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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING SALMETEROL AND BUDESONIDE FOR THE TREATMENT OF RESPIRATORY DISORDERS

(57) Abstract: Pharmaceutical composition for inhalation, containing as active ingredient effective amounts of salmeterol or a physiologically salt of salmeterol or a solvate thereof, and budesonide or a therapeutically salt of budesonide or a solvate thereof, wherein the molecular ratio of salmeterol component to budesonide component is in the range 1:2 to 1:50, together with a pharmaceutically acceptable carrier.

PHARMACEUTICAL COMPOSITION COMPRISING SALMETEROL AND BUDESONIDE FOR THE TREATMENT OF RESPIRATORY DISORDERS

FIELD OF THE INVENTION

The present invention relates to improvements in the treatment of asthma and other respiratory disorders. More particularly, it relates to the use of a composition comprising an effective dose of the long acting bronchodilator drug, salmeterol or a physiologically acceptable salt of salmeterol, and an effective dose of the steroidal anti-inflammatory drug budesonide or a physiologically acceptable salt of budesonide, for the treatment of respiratory disorders such as asthma and to pharmaceutical compositions containing the two active ingredients.

BACKGROUND OF THE INVENTION

Asthma is characterized by airway inflammation that is manifested by airway hyperresponsiveness to a variety of stimuli and by airway obstruction that is reversible spontaneously or in response to treatment; reversibility may be incomplete in some patients.

Asthma is the third leading cause of preventable hospitalization in United States. There are about 470,000 hospitalizations and more than 5,000 deaths a year from Asthma.

Asthma causes recurring episodes of coughing, wheezing, chest tightness, and difficult breathing. Asthma attacks can be life threatening. They can be prevented.

Asthma is a chronic inflammatory disorder of the airways. Chronically inflamed airways are hyperresponsive; they become obstructed and airflow is limited (by bronchoconstriction, mucus plugs, and increased inflammation) when airways are exposed to various stimuli, or triggers.

Common asthma triggers (that is factors that make asthma worse) include viral infections; allergens such as house dust mites (in bedding, carpets, and fabric-upholstered furnishings), animals with fur, cockroaches, pollens, and molds; tobacco smoke; air pollution, exercise; strong emotional expressions; chemical irritants, and drugs (such as aspirin and beta blockers).

Asthma attacks (or exacerbations) are episodic, but airway inflammation is chronically present. Asthma is a chronic disorder requiring long-term management. For many patients, this means taking preventive medication every day.

Asthma can change over time. Asthma can be mild, moderate or severe; asthma attacks can be life-threatening. The severity of asthma varies among individuals, and it can change in one individual over time. Treatment decisions are made based on the severity of asthma.

Asthma can be treated and controlled so that almost all patients can:

- prevent troublesome symptoms night and day
- prevent serious attacks
- require little or no quick-relief medication
- have productive, physically active lives
- have (near) normal lung function

Asthma may be preventable. For infants with a family history of asthma or atopy, it is highly likely that avoiding exposure to passive smoking and to house dust mites, cat and cockroach allergens will help prevent the initial development of asthma. For adults, avoiding exposure to chemical sensitizers in the workplace is helpful.

Salmeterol (F) is a selective β2 adrenoreceptor agonist which produces effective dose-proportional bronchodilation, which persists for up to 12 hours, in patients with reversible obstructive respiratory disease. Bronchodilation is significant within minutes of inhalation, maximal within 2 hours, and at therapeutic doses is equivalent to that produced by standard doses of traditional β2-agonists (salbutamol or albuterol, fenotenol, terbutaline).

Because of its long duration of action, salmeterol offers significant therapeutic advantages over shorter-acting β2-agonists in the treatment of nocturnal and exercise- induced asthma.

It has been demonstrated that inhaled salmeterol administered after or before inhaled corticosteroids was well tolerated.

Budesonide (FP) is a synthetic corticosteroid. Inhaled Budesonide at doses < or = 800 µg/day provided effective corticosteroid maintenance treatment in patients with mild to moderate asthma, in randomised, controlled clinical studies of 4 to 24 weeks in duration. Dosages of 100 to 400 µg twice daily have produced consistent improvement in spirometric measures of lung function, have reduced the frequency of as-needed β2-agonist bronchodilator use, asthma symptom scores and night-time awakenings, and have prevented asthma exacerbations compared with placebo.

