

The combination of salmeterol (as the xinafoate salt) and fluticasone propionate is marketed in the EU by Allen & Hanburys as Seretide[®], using either the Evohaler[®] pressurised metered-dose inhaler (pMDI) or the Accuhaler[®] dry powder inhaler (DPI). The Accuhaler[®] uses blisters filled with a blend of the micronised active agents and lactose monohydrate. It is marketed in three dosage strengths, each providing 50 micrograms of salmeterol xinafoate and 100, 250 or 500 micrograms of fluticasone propionate. The delivered doses are lower. In the US, the product is called Advair[®] and the inhaler is called Diskus[®].

Seretide is indicated in the regular treatment of asthma where use of a combination product (long-acting β_2 -agonist and inhaled corticosteroid) is appropriate. This is where either: patients are not adequately controlled with inhaled corticosteroids and as needed inhaled short acting β_2 -agonist; or patients are already adequately controlled on both inhaled corticosteroid and long-acting β_2 -agonist.

Seretide is also indicated for the symptomatic treatment of patients with COPD, with a FEV₁ <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. FEV₁ is a measurement used in spirometry which means the forced expiratory volume in one second. This is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. The measurement of FEV₁ is used by healthcare professionals to determine lung function.

Combination products are well established in the art and are known to improve patient convenience and compliance. A drawback of combination products are that control over the dose of the individual active ingredients is reduced. For the inhaled corticosteroid, this is not a serious concern because the therapeutic window of inhaled corticosteroids is wide. That is, it is difficult for a patient to exceed the recommended daily intake of inhaled corticosteroid. However, the β_2 -agonist is more of a concern since the therapeutic window is narrower and β_2 -agonists are associated with serious adverse effects, including cardiac side-effects.

Thus, there is a requirement in the art for an improved fluticasone/salmeterol combination product which retains the therapeutic effect of both products, but which reduces the adverse effects associated with the salmeterol.

Summary

Accordingly, the present invention provides a dry powder inhaler comprising: a dry powder medicament comprising fluticasone propionate, salmeterol xinafoate and a lactose carrier; wherein, the delivered dose of salmeterol per actuation is less than 50 μ g; and wherein the

dose provides a baseline-adjusted FEV₁ in a patient of more than 150 mL within 30 minutes of receiving the dose.

The present invention also provides a use of a dry powder medicament in the manufacture of a medicament for treatment of asthma or allergic rhinitis or COPD comprising fluticasone propionate, salmeterol xinafoate and a lactose carrier; wherein, the medicament is to be delivered at a dose of salmeterol per actuation is less than 50 µg; and wherein the dose provides a baseline-adjusted FEV₁ in a patient of more than 150 mL within 30 minutes of receiving the dose. Also disclosed is method for the treatment of asthma, allergic rhinitis, or COPD comprising administering to a patient a dry powder medicament according to any embodiment described herein. In one embodiment, the dry powder medicament comprises fluticasone propionate, salmeterol xinafoate and a lactose carrier; wherein, the delivered dose of salmeterol per actuation is less than 50 µg; and wherein the dose provides a baseline-adjusted FEV₁ in a patient of more than 150 mL within 30 minutes of receiving the dose. The method of treatment may use any inhaler, including any inhaler as described herein. In one embodiment, the method of treatment provides a dose of salmeterol that is less than 25 µg. In other embodiments, the method of treatment provides doses of fluticasone/salmeterol in µg that are 500/12.5, 400/12.5, 250/12.5, 200/12.5, 100/12.5, 50/12.5 or 25/12.5 per actuation.

The present invention also provides a method of measuring a delivered dose of active agent by an inhaler comprising: inserting the inhaler into a mouthpiece adapter; actuating the inhaler to provide a delivered dose through the mouthpiece adapter and into a dosage unit sampling apparatus; rinsing the mouthpiece adapter with a solvent and into the dosage unit sampling apparatus; dissolving the delivered dose in the dosage unit sampling apparatus; filtering the dissolved delivered dose to provide a filtered solution; and analyzing the filtered solution to determine the amount of the active agent in the delivered dose. The method of measuring may be carried out at the beginning, the middle and the end of the life of the inhaler.

