(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/12191 A2

(51) International Patent Classification[7]: A61K 31/425

(21) International Application Number: PCT/GB00/03112

(22) International Filing Date: 14 August 2000 (14.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9902936-5 18 August 1999 (18.08.1999) SE

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/12191 A2

(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The present invention provides a pharmaceutical composition, pharmaceutical product or kit comprising a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*-one or a pharmaceutically acceptable salt thereof, and a second active ingredient (B) being a glucocorticoid, for use in the treatment of obstructive airways diseases.

PHARMACEUTICAL COMPOSITIONS

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of obstructive airways diseases.

In accordance with the present invention, there is therefore provided a pharmaceutical composition comprising, in admixture, a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a second active ingredient (B) being a glucocorticoid.

The invention also provides a pharmaceutical product comprising, in combination, a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]-propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient (B) being a glucocorticoid for sequential or separate use in therapy.

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]-ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, a preparation of a second active ingredient (B) being a glucocorticoid, and instructions for the sequential or separate administration of the preparations to a patient in need thereof.

The combination of active ingredients according to the invention is advantageous because it is beneficial in the treatment of obstructive airways diseases including chronic obstructive pulmonary disease (COPD); and asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness).

4-Hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one and pharmaceutically acceptable salts thereof are described in WO 93/24473. The active ingredient (A) is most preferably 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one hydrochloride.

Examples of the active ingredient (B) include known glucocorticoids such as:

9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dione (dexamethasone);

(11β, 16α)-16,17-[Butylidenebis(oxy)]-11,21-dihydroxypregna-1,4-diene-3,20-dione, (budesonide);

(6α, 11β, 16α, 17α)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid S-(fluoromethyl) ester, (fluticasone propionate);

(11β, 16β)-9-Chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione dipropionate, (beclomethasone dipropionate);

(11β, 16β)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione 17-valerate, (betamethasone valerate);

(11β, 16α)-9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methylpregna-1,4-diene-3,20-dione, (mometasone furoate);

(6α, 11β, 16α)-6-Fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)-bis(oxy)]pregna-1,4-diene-3,20-dione, (flunisolide); and

(11β, 16α)-9-Fluoro-11,21-dihydroxy-16,17-[1-methylethylidenebis(oxy)]pregna-1,4-diene-3,20-dione, (triamcinolone acetonide).

Methods of assaying for corticoid activity are described, for example, by G. Tonelli et al in *Endocrinology*, 77(4), 625-634 (1965).

The pharmaceutical composition of the invention may be prepared by mixing the first active ingredient (A) with the second active ingredient (B). Therefore, in another aspect of

the present invention, there is provided a process for the preparation of a pharmaceutical composition which comprises mixing a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, with a second active ingredient (B) being a glucocorticoid. The pharmaceutical composition of the invention will typically comprise a total amount of first active ingredient (A) and second active ingredient (B) in the range from 0.05 to 99 %w (per cent by weight), more preferably in the range from 0.10 to 70 %w, and even more preferably in the range from 0.10 to 50 %w, all percentages by weight being based on total composition.

The first and second active ingredients (A) and (B) may alternatively be administered sequentially or separately in any suitable order to treat obstructive airways diseases. By sequential is meant that the first and second active ingredients are administered one immediately after the other. They still have the desired effect if they are administered separately but less than about 4 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

The active ingredients may, and indeed usually will, be used in admixture with one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants.

For the above-mentioned therapeutic uses the dosages administered will, of course, vary with the first and second active ingredients (A) and (B) employed, the mode of administration, the treatment desired and the disorder indicated. If the active ingredients are administered by inhalation, then the total daily dosage of first active ingredient (A) and second active ingredient (B) together is preferably in the range from 5 to 1500 μg, e.g. from 10 to 1450 μg or from 20 to 1400 μg. Alternatively, if the first active ingredient (A) is administered by inhalation, the total daily dosage of first active ingredient (A) is preferably

in the range from 5 to 1500 μg, e.g. from 10 to 1450 μg or from 20 to 1400 μg, and the second active ingredient (B) is administered orally, the total daily dosage of second active ingredient (B) is preferably in the range from 1 to 50 mg, particularly from 1, 2, 3, 4 or 5 to 40, preferably to 30 mg.

The pharmaceutical composition, pharmaceutical product or kit according to the invention may be administered as divided doses from 1 to 4 times a day, and preferably once or twice a day.

The first and second active ingredients (A) and (B) may be administered topically (to the lung and/or airways) in the form of solutions, suspensions, aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions.