Pharmaceutical compositions containing a combination of long-acting β2-agonists and corticosteroid agents are described in three patent applications. EP 416950 describes a composition containing salmeterol and beclomethasone. EP 416951 discloses a composition containing salmeterol and fluticasone. US 5,674,860 (corresponding to WO93/11773) describes a composition containing formoterol and budesonide. Not disclosed is a pharmaceutical composition comprising both salmeterol and budesonide (or salt) in a single composition and inhalable in one puff.

Several others have demonstrated that corticosteroids and long-acting β_2 mimetics, given in combination, may improve the symptoms related to asthma and/or allow to decrease the dose of corticosteroids needed (Mancini and al, Ferres and al, Nielsen and al). But all those studies were performed by combining two separate treatments, for instance, budesonide with one inhaler device and salmeterol with another inhaler device.

Consequently, some pharmaceutical companies have patented compositions comprising a corticosteroid and a β_2 mimetic in the same device or formulation, so allowing to take both products in one inhalation. This kind of combination clearly improves patient's comfort and compliance. For instance, a composition containing

budesonide and formoterol (US 5,674,860) or a composition containing fluticasone and salmeterol (EP416950) have been described.

Never described was a composition allowing to administrate to the patient an effective dose of budesonide and an effective dose of salmeterol in one single inhalation. In the present invention, both molecules are indeed preferably comprised in the same galenical formulations, whereby ensuring the administration by inhalation of budesonide and salmeterol in the right ratio. When budesonide and salmeterol are present in each microparticles to be inhaled, a correct molecular ratio of salmeterol active in the lung/budesonide active in the lung can be ensured. Another advantage of such a composition containing inhaled budesonide and salmeterol in the same formulation is economical. Indeed, the present invention only requires one device while the separate administration of budesonide and salmeterol requires two separate devices, so increasing the cost of the therapy.

BRIEF DESCRIPTION OF THE INVENTION

The invention relates to a pharmaceutical composition for inhalation, comprising as active ingredient an effective amount of salmeterol or a physiologically or therapeutically acceptable salt of salmeterol or a solvate thereof, an effective amount of budesonide or a physiologically or therapeutically acceptable salt of budesonide or a solvate thereof, and advantageously at least one pharmaceutically acceptable carrier which can be solid, partly solid, or liquid.

The composition is adapted for the substantially simultaneous, preferably simultaneous inhalation of the active ingredients with a molecular ratio salmeterol component/budesonide component in the range of 1:2 to 1:50.

The composition is advantageously in the form of a dose of active ingredient to be administered by inhalation to a patient in need, whereby the amount of salmeterol or salt or solvate (expressed in salmeterol base) is less than about 50 μg in said dose, advantageously less than 40μg, preferably less than 35 μg and most preferably less than 30μg. The dose can be contained in a container, such as a capsule containing a monodose. The dose can also be prepared by a device adapted

for taking a determined volume of composition from a multidose container, said predetermined volume corresponding to a dose or a portion of a maximum dose. The composition of the invention is advantageously adapted for ensuring a substantially simultaneous initial action of the salmeterol and of the budesonide.

The invention relates also to a method of treatment of asthma and other inflammatory respiratory disorders which comprises administering by inhalation to humans in need of such treatment effective amounts of salmeterol or a physiologically salt of salmeterol or a solvate thereof, and budesonide or a therapeutically salt of budesonide or a solvate thereof, wherein said effective amounts are administered substantially simultaneously, preferably simultaneously, to the human in need with a molecular ratio of the salmeterol component to the budesonide component is in the range 1:2 to 1:50, together with a pharmaceutically acceptable carrier. In the method of the invention, a composition of the invention is advantageously used.

The invention further relates to a process for the preparation of a composition for treating by inhalation a patient suffering asthma or other inflammatory respiratory disorders, in which effective amounts of salmeterol or a physiologically salt of salmeterol or a solvate thereof, and budesonide or a therapeutically salt of budesonide or a solvate thereof are mixed together with a pharmaceutically acceptable carrier and are processed in a form for substantially simultaneous administration to the human in need with a molecular ratio of the salmeterol component to the budesonide component is in the range 1:2 to 1:50.

