54-658/002.562

INHALATION MEDICAMENTS FOR TREATING RESPIRATORY DISORDERS

This invention relates to improvements in the treatment of asthma and other respiratory disorders. More particularly, it relates to the use of a bronchodilator drug in combination with a steroidal anti-inflammatory drug for the treatment of respiratory disorders such as asthma, and to pharmaceutical compositions containing the two active ingredients.

Asthma is a condition characterised by variable, reversible obstruction of the airways which is caused by a complex inflammatory process within the lungs. In most cases, this process is initiated and maintained by the inhalation of antigens by sensitive atopic individuals (extrinsic asthma). However, in some patients it is caused by other mechanisms which at present are poorly understood but do not involve an allergic process (intrinsic asthma). The disease has therefore two components, spasm of the bronchial (or breathing) tubes and inflammation or swelling of the breathing tubes.

Salbutamol, the first highly selective B_2-adrenoceptor stimulant has been used successfully and effectively by inhalation for the immediate relief of spasm in asthma. However, when given by inhalation, salbutamol has usually a four to six hour duration of action, which is too short either to control nocturnal asthma or for convenient maintenance of the disease in some patients.

Anti-inflammatory corticosteroids such as, for example, beclomethasone dipropionate have also been administered by inhalation in the treatment of asthma, although unlike salbutamol the therapeutic benefits may not be immediately apparent. Indeed, although the benefits of inhaled beclomethasone dipropionate and its

safety and efficacy in asthma therapy are well-established in clinical practice, the true nature of asthma as an inflammatory disease and the consequent fundamental effects of inhaled beclomethasone dipropionate in its treatment have only recently been realised.

It has, however, been recognised that asthma may be treated by using both a bronchodilator for immediate relief and a prophylactic anti-inflammatory corticosteroid to treat the underlying inflammation. Such combination therapy directed at the two main underlying events in the lung (i.e. relief of spasm in the breathing tubes and treatment of inflammation in the breathing tubes) using a combination of salbutamol and beclomethasone dipropionate has previously been proposed (Ventide, Glaxo Group trade mark), but suffers a number of disadvantages in view of the above-mentioned short duration of action exhibited by salbutamol. Thus the need for a 4-hourly dosing regimen may discourage effective patient compliance and also renders the product less than satisfactory in the treatment of nocturnal asthma since the bronchodilator may not remain effective for the duration of the night, leading to impaired sleep for asthmatics troubled by nocturnal cough, breathlessness and wheeze.

The present invention is based on the concept of a novel combination therapy which has greater efficiency and duration of bronchodilator action than previously known combinations and which permits the establishment of a twice daily (bis in diem - b.i.d) dosing regimen with consequent benefits in, for example, the treatment of asthma, particularly nocturnal asthma.

Thus we have found that if the β_2-adrenoreceptor stimulant bronchodilator salmeterol and/or a physioilogically acceptable salt thereof is combined with beclomethasone dipropionate in a form suitable for administration by inhalation, the resulting compositions

may be administered on a b.i.d. basis to provide effective treatment and/or prophylactic therapy for asthmatics. In particular such administration has been shown to lead to improvement in daytime lung function, requirement for additional symptomatic bronchodilator and almost complete abolition of nocturnal asthma while giving rise to minimal systemic side effects.

Salmeterol is one of a range of bronchodilators having extended duration of action which is described in British Patent Specification No. 2140800, and is systematically named 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol.

According to one aspect of the invention there are provided pharmaceutical compositions comprising effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and beclomethasone dipropionate as a combined preparation for simultaneous administration by inhalation in the treatment of respiratory disorders.

The invention additionally relates to the use of salmeterol (and/or a physiologically acceptable salt thereof) and beclomethasone dipropionate in the manufacture of pharmaceutical compositions as combined preparations for simultaneous administration of salmeterol and beclomethasone dipropionate by inhalation in the treatment of respiratory disorders.

Suitable physiologically acceptable salts of salmeterol include acid addition salts derived from inorganic and organic acids, such as the hydrochloride, hydrobromide, sulphate, phosphate, maleate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate,

methanesulphonate, ascorbate, salicylate, acetate, fumarate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynapthalenecarboxylate, e.g. 1-hydroxy- or 3-hydroxy-2-naphthalenecarboxylate or oleate. Salmeterol is preferably used in the form of its 1-hydroxyxy-2-napthalene carboxylate salt (hydroxynapthoate).