Several types of dry powder inhaler are known in the art. In a preferred embodiment of the present invention, the dry powder inhaler comprises the following features.

The preferred inhaler includes a delivery passageway for directing an inhalation-induced air flow through a mouthpiece, a channel extending from the delivery passageway to the medicament, and more preferably a mouthpiece for patient inhalation, a delivery passageway for directing an inhalation-induced air flow through the mouthpiece, a channel extending from the delivery passageway, and a reservoir for containing medicament, with the reservoir having a dispenser port connected to the channel. In a preferred form, the dose metering system includes a cup received in the channel, which is movable between the dispenser port and the delivery passageway, a cup spring biasing the cup towards one of the dispenser port and the passageway, and a yoke movable between at least two positions. The yoke includes a ratchet engaging the cup and preventing movement of the

Claims

1. A dry powder inhaler comprising:
a dry powder medicament comprising fluticasone propionate, salmeterol xinafoate and a lactose carrier;
- 5 wherein, the delivered dose of salmeterol per actuation is less than 50 µg; and
wherein the dose provides a baseline-adjusted Forced Expiratory Volume in the first second (FEV₁) in a patient of more than 150 mL within 30 minutes of receiving the dose.
2. The inhaler as claimed in claim 1, wherein the baseline-adjusted FEV₁ remains above 150 mL for at least 6 hours after receiving the dose.
- 10 3. The inhaler as claimed in claims 1 or 2, wherein the dose of salmeterol is less than 25 µg.
4. The inhaler as claimed in claim 3, wherein the doses of fluticasone/salmeterol in µg are 500/12.5, 400/12.5, 250/12.5, 200/12.5, 100/12.5, 50/12.5 or 25/12.5 per actuation.
5. The inhaler as claimed in any preceding claim, wherein the particle size of the
15 fluticasone propionate is d₁₀ = 0.4-1.1 µm, d₅₀ = 1.1-3.0 µm, d₉₀ = 2.6-7.5 µm and not less than (NLT)95% <10 µm, measured by laser diffraction as an aqueous dispersion.
6. The inhaler as claimed in any preceding claim, wherein the particle size of the salmeterol xinafoate is d₁₀ = 0.4-1.3 µm, d₅₀ = 1.4-3.0 µm, d₉₀ = 2.4-6.5 µm and NLT95% <10 µm, measured by laser diffraction as an aqueous dispersion.
- 20 7. The inhaler as claimed in any preceding claim, wherein the lactose carrier is composed of a coarse lactose and fine lactose, wherein the fine lactose is defined by a particle size of <10 µm, measured by laser diffraction as a dispersion in air.
8. The inhaler as claimed in claim 7, wherein the lactose contains 1-10 wt% of fine lactose.
- 25 9. The inhaler as claimed in any preceding claim, wherein the lactose particle size is d₁₀ = 15-50 µm, d₅₀ = 80-120 µm, d₉₀ = 120-200 µm.
10. The inhaler as claimed in any preceding claim, wherein the inhaler comprises a cyclone deagglomerator for breaking up agglomerates of the dry powder.
11. The inhaler as claimed in claim 10, wherein the deagglomerator comprises:
30 an inner wall defining a swirl chamber extending along an axis from a first end to a second end;
a dry powder supply port in the first end of the swirl chamber for providing fluid communication between a dry powder delivery passageway of the inhaler and the first end of the swirl chamber;

at least one inlet port in the inner wall of the swirl chamber adjacent to the first end of the swirl chamber providing fluid communication between a region exterior to the deagglomerator and the first end of the swirl chamber;

an outlet port providing fluid communication between the second end of the swirl chamber and a region exterior to the deagglomerator; and

5 vanes at the first end of the swirl chamber extending at least in part radially outwardly from the axis of the chamber, each of the vanes having an oblique surface facing at least in part in a direction transverse to the axis; whereby a breath induced low pressure at the outlet port causes air flows into the swirl chamber through the dry powder supply port and the
10 inlet port.