DESCRIPTION OF THE INVENTION

The combination of a first generation β2-agonist agent (like salbutamol, fenoterol, ...) together with a corticosteroid agent, although potentially beneficial, was not possible in the past, since the duration of action of the two classes of drugs were

different, respectively 4 to 6 hours for the β2-agonist and approximately 12 hours for the corticosteroid.

With the apparition of long-acting β2-agonist bronchodilators, which are active for approximately twelve hours, the combination of such agents with corticosteroids became possible, using a twice daily administration of the drug combination.

The present invention is based on the concept of a novel combination therapy whereby salmeterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide (and/or a physiologically salt and/or solvent thereof) are administered at least substantially simultaneously, preferably simultaneously, by inhalation. The invention particularly relates to a pharmaceutical composition for inhalation containing therapeutically active amounts of salmeterol (or salt) and budesonide (or salt). The composition comprises advantageously at least one carrier. The inhaled pharmaceutical composition may be a Dry Powder Inhaler (DPI), a Metered Dose Inhaler (MDI) or a powder/solution for nebulization.

The new combination has not only a greater efficacy and duration of bronchodilator action but the combination has also a rapid onset of action.

Another significant advantage is the higher compliance of the patient since two drugs are inhaled at one time, thereby avoiding the necessity of using two different inhalers. This simplifies life considerably and makes life more comfortable and secure.

The rapid onset of action of salmeterol as a bronchodilator gives the patient immediate confirmation that he has taken an adequate dose and thereby avoiding overdosing of the β2-agonist agent and the corticosteroid.

The combination according to the present invention permits a twice daily regimen as a basic treatment of asthma and particularly allows for coverage of nocturnal asthma.

The present invention provides a medicine or drug containing a combination of a therapeutically active amount of (i) salmeterol (and/or a physiologically acceptable salt and/or solvate thereof) and (ii) budesonide (and/or a physiologically acceptable salt and/or solvate thereof).

The invention also provides a pharmaceutical composition for administration by inhalation in the treatment of respiratory disorders which comprises salmeterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide (and/or a physiologically acceptable salt and/or solvate thereof).

The invention also relates to the manufacture of salmeterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide (and/or a physiologically acceptable salt and/or solvate thereof) in the manufacture of a medicine for combination therapy in the treatment of respiratory disorders.

The molecular ratio of salmeterol or salmeterol containing component to budesonide or budesonide containing component is preferably within the range 1:2 to 1:50.

The intended dose regimen is a twice daily administration, where the suitable daily dose of salmeterol (expressed as salmeterol base) is in the range 10 to 100 μg with a preferred dose of 20 to 40 μg and the suitable daily dose for budesonide is 50 to 2000 μg with a preferred dose of 100 to 800 μg.

The dose actually used will strongly depend on the patient and the severity of the disease.

The combination may be suitably inhaled from a nebulizer, from a pressurized Metered Dose Inhaler or from a Dry Powder Inhaler.

The dry powder inhaler may be either a multidose system (reservoir system) or a monodose system in which the powder is pre-packaged in either capsules (hard gelatin, HPMC or other pharmaceutically acceptable capsules) or in blisters.

When used as dry formulation, the composition of the invention is advantageously in the form of a powder with a mean particle size lower than 50μm, advantageously lower than 25μm, preferably lower than 10μm, especially lower than 5μm, such as about 3 or 4μm. For example, at least 90% by weight of the particles have a size lower than 10μm, while less than 5% by weight of the particles have a size lower than 0.1μm.

Such a dry formulation may consist of a simple mixing of particles containing one distinct active agent, such as a mix of budesonide containing particles and salmeterol containing particles. However, in specific embodiments, each active particles contain budesonide and salmeterol, preferably in the appropriate range of 1:2 to 1:50 (ratio salmeterol/budesonide).