For administration by inhalation, the compositions according to the invention are conveniently delivered by conventional means i.e. in the form of a metered dose inhaler prepared in a conventional manner or in combination with a spacer device such as the Volumatic (Glaxo Group trade mark) device. In the case of a metered dose inhaler, a metering valve is provided to deliver a metered amount of the composition. Spray compositions may for example be formulated as aqueous solutions or suspensions and may be administered by a nebuliser. Aerosol spray formulations for example in which the active ingredients are suspended, optionally together with one or more stabilisers, in a propellant, e.g. a halgenated hydrocarbon such as trichlorofluoromethane, dichlorodifluoromethane, 1,2-dichlorotetrafluoroethane, trichlorotrifluoroethane, monochloropentafluoroethane, chloroform or methylene chloride may also be employed.

Alternatively, for administration by inhalation or insufflation, the compositions according to the invention may take the form of a dry powder composition, for example a powder mix of the active ingredients and a suitable carrier such as lactose. The powder compositions may be presented in unit dosage form in, for example, capsules, cartrides or blister packs from which the powder may be administered with the aid of an inhaler such as the Rotahaler inhaler (Glaxo Group trade mark) or in the case of blister packs by means of the Diskhaler Inhaler (Glaxo Group trade mark).

The ratio of salmeterol to beclomethasone dipropionate in the compositions according to the invention is preferably within the range 2:1 to 1:40. Each metered dose or actuation of the inhaler will generally contain from 25 μg to 100 μg of salmeterol and from 50 μg to 1000 μg of beclomethasone dipropionate. As hereinbefore indicated, it is intended that the pharmaceutical compositions will be administered twice daily.

A suitable daily dose of salmeterol for inhalation is in the range 20 μg to 200 μg.

A suitable daily dose of beclomethasone dipropionate for inhalation is in the range of 100 μg to 2000 μg depending on the severity of the disease.

The precise dose employed will of course depend on the method of administration the age, weight and condition of the patient and will be determined by the clinician depending on the severity and the type of asthma.

In order that the invention may be more fully understood, the following examples are given by way of illustration only.

EXAMPLE 1 - Metered Dose Inhaler

Active Ingredient	Target per Actuation	Per Inhaler % w/w
Salmeterol (as hydroxynapthoate)	25.0 µg	0.0448
Beclomethasone dipropionate BP	50.0 µg	0.0647
Stabiliser	7.5 µg	0.0110
Trichlorofluoromethane	23.67 mg	27.8207
Dichlorodifluoromethane	61.25 mg	72.0588

EXAMPLE 2 - Metered Dose Inhaler

Active Ingredient	Target per Actuation	Per Inhaler % w/w
Salmeterol (as hydroxynapthoate)	25.0 µg	0.0448
Beclomethasone dipropionate BP	100.0 µg	0.1294
Stabiliser	10.5 µg	0.0129
Trichlorofluoromethane	23.62 mg	27.7541
Dichlorodifluoromethane	61.25 mg	72.0588

EXAMPLE 3 - Metered Dose Inhaler

Active Ingredient	Target per Actuation	Per Inhaler % w/w
Salmeterol (as hydroxynapthoate)	25.0 μg	0.0448
Beclomethasone dipropionate BP	250.0 μg	0.3235
Stabiliser	25.0 μg	0.0324
Trichlorofluoromethane	23.45 mg	27.5405
Dichlorodifluoromethane	61.25 mg	72.0588

EXAMPLE 4 Metered Dose Inhaler

Active Ingredient	Target per Actuation	Per Inhaler % w/w
Salmeterol (as hydroxynaphthoate)	100.0 μg	0.1791
Beclomethasone dipropionate BP	125.0 μg	0.3235
Stabiliser	25.0 μg	0.0324
Trichlorofluoromethane	23.43 mg	27.4062
Dichlorodifluoromethane	61.25 mg	72.0588

In Examples 1 to 4 micronised beclomethasone dipropionate (as the trichlorofluoromethane solvate) and

micronised salmeterol (as the hydroxynapthoate) are added in the proportions given above either dry or after predispersal in a small quantity of stabiliser (disodium dioctylsulphosuccinate, lecithin, oleic acid or sorbitan trioleate)/trichlorofluoromethane solution to a suspension vessel containing the main bulk of the trichlorofluoromethane solution. The resulting suspension is further dispersed by an appropriate mixing system using, for example, a high sheer blender, ultrasonics or a microfluidiser until an ultrafine dispersion is created. The suspension is then continuously recirculated to suitable filling equipment designed for cold fill or pressure filling of dichlorodifluoromethane. Alternatively, the suspension may be prepared in a suitable chilled solution of stabiliser, in trichlorofluoromethane/ dichlorodiflurомethane.

