophobic components which will provide a pharmaceutical composition of that hydrophobic drug which can be dosed orally to provide a reasonable oral bioavailability.

The many and various pharmaceutical compositions of the hydrophobic drug cyclosporin illustrate the complexities in this field of pharmaceutical research.

Thus, for example, it is disclosed in UK Patent Application No. 2 222 770 that cyclosporin may be formulated in a mixture of an oil such as a medium chain fatty acid triglyceride, a hydrophilic phase such as a mono- or di-alkyl ether of a polyoxyalkanediol, and a surfactant such as a hydrophilic or lipophilic surfactant or mixtures thereof.

Further it is disclosed in UK Patent Application No. 2 257 359 that cyclosporin may be formulated in a mixture of an oil such as a mixture of mono-, di- and tri-glycerides, a hydrophilic surfactant such as a surfactant having a HLB of at least 10, and the hydrophilic solvent 1,2-propylene glycol.

In addition it is disclosed in UK Patent Application No. 2 228 198 that cyclosporin may be formulated in a mixture of an oil such as a fatty acid triglyceride, a lipophilic surfactant such as a glycerol fatty acid partial ester, and a hydrophilic surfactant having a HLB of at least 10.

It has also been disclosed in PCT Patent Application WO 95/24893 that a hydrophobic drug may, for example, be formulated in a mixture of an oil such as a complete or partial ester of a medium chain or long chain fatty acid with a low molecular weight mono-, di- or polyhydric alcohol (for example a vegetable oil), a lipophilic surfactant such as a fatty acid or a mono- or di-glyceride of a fatty acid, and a hydrophilic surfactant having a HLB of greater than 10.

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