According to a specific embodiment, the active microgranules containing both budesonide (as such, or as a salt or solvate) and salmeterol (as such, or as salt or solvate) have an average molecular ratio of salmeterol component to budesonide component. In said embodiment, at least 50% by weight, advantageously at least 70% by weight, preferably at least 90% by weight of the active microgranules have a molecular ratio of salmeterol component to budesonide component comprised between 0.5 and 1.5 times the average molecular ratio, advantageously between 0.7 and 1.3 times the average molecular ratio, preferably between 0.85 and 1.15 times the average molecular ratio.

When using dry microparticles, the amount of carrier is advantageously such that the weight ratio carrier/active ingredients is comprised between 1 and 500, advantageously between 5 and 100, preferably between 10 and 50.

The particles containing salmeterol, budesonide or the both can also be be prepared by using the process disclosed in US 6,221,398, the content of which is incorporated by reference.

The present invention is further illustrated by means of some examples.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1 shows the influence of the inhalation airflow on the in vitro lung deposition (FPD) of a composition combining budesonide 200 µg and salmeterol xinafoate 76.2 µg (= 50 µg of salmeterol base) inhaled with a Miat Monodose Inhaler (n=3, 4 liters of air).

DESCRIPTION OF EXAMPLES

In the examples, salmeterol xinafoate is used. The amount of salmeterol xinafoate used in the various formulation is expressed as salmeterol base. Formulation 1 contains thus 0.05 mg salmetrol base, formulation 2 : 0.025 mg salmeterol base, etc.

Example 1

Formulation 1

Active ingredients	mg/capsule	mg/capsule	mg/capsule
Salmeterol (as xinafoate)	0.050	0.050	0.050
Budesonide	0.400	0.200	0.100
Inactive ingredients			
anhydrous lactose	17.32	17.50	17.50
lactose monohydrate	7.42	7.50	7.50

The mix of active ingredients with lactose is filled into nr.3 hypromellose capsules. As said capsules correspond to a monodose, the patient in need knows that after inhalation, he received simultaneously salmeterol and budesonide.

Example 2

Formulation 2

Active ingredients	mg/dose	mg/dose
Salmeterol (as xinafoate)	0.025	0.025
Budesonide	0.200	0.400
Inactive ingredients		
anhydrous lactose	25.000	25.000

The mix of active ingredients with lactose is filled in nr. 3 hard gelatine capsules. In said composition, the lactose inactive ingredient forms a mixture of particles with a size comprised between 50 and 200µm, such as between 100 and 160µm. As said capsules correspond to a monodose, the patient in need knows that after inhalation, he received simultaneously salmeterol and budesonide.

Example 3

Metered Dose Inhaler

Active ingredients	mg/dose
Salmeterol (as xinafoate)	0.050
Budesonide	0.200
Inactive ingredients	
Propellant	50 µl
Stabilizer	0.200

Example 4

Active ingredients	mg/capsule
Salmeterol (as xinafoate)	0.025
Budesonide	0.400
Inactive ingredients	
anhydrous lactose	17.32
lactose monohydrate	7.42

Example 5 : combined particles containing salmeterol and budesonide

Combined particles of budesonide and salmeterol xinafoate have been prepared from a solution containing budesonide and salmeterol in soluble form (for example an ethanol or a chloroform solution) or from a solution in which salmeterol is soluble, but the budesonide particles are insoluble.

When using a solution containing both active ingredients in soluble form, it is often advantageous to use a mixture of solvents selected from the group comprising methanol, ethanol, water, chloroform, acetone, isopropanol, chloroform, etc.

When using a solution in which salmeterol is soluble but in which budesonide is insoluble, the salmeterol solution can be used for coating the particles of budesonide. For example an aqueous solution of salmeterol xinafoate is spray dried on budesonide particles.

The following table gives the content of various compositions comprising active particles containing salmeterol and budesonide with a mean particle size of 3 – 4 μm, and inactive particles of anhydrous lactose with a particle size of 100-160μm.

composition	8	9	10
Budesonide/salmeterol xinafoate weight ratio for the active particles	8	4	2
Weight ratio Inactive particles/active particles	50	100	180

These compositions can be placed in capsules (hard gelatin, hypromellose capsule) for the preparation of mono dose, each capsule containing an amount of salmeterol xinafoate corresponding to a dose of 25µg of salmeterol base.