EXAMPLE 5 - Metered Dose Dry Powder Formulation

Active Ingredient		µg/cartridge or blister
Salmeterol (as hydroxynaphthoate)		36.3
Beclomethasone dipropionate BP (anhydrous or as monohydrate)		50.00
Lactose Ph.Eur.	to to	12.5 mg or 25.0mg

EXAMPLE 6 - Metered Dose Dry Powder Formulation

Active Ingredient		µg/cartridge or blister
Salmeterol (as hydroxynaphthoate)		36.25
Beclomethasone dipropionate BP (anhydrous or as monohydrate)		100.00
Lactose Ph.Eur.	to to	12.5 mg or 25.0 mg

EXAMPLE 7 - Metered Dose Dry Powder Formulation

Active Ingredient		µg/cartridge or blister
Salmeterol (as hydroxynaphthoate)		72.5
Beclomethasone dipropionate (anhydrous or as monohydrate)		100.00
Lactose Ph.Cur.	to to	12.5 mg or 25.0 mg

EXAMPLE 8 - Metered Dose Dry Powder Formulation

Active Ingredient		µg/cartridge or blister
Salmetreol (as hydroxynaphthoate)		72.5
Beclomethasone dipropionate BP (anhydrous or as monohydrate)		200.00
Lactose Ph.Eur.	to to	12.5 mg or 25.0 mg

EXAMPLE 9 - Metered Dose Dry Powder Formulation

Active Ingredient		ug/cartridge or blister
Salmeterol (as hydroxynaphthoate)		72.5
Beclomethasone dipropionate BP (anyhydrous or as monohydrate)		500.0
Lactose Ph.Eur.	to to	12.5 mg or 25.0 mg

EXAMPLE 10 - Metered Dose Dry Powder Formulation

Active Ingredient		µg/cartridge or blister
Salmeterol (as hydroxynaphthoate)		72.5
Beclomethasone dipropionate BP (anhydrous or as monohydrate)		1000.0
Lactose Ph. eur.	to to	12.5 mg or 25.0 mg

EXAMPLE 11 - Metered Dose Dry Powder Formulation

Active Ingredient		μg/cartridge or blister
Salmeterol (as hydroxynaphthoate)		145.0
Beclomethasone dipropionate (anydrous or as monohydrate)		250.0
Lactose Ph. Eur.	to to	12.5 mg or 25.0 mg

In Examples 5 to 11 the active ingredients are micronised and bulk blended with the lactose in the proportions given above. The blend is filled into hard gelatin capsules or cartridges or in specifically constructed double foil blister packs (Rotadisks blister packs, Glaxo Group trade mark) to be administered by an inhaler such as the Rotahaler inhaler (Glaxo Group trade mark) or in the case of the blister packs with the Diskhaler inhaler (Glaxo Group trade mark).

CLAIMS:

1. Pharmaceutical compositions comprising effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and beclomethasone dipropionate as a combined preparation for simultaneous administration by inhalation in the treatment of respiratory disorders.

2. Compositions as claimed in claim 1 wherein salmeterol is present as its 1-hydroxy-2-naphthalenecarboxylate salt.

3. Compositions as claimed in claim 1 or claim 2 presented in the form of a metered dose inhaler or a metered dry powder composition.

4. Compositions as claimed in any of claims 1 to 3 in dosage unit form containing 25-100μg of salmeterol (optionally in the form of a physiologically acceptable salt thereof) and 50-1000μg of beclomethasone dipropionate per dosage unit.

5. The use of salmeterol (and/or a physiologically acceptable salt thereof) and beclomethasone dipropionate in the manufacture of pharmaceutical compositions as combined preparations for simultaneous administration of salmeterol and beclomethasone dipropionate by inhalation in the treatment of respiratory disorders.

6. The use of salmeterol (and/or a physiologically acceptable salt thereof) and beclomethasone dipropionate according to claim 5 in the manufacture of pharmaceutical compositions for administration on a twice daily basis.