12. The inhaler as claimed in any preceding claim, wherein the inhaler comprises a reservoir for containing the medicament and an arrangement for delivering a metered dose of the medicament from the reservoir.

13. The inhaler as claimed in any preceding claim, wherein the inhaler comprises a
15 delivery passageway for directing an inhalation-induced air flow through a mouthpiece, a channel extending from the delivery passageway to the medicament.

14. The inhaler as claimed in any of the preceding claims, comprising:
a sealed reservoir including a dispensing port;
a channel communicating with the dispensing port and including a pressure relief port;
20 a conduit providing fluid communication between an interior of the sealed reservoir and the pressure relief port of the channel; and
a cup assembly movably received in the channel and including, a recess adapted to receive medicament when aligned with the dispensing port, a first sealing surface adapted to seal the dispensing port when the recess is unaligned with the dispensing port, and a
25 second sealing surface adapted to sealing the pressure relief port when the recess is aligned with the dispensing port and unseal the pressure relief port when the recess is unaligned with the dispensing port.

15. The inhaler as claimed in any preceding claim for use the treatment of asthma or COPD.

30 16. Use of a dry powder medicament in the manufacture of a medicament for treatment of asthma or allergic rhinitis or COPD comprising fluticasone propionate, salmeterol xinafoate and a lactose carrier; wherein, the medicament is to be delivered at a dose of salmeterol per actuation is less than 50 μg ; and wherein the dose provides a baseline-adjusted FEV_1 in a patient of more than 150 mL within 30 minutes of receiving the dose.

35 17. The use as claimed in claim 16, wherein the dose of salmeterol is less than 25 μg .

18. The use as claimed in claim 16, wherein the dose of fluticasone/salmeterol in μg is 500/12.5, 400/12.5, 250/12.5, 200/12.5, 100/12.5, 50/12.5 or 25/12.5 per actuation.

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Seretide is also indicated for the symptomatic treatment of patients with COPD, with a FEV₁ <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. FEV₁ is a measurement used in spirometry which means the forced expiratory volume in one second. This is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. The measurement of FEV₁ is used by healthcare professionals to determine lung function.

Combination products are well established in the art and are known to improve patient convenience and compliance. A drawback of combination products are that control over the dose of the individual active ingredients is reduced. For the inhaled corticosteroid, this is not a serious concern because the therapeutic window of inhaled corticosteroids is wide. That is, it is difficult for a patient to exceed the recommended daily intake of inhaled corticosteroid. However, the β_2 -agonist is more of a concern since the therapeutic window is narrower and β_2 -agonists are associated with serious adverse effects, including cardiac side-effects.

Thus, there is a requirement in the art for an improved fluticasone/salmeterol combination product which retains the therapeutic effect of both products, but which reduces the adverse effects associated with the salmeterol.

Summary

Accordingly, the present invention provides a dry powder inhaler comprising: a dry powder medicament comprising fluticasone propionate, salmeterol xinafoate and a lactose carrier; wherein the particle size of the salmeterol xinafoate is d₁₀ = 0.4-1.3 μ m, d₅₀ = 1.4-3.0 μ m, d₉₀ = 2.4-6.5 μ m and NLT95% <10 μ m, measured by laser diffraction as an aqueous dispersion and wherein, the delivered dose of salmeterol per actuation is less than 50 μ g; and wherein the

dose provides a baseline-adjusted Forced Expiratory Volume in the first second (FEV₁) in a patient of more than 150 mL within 30 minutes of receiving the dose; and wherein the inhaler comprises a cyclone deagglomerator for breaking up agglomerates of the dry powder.