Example 6 : in vitro deposition tests

In vitro deposition tests (assessment of Fine Particle Dose) have been performed on the formulation given in example 1 (budesonide 200 µg + salmeterol 50 µg) called F1 hereinbelow. This formulation has been tested using the Miat Monodose Inhaler.

The recommendations of the European Pharmacopoeia (4th Ed., 2002, 2.9.18.) concerning the way to perform the in-vitro testing for DPIs are now well established.

The in vitro deposition results performed on the Multistage Liquid Impinger (MLI) (E.P. 4th Ed., 2002, 2.9.18 Apparatus C).

The results of Fine particle dose (FPD) is the dose in µg of particles having a diameter inferior to 5 µm, Mass Median aerodynamic diameter (MMAD) and Geometric standard deviation (GSD) obtained are given in the table herebelow. The values of FPD is considered to be directly proportional to the amount of drugs able to reach the pulmonary tract in vivo. Consequently the lower the values of FPD the lower,, the estimated lung deposition.

In order to make a comparative assessment of the composition making the object of the present invention, the in vitro deposition test has also been performed on a marketed form of budesonide (Pulmicort® Turbuhaler® 200 µg, Astra Zeneca) and a marketed form of salmeterol xinafoate (Serevent® Diskus® 50 µg, Glaxo Smithkline). Each device has been tested at the airflow defined by the European

Pharmacopoeial test i.e. 60 Liters / minute for the Pulmicort® Turbuhaler® , 70 liters / minute for the Serevent® Diskus® and 100 L/ minute for the monodose Miat inhaler used for administering the present invention. The volume of air inhaled through the apparatus was 4 liters for each device.

Table 1 : Assessment of Fine Particle Dose (n=3)

Parameter	F1 (budesonide 200 µg + salmeterol 50 µg) Miat Monodose Inhaler		Pulmicort® Turbuhaler® 200 µg	Serevent® Diskus® 50 µg
	salmeterol	budesonide	budesonide	salmeterol
FPD (ug / dose)	18.1 ± 0.87	47.6 ± 4.2	45.2 ± 3.5	7.89 ± 0.53
MMAD	3.23 ± 0.06	3.76 ± 0.12	3.85 ± 0.09	4.02 ± 0.09
GSD	1.72 ± 0.1	1.74 ± 0.08	1.62 ± 0.11	1.48 ± 0.08

As it can be observed, the DPI composition containing a combination of budesonide 200 µg and salmeterol 50 µg, presents a similar FPD for budesonide than the reference (Pulmicort® Turbuhaler® 200 µg, Astra Zeneca) and a more than twice as high value of FPD for salmeterol than the reference (Serevent® Diskus® 50 µg, Glaxo Smithkline).

Example 7 : In vitro deposition in function of the airflow

As the present invention is primarily destinated to patients with asthma and / or bronchopneumopathy chronic obstructive (BPCO) i.e. patients with relatively weak lung functions, it was of interest to assess the dependence of the FPD to the airflow. Indeed, moderate or severely ill patients, children and elderly people present lower lung functions and are therefore unable to inhale at the airflow recommended by the European Pharmacopoeia. The lung deposition of the present

invention has therefore been assessed at different airflow i.e. 40, 60, 80 and 100 L / minute). The results obtained are given in the figure 1 attached to the present specification, said figure showing the influence of the inhalation airflow on the in vitro lung deposition (FPD) of a composition combining budesonide 200 µg and salmeterol 50 µg inhaled with a Miat Monodose Inhaler (n=3, 4 liters of air).

This figure shows that, the ratio inhalable budesonide (FDP budesonide in µg) / inhalable salmeterol (FDP salmeterol in µg) is substantially independent from the air flow, said ratio being about 2.3 – 2.4.

As shown in figure 1, the FPD of budesonide and salmeterol is very lowly influenced by the value of the airflow so insuring that even patients with low lung functions will be able to inhale the drugs properly and hence to obtain a therapeutical dose in the lungs.

