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(54) Title: A PHARMACEUTICAL COMPOSITION COMPRISING A BENZOPYRAN-3-OL.

(57) Abstract

A pharmaceutical composition comprising trans (3S,4R)-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-6-pentafluoroethyl-2H-1- benzopyran-3-ol ('Compound I'), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefore, wherein the composition comprises 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of Compound I; a method for preparing such a composition and the use of such a composition in medicine.

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(56) Documents cited: EP 376524 A1 EP 296975 A1 EP 93535 EP 76075 A1

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PHARMACEUTICAL COMPOSITION

This invention relates to a pharmaceutical composition, to processes for the preparation of such a composition and to the use of such a composition in medicine.

European Patent Application, Publication Number 0376524 discloses certain benzopyran derivatives which are stated *inter alia* to be potentially useful as bronchodilators in the treatment of disorders of the respiratory tract, such as reversible airways obstruction and asthma, and also in the treatment of hypertension.

EP 0376524 also discloses trans (3S, 4R)-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-6-pentafluoroethyl-2H-1- benzopyran-3-ol ('Compound I').

It has now been discovered that a discrete and particular pharmaceutical composition comprising Compound I or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, is particularly useful for the treatment in humans of disorders of the respiratory tract, such as reversible airways obstruction and asthma: the hypotensive activity of such composition is largely reduced.

Accordingly, in one aspect the present invention provides a pharmaceutical composition comprising Compound I or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and optionally a pharmaceutically acceptable carrier therefore, characterised in that the composition comprises 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of Compound I.

Particular compositions comprise 0.3 to 0.8 mg, 0.4 to 0.7 mg, 0.2 to 0.5 mg, 0.5 to 0.9 mg, 1.1 to 1.5 mg, 1.5 to 1.9 mg, 2.1 to 2.5 mg or 2.5 to 3.0 mg of active compound.

Examples of compositions are those comprising 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 , 0.9, 1.1, 1.5, 1.9, 2.1, 2.5 or 3.0 mg of active compound.

Suitable pharmaceutically acceptable salts include those described in

EP0376524. Generally, Compound I is not in a salted form.

Suitable pharmaceutically acceptable solvates include those described in EP0376524, in particular hydrates.

Compound I or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP0376524. The disclosures of EP0376524 are incorporated herein by reference.

In one aspect, the invention provides a process for preparing a pharmaceutical composition comprising 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of Compound I, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and optionally a pharmaceutically acceptable carrier therefor, which process comprises formulating Compound I, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof and optionally comprises admixing the pharmaceutically acceptable carrier.

The composition of the invention is preferably adapted for oral administration. However, it may be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and 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 glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline

cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations 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 preparations 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; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Compositions of this invention, especially for the treatment of reversible airways obstruction and asthma, may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 microns, preferably less than 10 microns for example diameters in the range of 1-50 microns, 1-10 microns or 1-5 microns. Where appropriate, small amounts of other anti-asthmatics and bronchodilators, for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; xanthine derivatives such as theophylline and aminophylline and corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration. A preferred range for inhaled administration is 10-99%, especially 60-99%, for example 90, 95 or 99%.

The present invention further provides a pharmaceutical composition, in particular a composition for inhaled administration, which comprises 0.2 to 3.0 mg of Compound I or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, in the form of a microfine powder and optionally a pharmaceutically acceptable carrier. Suitable carriers are those used conventionally in the art, for example lactose.

Preferably the composition for inhaled administration comprises 0.2 to 0.9 mg for example 0.2 to 0.5 mg, or 0.2 , 0.3, 0.4 or 0.5 mg, of active compound.

Microfine powder formulations may suitably be administered in an aerosol as a metered dose or by means of a suitable breath-activated device.

Suitable metered dose aerosol formulations comprise conventional propellants, cosolvents, such as ethanol, surfactants such as oleyl alcohol, lubricants such as oleyl alcohol, desiccants such as calcium sulphate and density modifiers such as sodium chloride.

Suitable solutions for a nebulizer are isotonic sterilised solutions, optionally buffered, at for example between pH 4-7, containing up to 20mg ml^{-1} of compound but more generally 0.1 to 10mg ml^{-1}, for use with standard nebulisation equipment.

The compositions of the invention may be prepared and formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) and Harry's Cosmeticology (Leonard Hill Books).

The present invention further provides a method for the treatment of respiratory tract disorders, such as reversible airways obstruction and, especially asthma, in humans which method comprises administering a total daily dose of 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of Compound I, or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, to a human in need thereof.

The medicament may be administered from 1 to 6 times a day, more usually from 2 to 4 times a day, preferably 1 or 2 times per day providing the total daily dose is 0.2 to 0.9 mg, 1.1 to 1.9 mg or 2.1 to 3.0 mg.

