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(* ) Notice: This patent is subject to a terminal disclaimer.

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ABSTRACT
Pharmaceutical compositions comprising effective amounts of salmeterol (and a physiologically acceptable salt thereof) and fluctuations propionate as a combined preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders.

7 Claims, No Drawings
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MATTER enclosed in heavy brackets [ ] appears in the
original patent but forms no part of this reissue specifi-
cation; matter printed in italics indicates the additions
made by reissue.

[This application is a continuation of U.S. patent appli-
cation Ser. No. 07/578,601, filed Sept. 7, 1990.]

This application is a continuation of U.S. patent appli-
cation Ser. No. 07/578,601, filed Sep. 7, 1990, now aban-
donned.

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 steroid anti-inflammatory drug for the treatment of
respiratory disorders such as asthma, and to pharmaceuti-
cally compositions containing the two active ingredients.

Asthma is a condition characterized by variable, re-
versible 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 β2-adrenoceptor
stimulant has been used successfully and effectively by
inhalation for the immediate relief of spasm in asthma. How-
ever, 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,
beclometasone dipropionate have also been administered
by inhalation in the treatment of asthma, although unlike
salbutamol the therapeutic benefits resulting from reduced
inflammation may not be immediately apparent.

It has been recognized that asthma may be treated by
using both a bronchodilator or 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 beclometasone 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 no longer 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 markedly greater efficiency
and duration of bronchodilator action than previously known
combinations and which permits the establishment of a
twice daily (bis in dience—b.i.d.) dosing regimen with con-
squent substantial benefits in, for example, the treatment of
asthma, particularly nocturnal asthma.

Thus [we have found] we believe that if the
β2-adrenoceptor stimulant bronchodilator salmeterol and/or
a physiologically acceptable salt thereof is combined with
the anti-inflammatory corticosteroid fluticasone propionate
in a form suitable for administration by inhalation, the
resulting compositions may be administered on a b.i.d. basis
to provide highly effective treatment and/or prophylactic
therapy for asthmatics. In particular we believe that such
administration will lead to significant improvement in daytime lung functions, 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
defined 4-hydroxy-α-[6-(4-phenylbutoxy)hexyl]amino-
[1,3-benzendimethanol. Fluticasone propionate is
one of a range of topical anti-inflammatory corticosteroids
with minimal liability to undesired systemic side effects
which is described in British Patent Specification No.
2088877, and is systematically defined S-fluoromethyl
6α,9α-difluoro-11β-hydroxy-16β-methyl-17α-
propionyloxy-3-oxoadenos-1,4-diene-17β-carbothionate.
[We have found] We believe these two compounds to be
particularly compatible and complementary in their activity
and thus highly effective in the treatment of asthma and
other respiratory disorders.

Thus 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 fluticasone propionate as a combined
preparation for simultaneous, sequential or separate admin-
istration by inhalation in the treatment of respiratory disor-
ders.

The invention additionally relates to the use of salmeterol
(and/or a physiologically acceptable salt thereof) and fluti-
casone propionate in the manufacture of pharmaceutical
composition as combined preparations for simultaneous,
sequential or separate administration of salmeterol and fluti-
casone propionate by inhalation in the treatment of respira-
tory element.

According to further feature of the invention there is
provided a method of treating respiratory disorders which
comprises the simultaneous, sequential or separate admin-
istration by inhalation of effective amounts of salmeterol
(and/or a physiologically acceptable salt thereof) and fluti-
casone propionate.

Suitable physiologically acceptable salts of salmeterol
include acid addition salts derived from inorganic and
organic acids, such as the hydrochloride, hydrobromide,
sulphate, sulphonate, maleate, tartrate, citrate, benzoate,
4-methoxybenzoate, 2- or 4-hydroxybenzoate,
4-chlorobenzoate, p-toluene sulphonic, methanesulphonate,
ascorbate, salicylate acetate, fumarate, succinate, lactate,
gluatrate, gluconate, tricarballylate, hydroxypropylencarb-
boxylate e.g. 1-hydroxy- or 3-hydroxy-2-
naphthalencarboxylate, or oleate. Salmeterol is preferably
used in the form of its 1-hydroxy-2-naphthalene carboxylate
salt (hydroxypropionate).

