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(54) Title: TREATMENT OF GENERALIZED ANXIETY DISORDER WITH PAROXETINE

(57) Abstract

A method of treatment of generalised anxiety disorder, which method comprises administering an effective, non–toxic amount of paroxetine or a pharmaceutically acceptable salt or solvate thereof, to a human or non–human animal in need thereof.

TREATMENT OF GENERALIZED ANXIETY DISORDER WITH PAROXETINE

The present invention relates to a method for treatment of generalised anxiety disorder, and especially to the use of paroxetine in such treatment.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-) *trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylene-dioxyphenoxymethyl)-piperidine (see Example 2 of US-A-4007196). The hydrochloride salt of paroxetine is approved for human use in therapy to treat *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

In commercial use, paroxetine hydrochloride is supplied as a crystalline hemihydrate (see EP-A-0223403 of Beecham Group). Various crystalline anhydrate forms are also known (see WO96/24595 of SmithKline Beecham plc).

It has now been surprisingly discovered that paroxetine has potential therapeutic utility as a medicament for treatment of generalised anxiety disorder.

Accordingly, the present invention provides a method treatment of generalised anxiety disorder, which method comprises administering an effective, non-toxic amount of paroxetine or a pharmaceutically acceptable salt or solvate there of, to a human or non-human animal in need thereof.

The present invention also provides the use of paroxetine or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for use in treatment of generalised anxiety disorder.

A preferred pharmaceutically acceptable salt of paroxetine is crystalline hydrochloride. Suitable procedures for preparing paroxetine hydrochloride include those mentioned in US Patents 4009196, 4721723, 4902801, 4861893 and 5039803 and PCT/GB93/00721. Especially preferred is the hemi-hydrate, prepared as EP-A-0223403.

A medicament, for use in treatment of generalised anxiety disorder may be prepared by admixture of paroxetine or a pharmaceutically acceptable salt or solvate thereof with an appropriate carrier, which may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

Preferably, the medicament is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as a treatment of generalised anxiety disorder.

The suitable dosage range for paroxetine or a pharmaceutically acceptable salt or solvate depends on the severity of the generalised anxiety disorder and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

Paroxetine or a pharmaceutically acceptable salt or solvate thereof may be formulated for administration by any route, and examples are oral, sub-lingual, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may, if desired, be designed to give slow release of the paroxetine or a pharmaceutically acceptable salt or solvate thereof.

The medicaments may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The medicaments, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycerine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid medicaments may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute paroxetine or a salt or solvate thereof throughout those medicaments employing large quantities of fillers. When the medicament is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The medicament may also be in the form of an ingestible capsule, for example of gelatin containing paroxetine or a salt thereof if desired with a carrier or other excipients.

Medicaments for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid medicaments may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Paroxetine or a pharmaceutically acceptable salt or solvate thereof may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the medicaments may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi-dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

As mentioned hereinbefore, the effective dose of the paroxetine or pharmaceutically acceptable salt or solvate depends on the severity of generalised anxiety disorder to be treated, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 2 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 20, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day, for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Preferably the unit dose will contain from 2 to 20 mg of paroxetine (calculated as free base) and be administered in multiples, if desired, to give the preceding daily dose.

The present invention further provides a pharmaceutical composition for use in treatment of generalised anxiety disorder which comprises an effective amount of paroxetine or a pharmaceutically acceptable salt or solvate thereof and a

pharmaceutically acceptable carrier. Such compositions may be prepared in the manner as hereinbefore described.

The following Example discloses a suitable pharmaceutical composition for use in the present invention.

Example

The following are mixed together in a conventional manner and compressed into tablets of ca. 300 mg weight containing ca. 20 mg of paroxetine (calculated as the free base)

Paroxetine hydrochloride hemihydrate	228.8 g
Dibasic calcium phosphate dihydrate	2441.2 g
Hydroxypropylmethyl cellulose 2910	150.0 g
Sodium starch glycollate	150.0 g
Magnesium Stearate	30.0 g
Total tablet weight	3000.0 g



Claims

1. A method of treatment of generalised anxiety disorder, which method comprises administering an effective, non-toxic amount of paroxetine or a pharmaceutically acceptable salt or solvate there of, to a human or non-human animal in need thereof.

2. Use of paroxetine or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for use in treatment of generalised anxiety disorder.

3. A pharmaceutical composition for use in treatment of generalised anxiety disorder which comprises an effective amount of paroxetine or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier.

4. A method according to claim 1, use according to claim 2, or a pharmaceutical composition according to claim 3, wherein the pharmaceutically acceptable salt of paroxetine is the hydrochloride.