The present invention also provides a use of a dry powder medicament in the manufacture of a

5 medicament for treatment of asthma or allergic rhinitis or COPD comprising fluticasone propionate, salmeterol xinafoate and a lactose carrier; wherein, the medicament is to be delivered at a dose of salmeterol per actuation is less than 50 µg; and wherein the dose provides a baseline-adjusted FEV₁ in a patient of more than 150 mL within 30 minutes of receiving the dose. Also disclosed is method for the treatment of asthma, allergic rhinitis, or
10 COPD comprising administering to a patient a dry powder medicament according to any embodiment described herein. In one embodiment, the dry powder medicament comprises fluticasone propionate, salmeterol xinafoate and a lactose carrier; wherein, the delivered dose of salmeterol per actuation is less than 50 µg; and wherein the dose provides a baseline-adjusted FEV₁ in a patient of more than 150 mL within 30 minutes of receiving the dose. The
15 method of treatment may use any inhaler, including any inhaler as described herein. In one embodiment, the method of treatment provides a dose of salmeterol that is less than 25 µg. In other embodiments, the method of treatment provides doses of fluticasone/salmeterol in µg that are 500/12.5, 400/12.5, 250/12.5, 200/12.5, 100/12.5, 50/12.5 or 25/12.5 per actuation.

The present invention also provides a method of measuring a delivered dose of active agent by
20 an inhaler comprising: inserting the inhaler into a mouthpiece adapter; actuating the inhaler to provide a delivered dose through the mouthpiece adapter and into a dosage unit sampling apparatus; rinsing the mouthpiece adapter with a solvent and into the dosage unit sampling apparatus; dissolving the delivered dose in the dosage unit sampling apparatus; filtering the dissolved delivered dose to provide a filtered solution; and analyzing the filtered solution to
25 determine the amount of the active agent in the delivered dose. The method of measuring may be carried out at the beginning, the middle and the end of the life of the inhaler.

Several types of dry powder inhaler are known in the art. In a preferred embodiment of the present invention, the dry powder inhaler comprises the following features.

The preferred inhaler includes a delivery passageway for directing an inhalation-induced air flow
30 through a mouthpiece, a channel extending from the delivery passageway to the medicament, and more preferably a mouthpiece for patient inhalation, a delivery passageway for directing an inhalation-induced air flow through the mouthpiece, a channel extending from the delivery passageway, and a reservoir for containing medicament, with the reservoir having a dispenser port connected to the channel. In a preferred form, the dose metering system includes a cup received in
35 the channel, which is movable between the dispenser port and the delivery passageway, a cup spring biasing the cup towards one of the dispenser port and the passageway, and a yoke movable between at least two positions. The yoke includes a ratchet engaging the cup and preventing movement of the

Claims

1. A dry powder inhaler comprising:

a dry powder medicament comprising fluticasone propionate, salmeterol xinafoate and a lactose carrier;

5 wherein the particle size of the salmeterol xinafoate is $d_{10} = 0.4\text{-}1.3\text{ }\mu\text{m}$, $d_{50} = 1.4\text{-}3.0\text{ }\mu\text{m}$, $d_{90} = 2.4\text{-}6.5\text{ }\mu\text{m}$ and NLT95% $<10\text{ }\mu\text{m}$, measured by laser diffraction as an aqueous dispersion and the delivered dose of salmeterol per actuation is less than $50\text{ }\mu\text{g}$; and wherein the dose provides a baseline-adjusted Forced Expiratory Volume in the first second (FEV₁) in a patient of more than 150 mL within 30 minutes of receiving the dose; and wherein the inhaler comprises a cyclone deagglomerator for breaking up agglomerates of the dry powder.

2. The inhaler as claimed in claim 1, wherein the baseline-adjusted FEV₁ remains above 150 mL for at least 6 hours after receiving the dose.

3. The inhaler as claimed in claims 1 or 2, wherein the dose of salmeterol is less than 15 $25\text{ }\mu\text{g}$.

4. The inhaler as claimed in claim 3, wherein the doses of fluticasone/salmeterol in μg are 500/12.5, 400/12.5, 250/12.5, 200/12.5, 100/12.5, 50/12.5 or 25/12.5 per actuation.