For administration by inhalation, the compositions
according to the invention are conveniently delivered by
conventional means, e.g. in the form of a metered dose
inhaler prepared in a conventional manner or in combina-
tions 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
formations, for example in which the active ingredients are suspended, optionally together with one or more stabilisers, in a propellant, e.g. a halogenated hydrocarbon such as trichlorofluoromethane, dichlorodifluoromethane, 1,2-dichlorotetrafluoroethane, trichlorotrifluoroethane, monochloropentfluoroethane, chloroform or methylene chloride, may also be employed. The two drugs may be administered separately in similar ways.

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 dosages form in, for example, capsules, cartridges 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 fluctuations propionate in the compositions according to the invention is preferably within the range of 4:1 to 1:20. The two drugs may be administered separately in the same ratio. Each metered dose or actuation of the inhaler will generally contain from 25 µg to 100 µg of salmeterol and from 25 µg to 500 µg of fluticasone propionate. 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 50 µg to 200 µg.

A suitable daily dose of fluticasone propionate for inhalation is in the range 50 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 example are given by way of illustration only.

EXAMPLE 1
Metered Dose Inhaler

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Target per Actuation</th>
<th>Per Inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol (as hydroxynaphthoate)</td>
<td>25.0 µg</td>
<td>0.0448</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>25.0 µg</td>
<td>0.0309</td>
</tr>
<tr>
<td>Stabiliser</td>
<td>5.0 µg</td>
<td>0.0076</td>
</tr>
<tr>
<td>Trichlorofluoromethane</td>
<td>23.70 mg</td>
<td>27.8240</td>
</tr>
<tr>
<td>Dichlorodifluoromethane</td>
<td>61.25 mg</td>
<td>72.0588</td>
</tr>
</tbody>
</table>

EXAMPLE 2
Metered Dose Inhaler

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Target per Actuation</th>
<th>Per Inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol (as hydroxynaphthoate)</td>
<td>25.0 µg</td>
<td>0.0448</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>50.0 µg</td>
<td>0.0618</td>
</tr>
<tr>
<td>Stabiliser</td>
<td>7.5 µg</td>
<td>0.0106</td>
</tr>
<tr>
<td>Trichlorofluoromethane</td>
<td>23.67 mg</td>
<td>27.8240</td>
</tr>
<tr>
<td>Dichlorodifluoromethane</td>
<td>61.25 mg</td>
<td>72.0588</td>
</tr>
</tbody>
</table>

EXAMPLE 3
Metered Dose Inhaler

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Target per Actuation</th>
<th>Per Inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol (as hydroxynaphthoate)</td>
<td>25.0 µg</td>
<td>0.0448</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>250.0 µg</td>
<td>0.3088</td>
</tr>
<tr>
<td>Stabiliser</td>
<td>25.0 µg</td>
<td>0.0309</td>
</tr>
<tr>
<td>Trichlorofluoromethane</td>
<td>23.45 mg</td>
<td>27.5567</td>
</tr>
<tr>
<td>Dichlorodifluoromethane</td>
<td>61.25 mg</td>
<td>72.0588</td>
</tr>
</tbody>
</table>

EXAMPLE 4
Metered Dose Inhaler

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Target per Actuation</th>
<th>Per Inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol (as hydroxynaphthoate)</td>
<td>25.0 µg</td>
<td>0.0448</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>125.0 µg</td>
<td>0.1544</td>
</tr>
<tr>
<td>Stabiliser</td>
<td>15.0 µg</td>
<td>0.0175</td>
</tr>
<tr>
<td>Trichlorofluoromethane</td>
<td>23.56 mg</td>
<td>27.7244</td>
</tr>
<tr>
<td>Dichlorodifluoromethane</td>
<td>61.25 mg</td>
<td>72.0588</td>
</tr>
</tbody>
</table>

EXAMPLE 5
Metered Dose Inhaler

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Target per Actuation</th>
<th>Per Inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol (as hydroxynaphthoate)</td>
<td>100.0 µg</td>
<td>0.1791</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>250.0 µg</td>
<td>0.3088</td>
</tr>
<tr>
<td>Stabiliser</td>
<td>25.0 µg</td>
<td>0.0309</td>
</tr>
<tr>
<td>Trichlorofluoromethane</td>
<td>23.43 mg</td>
<td>27.4224</td>
</tr>
<tr>
<td>Dichlorodifluoromethane</td>
<td>61.25 mg</td>
<td>72.0588</td>
</tr>
</tbody>
</table>