For example metered dose inhaler devices may be used to administer the active ingredient(s), dispersed in a suitable propellant and with or without additional excipients such as ethanol, surfactants, lubricants or stabilising agents.

Suitable propellants include hydrocarbon, chlorofluorocarbon and hydrofluoroalkane (e.g. heptafluoroalkane) propellants, or mixtures of any such propellants. Especially preferred propellants are HFA-134a and HFA-227, each of which may be used alone or in combination with other propellants and/or surfactants and/or other excipients.

Nebulised aqueous suspensions or, preferably, solutions may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose formulations.

Dry powder inhalers may be used to administer the active ingredient(s), alone or in combination with a pharmaceutically-acceptable carrier, in the latter case either as a finely

divided powder or as an ordered mixture. The dry powder inhaler may be single dose or multi-dose and may utilise a dry powder or a powder-containing capsule.

Metered dose inhaler, nebuliser and dry powder inhaler devices are well known and a variety of such devices are available.

Tablets and gelatin capsules, which may be coated if desired, containing the active ingredient(s) may, for example, also include one or more diluents, carriers, binders, lubricants or stabilising agents.

Injectable solutions of the active ingredient(s) may also contain, for example, one or more preservatives, stabilising agents, viscosity-regulating agents, emulsifying agents or buffering agents.

The present invention further provides the use of a pharmaceutical composition, pharmaceutical product or kit according to the invention in the manufacture of a medicament for the treatment of an obstructive airways disease.

Also, the present invention provides a method of treating, or reducing the risk of, an obstructive airways disease in a patient suffering from, or at risk of, the disease, which comprises administering to the patient a therapeutically effective amount of a pharmaceutical composition of the invention.

Still further, the present invention provides a method of treating, or reducing the risk of, an obstructive airways disease which comprises sequentially or separately administering (in any suitable order) to a patient suffering from, or at risk of, the disease

(a) a (therapeutically effective) dose of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof; and

(b) a (therapeutically effective) dose of a second active ingredient (B) being a glucocorticoid.

The present invention will now be further explained by reference to the following illustrative example.

Example 1

Pharmacological Analysis

Female CR/CD rats weighing 250-300g were dosed orally at 1ml.kg^{-1} with either distilled water (DIH_20) or dexamethasone (active ingredient (B)) (see table 1). Sixty (60) minutes later they were placed into open fronted holding cones that were attached to a cylindrical metal aerosol chamber. Their noses were exposed to an aerosol of either saline or 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one hydrochloride (active ingredient (A)) (see table 1) for 30 minutes before being exposed, for another 30 min, to an aerosol of 0.1mg.ml^{-1} lipopolysaccharide (LPS). Aerosols were generated using two jet nebulisers to each column with airflow of 12 l.min^{-1} (6 l.min^{-1} per nebuliser). 10 ml of agent was placed into each nebuliser at the beginning of the aerosol challenge and after 15 min aerosolisation the solution was removed and replaced with fresh.

Table 1 Experimental groups

Group	N	Dexamethasone (Active Ingredient (B)) µg/kg p.o.	Distilled Water p.o.	Active Ingredient (A) mg/ml	Vehicle for (A)	LPS
1	8	-	Yes	-	Yes	Yes
2	8	3	-	-	Yes	Yes
3	8	10	-	-	Yes	Yes
4	8	30	-	-	Yes	Yes
5	8	100	-	-	Yes	Yes
6	8	-	Yes	0.1	-	Yes
7	8	-	Yes	0.3	-	Yes
8	8	-	Yes	1	-	Yes
9	8	1	-	0.1	-	Yes
10	8	3	-	0.1	-	Yes
11	8	10	-	0.1	-	Yes

End points

Six hours after LPS exposure the rats from each group were terminally anaesthetised with 0.5ml Euthatal and blood samples taken from the dorsal vena cava for analysis in Clinical Pathology. Following exsanguination, the trachea was exposed and cannulated, the lungs were lavaged with 3 x 3ml aliquots of Hanks Buffered Salt Solution (HBSS). Each 3ml was gently pushed in and, while gently massaging the chest, withdrawn 10 seconds later. The first wash was placed into a 15ml conical polypropylene centrifuge tube A while the second and third washes were pooled in similar tubes. Samples were kept on ice at all times. The lavages were centrifuged at 1800 rpm for 10 min at 4°C. The supernatant from tube A was kept for future mediator analysis, and the remaining supernatant poured away into Trigene. The cell pellets from the remaining two tubes were resuspended in a total of

1ml HBSS. A 1 in 10 dilution of the lavage suspension was made in Kimura's stain and using an improved Neubauer counting chamber, the number of neutrophils counted. The number of cells found for each rat was calculated using the following formula:
Number of cells x dilution (10) x volume (1ml) = total cell count per rat ($x10^6$).