It will be appreciated that a unit dose for use in the method of the invention may comprise less than the stated total daily dose (e.g. less than 0.2 to 0.9 mg) of active compound in order to achieve the required total daily dose.

The present invention also provides a pharmaceutical composition comprising 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of Compound I or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic substance.

In particular, the present invention provides a pharmaceutical composition comprising 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of Compound I, or a pharmaceutically acceptable salt thereof, or a

pharmaceutically acceptable solvate thereof, for use in the treatment of respiratory tract disorders. Also the present invention provides the use of a pharmaceutical composition comprising 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of Compound I, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor for the manufacture of a medicament for the treatment of respiratory tract disorders.

The following Example illustrates the invention but does not limit it in any way.

Example

Male Sprague-Dawley rats were anaesthetized using urethane and prepared for determination of airways resistance (R_{aw}), dynamic lung compliance (C_{dyn}) and blood pressure as described by N.E. Bowring *et al.*, 1991, Pulmonary Pharmacolgoy **4**, 99-105.

The rats were challenged with an aerosol of methacholine for 2 minutes at 15 minute intervals using a concentration (0.25 to 2.5 mol) sufficient to raise resistance by about 100% and reduce compliance by about 40%. When consistent responses had been established Compound 1 was given intravenously 2 minutes before the methacholine challenge, the challenge being repeated at 15 minute intervals until its effect on R_{aw} and C_{dyn} had returned to near pre-Compound I values, after which point a higher dose of Compound I was given. Blood pressure was measured just prior to each methacholine challenge. When the dose of Compound I was sufficiently high to elicit an effect on blood pressure, this effect was maximal within 2 minutes. Results are means of 5 values ± S.E. and are expressed as percentage falls in blood pressure or inhibitions of pre-Compound I responses to the methacholine challenge.

RESULTS

Dose of Compound I (µg/kg. i.v.)	2			4			8		
Time post-dose (min)	2	17	32	2	17	32	2	17	32
% Inhibition R_{aw}	19±8	15±8	17±10	38±11*	31±7*	36±14	54±10**	37±11*	31±9*
% Inhibition C_{dyn}	14±5	17±7	11±6	25±7*	24±2***	18±14	44±9**	37±4***	22±10
% Fall mean blood pressure	0±0			0±6			11±3*		

*P<0.05; **P<0.01; ***P<0.001 compound to pre-Compound I values.

having now particularly described and ascertained my/our said invention and in what manner it is to be performed I/we declare that what I/we claim is :—

Claims

1. A pharmaceutical composition comprising trans (3S,4R)-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-6-pentafluoroethyl-2H-1-benzopyran-3-ol ('Compound I'), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefore, characterised in that, the composition comprises 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of Compound I.

2. A composition according to claim 1, comprising 0.3 to 0.8 mg, 0.4 to 0.7 mg, 0.2 to 0.5 mg, 0.5 to 0.9 mg, 1.1 to 1.5 mg, 1.5 to 1.9 mg, 2.1 to 2.5 mg or 2.5 to 3.0 mg of active compound.

3. A composition according to claim 1 or claim 2, comprising 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 , 0.9, 1.1, 1.5, 1.9, 2.1, 2.5 or 3.0 mg of active compound.

4. A composition according to any one of claims 1 to 3, adapted for oral administration, parenteral administration, sublingual or transdermal administration.

5. A composition according to any one of claims 1 to 4, adapted for oral administration.

6. A composition according to any one of claims 1 to 5, in the form of a unit dose.

7. A composition according to any one of claims 1 to 6, adapted for administration to the respiratory tract as a snuff, an aerosol, a solution for a nebulizer, or as a microfine powder for insufflation.

8. A pharmaceutical composition for inhaled administration, which comprises 0.2 to 3.0 mg of trans (3S,4R)-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-6-pentafluoroethyl-2H-1- benzopyran-3-ol ('Compound I'), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, in the form of a microfine powder and optionally a pharmaceutically acceptable carrier.

9. A process for preparing a pharmaceutical composition as claimed in any one of claims 1 to 8, which process comprises formulating Compound I, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and optionally comprises admixing the pharmaceutically acceptable carrier.

10. A pharmaceutical composition comprising 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of trans (3S,4R)-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-6-pentafluoroethyl-2H-1-benzopyran-3-ol ('Compound I'), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic substance.

11. A pharmaceutical composition comprising 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of trans (3S,4R)-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-6-pentafluoroethyl-2H-1- benzopyran-3-ol ('Compound I'), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for use in the treatment of respiratory tract disorders.

12. The use of a pharmaceutical composition comprising 0.2 to 0.9 mg or 1.1 to 1.9 mg or 2.1 to 3.0 mg of trans (3S,4R)-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-6-pentafluoroethyl-2H-1- benzopyran-3-ol ('Compound I'), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor for the manufacture of a medicament for the treatment of respiratory tract disorders.