In Examples 1 to 5 micronised fluticasone propionate and micronised salmeterol (as the hydroxynaphthoate) are added in the proportions given above either dry or after dispersal 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 shear blender, ultrasonic 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/dichlorodifluoromethane.
### EXAMPLE 6
Metered Dose Dry Powder Formulation

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>µg/cartridge or blister</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>36.3</td>
</tr>
<tr>
<td>(as hydroxynaphthoate)</td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>50.00</td>
</tr>
<tr>
<td>Lactose Ph. Eur.</td>
<td>to 12.5 mg or</td>
</tr>
<tr>
<td></td>
<td>to 25.0 mg</td>
</tr>
</tbody>
</table>

### EXAMPLE 7
Metered Dose Dry Powder Formulation

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>µg/cartridge or blister</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>72.5</td>
</tr>
<tr>
<td>(as hydroxynaphthoate)</td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>50.00</td>
</tr>
<tr>
<td>Lactose Ph. Eur.</td>
<td>to 12.5 mg or</td>
</tr>
<tr>
<td></td>
<td>to 25.0 mg</td>
</tr>
</tbody>
</table>

### EXAMPLE 8
Metered Dose Dry Powder Formulation

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>µg/cartridge or blister</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>72.5</td>
</tr>
<tr>
<td>(as hydroxynaphthoate)</td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>100.00</td>
</tr>
<tr>
<td>Lactose Ph. Eur.</td>
<td>to 12.5 mg or</td>
</tr>
<tr>
<td></td>
<td>to 25.0 mg</td>
</tr>
</tbody>
</table>

### EXAMPLE 9
Metered Dose Dry Powder Formulation

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>µg/cartridge or blister</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>72.5</td>
</tr>
<tr>
<td>(as hydroxynaphthoate)</td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>250.00</td>
</tr>
<tr>
<td>Lactose Ph. Eur.</td>
<td>to 12.5 mg or</td>
</tr>
<tr>
<td></td>
<td>to 25.0 mg</td>
</tr>
</tbody>
</table>

### EXAMPLE 10
Metered Dose Dry Powder Formulation

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>µg/cartridge or blister</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>72.5</td>
</tr>
<tr>
<td>(as hydroxynaphthoate)</td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>50.00</td>
</tr>
<tr>
<td>Lactose Ph. Eur.</td>
<td>to 12.5 mg or</td>
</tr>
<tr>
<td></td>
<td>to 25.0 mg</td>
</tr>
</tbody>
</table>

In Examples 6 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 packets (Rotadisks blister packs, Glaxo Group trade mark) to be administrated 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).  

#### 1 claim:
1. A pharmaceutical composition comprising effective amounts of salmeterol or a physiologically acceptable salt thereof and fluticasone propionate as a combined preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders.

#### 2. A composition as claimed in claim 1, wherein salmeterol is present as its 1-hydroxy-2-naphthalencarboxylate salt.

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

#### 4. A composition as claimed in claim 1 in dosage unit form containing 25–100 μg of salmeterol or a physiologically acceptable salt thereof and 25–500 μg of fluticasone propionate per dosage unit.

#### 5. A composition as claimed in claim 2 presented in the form of a metered dose inhaler or a metered dry powder composition.

#### 6. A composition as claimed in claim 2 in dosage unit form comprising 25–100 μg of the 1-hydroxy-2-naphthalencarboxylate salt of salmeterol and 25–500 μg of fluticasone propionate per dosage unit.

#### 7. A composition as claimed in claim 6 presented in the form of a metered dose inhaler or a metered dry powder composition.

#### [8. The use of salmeterol or a physiologically acceptable salt thereof and fluticasone propionate in the manufacture of pharmaceutical compositions as combined preparations for simultaneous, sequential or separate administration of salmeterol and fluticasone propionate by inhalation in the treatment of respiratory disorders.]

#### [9. A method of treating respiratory disorders which comprises the simultaneous, sequential or separate administration by inhalation of effective amounts of salmeterol or a physiologically acceptable salt thereof and fluticasone propionate.]

#### [10. A method as claimed in claim 9 wherein the salmeterol or a physiologically acceptable salt thereof and the fluticasone propionate are administered on a twice daily basis.]

#### [11. A method as claimed in claim 10 wherein the effective amount of salmeterol or a physiologically acceptable salt thereof 50–200 μg per day and the effective amount of fluticasone propionate is 50–1000 μg per day.]

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