All results are expressed as percentage inhibition of the vehicle LPS treated group. Statistical significance was evaluated using a Mann-Whitney U-test following a Kruskal-Wallis (non-parametric ANOVA) and significance was accepted when $p<0.05$.

Results

Oral treatment 60 min pre LPS	**Aerosol treatment 30 min pre LPS**	**(A) alone % inhibition**	**(B) alone % inhibition**	**Combination (A) + (B) % inhibition**
Dexamethasone (Active Ingredient (B)) 1 µg/kg	Active Ingredient (A) 0.1 mg/ml	0	Not tested	33%
Dexamethasone 3 µg/kg	Active Ingredient (A) 0.1 mg/ml	0	12%	44% *
Dexamethasone 10 µg/kg	Active Ingredient (A) 0.1 mg/kg	0	29%	52% *
Dexamethasone 30 µg/kg	-	-	54% *	-
Dexamethasone 100 µg/kg	-	-	73% *	-

Oral treatment 60 min pre LPS	**Aerosol treatment 30 min pre LPS**	**(A) alone % inhibition**	**(B) alone % inhibition**	**Combination (A) + (B) % inhibition**
-	Active Ingredient (A) 0.3 mg/kg	17%	-	-
-	Active Ingredient (A) 1 mg/kg	Compound insoluble and could not be tested	-	-

* $p<0.05$ using a Mann-Whitney U-test following a Kruskal-Wallis

Glucocorticoids such as dexamethasone are known to have anti-inflammatory properties and as the above data clearly demonstrate, such compounds in combination with the active ingredient (A) show an advantageous synergistic improvement in these properties.

CLAIMS

1. A pharmaceutical composition comprising, in admixture, a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a second active ingredient (B) being a glucocorticoid.

2. A composition according to claim 1, wherein, as first active ingredient (A), 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one hydrochloride is used.

3. A composition according to claim 1 or claim 2, wherein, as second active ingredient (B), dexamethasone, budesonide, fluticasone propionate, beclomethasone dipropionate, betamethasone valerate, mometasone furoate, flunisolide or triamcinolone acetonide is used.

4. A process for the preparation of a pharmaceutical composition as defined in claim 1 which comprises mixing a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, with a second active ingredient (B) being a glucocorticoid.

5. Use of a pharmaceutical composition as claimed in any one of claims 1 to 3 in the manufacture of a medicament for the treatment of an obstructive airways disease.

6. Use according to claim 5 wherein the obstructive airways disease is chronic obstructive pulmonary disease or asthma.

7. A method of treating, or reducing the risk of, an obstructive airways disease in a patient suffering from, or at risk of, the disease, which comprises administering to the

patient a therapeutically effective amount of a pharmaceutical composition as defined in any one of claims 1 to 3.

8. A method according to claim 7, wherein the obstructive airways disease is chronic obstructive pulmonary disease or asthma.

9. A pharmaceutical product comprising, in combination, a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]-ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient (B) being a glucocorticoid for sequential or separate use in therapy.

10. A product according to claim 9, wherein, as first active ingredient (A), 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one hydrochloride is used.

11. A product according to claim 9 or claim 10, wherein, as second active ingredient (B), dexamethasone, budesonide, fluticasone propionate, beclomethasone dipropionate, betamethasone valerate, mometasone furoate, flunisolide or triamcinolone acetonide is used.

12. Use of a product as claimed in any one of claims 9 to 11 in the manufacture of a medicament for the treatment of an obstructive airways disease.

13. Use according to claim 12 wherein the obstructive airways disease is chronic obstructive pulmonary disease or asthma.

14. A kit comprising a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, a preparation of a second active ingredient (B)

being a glucocorticoid, and instructions for the sequential or separate administration of the preparations to a patient in need thereof.

15. A kit according to claim 14, wherein, as first active ingredient (A), 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one hydrochloride is used.

16. A kit according to claim 14 or claim 15, wherein, as second active ingredient (B), dexamethasone, budesonide, fluticasone propionate, beclomethasone dipropionate, betamethasone valerate, mometasone furoate, flunisolide or triamcinolone acetonide is used.

17. A method of treating, or reducing the risk of, an obstructive airways disease which comprises sequentially or separately administering to a patient suffering from, or at risk of, the disease

(a) a dose of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]-propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof; and

(b) a dose of a second active ingredient (B) being a glucocorticoid.