5. The inhaler as claimed in any preceding claim, wherein the particle size of the fluticasone propionate is $d_{10} = 0.4\text{-}1.1\text{ }\mu\text{m}$, $d_{50} = 1.1\text{-}3.0\text{ }\mu\text{m}$, $d_{90} = 2.6\text{-}7.5\text{ }\mu\text{m}$ and not less than (NLT)95% $<10\text{ }\mu\text{m}$, measured by laser diffraction as an aqueous dispersion.

6. The inhaler as claimed in any preceding claim, wherein the lactose carrier is composed of a coarse lactose and fine lactose, wherein the fine lactose is defined by a particle size of $<10\text{ }\mu\text{m}$, measured by laser diffraction as a dispersion in air.

7. The inhaler as claimed in claim 6, wherein the lactose contains 1-10 wt% of fine lactose.

8. The inhaler as claimed in any preceding claim, wherein the lactose particle size is $d_{10} = 15\text{-}50\text{ }\mu\text{m}$, $d_{50} = 80\text{-}120\text{ }\mu\text{m}$, $d_{90} = 120\text{-}200\text{ }\mu\text{m}$.

9. The inhaler as claimed in claim 8, wherein the deagglomerator comprises:

an inner wall defining a swirl chamber extending along an axis from a first end to a second end;

a dry powder supply port in the first end of the swirl chamber for providing fluid communication between a dry powder delivery passageway of the inhaler and the first end of the swirl chamber;

at least one inlet port in the inner wall of the swirl chamber adjacent to the first end of the swirl chamber providing fluid communication between a region exterior to the deagglomerator and the first end of the swirl chamber;

an outlet port providing fluid communication between the second end of the swirl chamber and a region exterior to the deagglomerator; and

vanes at the first end of the swirl chamber extending at least in part radially outwardly from the axis of the chamber, each of the vanes having an oblique surface facing at least in part in a direction transverse to the axis; whereby a breath induced low pressure at the outlet port causes air flows into the swirl chamber through the dry powder supply port and the inlet port.

10. The inhaler as claimed in any preceding claim, wherein the inhaler comprises a reservoir for containing the medicament and an arrangement for delivering a metered dose of the medicament from the reservoir.

11. The inhaler as claimed in any preceding claim, wherein the inhaler comprises a delivery passageway for directing an inhalation-induced air flow through a mouthpiece, a channel extending from the delivery passageway to the medicament.

12. The inhaler as claimed in any of the preceding claims, comprising:

a sealed reservoir including a dispensing port;

a channel communicating with the dispensing port and including a pressure relief port;

a conduit providing fluid communication between an interior of the sealed reservoir and the pressure relief port of the channel; and

a cup assembly movably received in the channel and including, a recess adapted to receive medicament when aligned with the dispensing port, a first sealing surface adapted to seal the dispensing port when the recess is unaligned with the dispensing port, and a second sealing surface adapted to sealing the pressure relief port when the recess is aligned with the dispensing port and unseal the pressure relief port when the recess is unaligned with the dispensing port.

13. The inhaler as claimed in any preceding claim for use in the treatment of asthma or COPD.

14. Use of a dry powder medicament in the manufacture of a medicament for treatment of asthma or allergic rhinitis or COPD comprising fluticasone propionate, salmeterol xinafoate and a lactose carrier; wherein the particle size of the salmeterol xinafoate is $d_{10} = 0.4-1.3 \mu\text{m}$, $d_{50} = 1.4-3.0 \mu\text{m}$, $d_{90} = 2.4-6.5 \mu\text{m}$ and $\text{NLT}_{95\%} < 10 \mu\text{m}$, measured by laser diffraction as an aqueous dispersion and the medicament is to be delivered at a dose

of salmeterol per actuation is less than 50 µg; and wherein the dose provides a baseline-adjusted FEV₁ in a patient of more than 150 mL within 30 minutes of receiving the dose.

15. The use as claimed in claim 14, wherein the dose of salmeterol is less than 25 µg.

16. The use as claimed in claim 14, wherein the dose of fluticasone/salmeterol in µg is
5 500/12.5, 400/12.5, 250/12.5, 200/12.5, 100/12.5, 50/12.5 or 25/12.5 per actuation.