CLAIMS

1. A pharmaceutical composition for inhalation, comprising as active ingredient effective amounts of salmeterol or a physiologically salt of salmeterol or a solvate thereof, and budesonide or a therapeutically salt of budesonide or a solvate thereof, together with a pharmaceutically acceptable carrier, wherein the composition is adapted for the substantially simultaneous inhalation of active ingredient with a molecular ratio of salmeterol component to budesonide component in the range 1:2 to 1:50.
2. The pharmaceutical composition according to claim 1, in the form of a dose of active ingredient to be administered by inhalation to a patient in need, whereby the amount of salmeterol or physiologically salt of salmeterol or a solvate thereof, expressed in salmeterol base, is less than about 50 μg in said dose, advantageously less than 40 μg preferably less than 35 μg and most preferably less than 30 μg.
3. The pharmaceutical composition according to claim 1, wherein said pharmaceutical composition is in a form for administration using a dry powder inhaler.
4. The pharmaceutical composition according to claim 1, wherein said pharmaceutical composition is in a liquid or a powder form for administration by nebulization.
5. The pharmaceutical composition according to claim 1, wherein said pharmaceutical composition is in a form for administration as a metered dose inhaler formulation.
6. The pharmaceutical composition according to claim 1, wherein said composition comprises active microgranules comprising salmeterol or a physiologically salt of salmeterol or a solvate thereof, budesonide or a therapeutically salt of budesonide or a solvate thereof, and advantageously at least one carrier, said active microgranules having a size of less than 10μm, preferably less than 5 μm.

7. The pharmaceutical composition according to claim 6, wherein the molecular ratio of salmeterol component to budesonide component of the active microgranules is in the range 1:2 to 1:50.
8. The pharmaceutical composition according to claim 7, wherein microgranules containing the active ingredients have an average molecular ratio of salmeterol component to budesonide component and wherein at least 50% by weight, advantageously at least 70% by weight, preferably at least 90% by weight of the active microgranules have a molecular ratio of salmeterol component to budesonide component comprised between 0.5 and 1.5 times the average molecular ratio, advantageously between 0.7 and 1.3 times the average molecular ratio, preferably between 0.85 and 1.15 times the average molecular ratio.
9. The pharmaceutical composition according to claim 6, wherein the microgranules containing the active ingredients comprises only one carrier selected from the group consisting of anhydrous lactose, lactose monohydrate and their mixtures.
10. The pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable carrier is lactose or another pharmaceutical acceptable sugar or a mix of them
11. The pharmaceutical composition according to claim 1, in the form of a dry powder formulation, whereby a monodose of the dry powder formulation is filled into a pharmaceutically acceptable capsule, advantageously a hard gelatin capsule or a hypromellose capsule, for administration with a monodose dry powder inhaler device.
12. The pharmaceutical composition of claim 1, wherein the composition is in a dry form for administration using a multi-dose inhalation device.
13. The pharmaceutical composition according to claim 1, wherein the salmeterol component is in the form of xinafoate.
14. The pharmaceutical composition of claim 1 wherein the salmeterol component and the budesonide component are in a form adapted for simultaneous administration, advantageously for simultaneous initial action after administration.

15. A method for the treatment of asthma and other inflammatory respiratory disorders which comprises administering by inhalation to humans in need of such treatment effective amounts of salmeterol or a physiologically salt of salmeterol or a solvate thereof, and budesonide or a therapeutically salt of budesonide or a solvate thereof, wherein said effective amounts are administered substantially simultaneously to the human in need with a molecular ratio of the salmeterol component to the budesonide component is in the range 1:2 to 1:50, together with a pharmaceutically acceptable carrier.

16. The method according to claim 15, wherein said effective amounts are administered in the form of active microgranules comprising salmeterol or a physiologically salt of salmeterol or a solvate thereof, budesonide or a therapeutically salt of budesonide or a solvate thereof, and advantageously at least one carrier, said active microgranules having a size of less than 10μm, preferably less than 5 μm.

17. The method according to claim 16, wherein the molecular ratio of salmeterol component to budesonide component of the active microgranules is in the range 1:2 to 1:50.

18. The method according to claim 17, wherein the active microgranules have an average molecular ratio of salmeterol component to budesonide component and wherein at least 50% by weight, advantageously at least 70% by weight, preferably at least 90% by weight of the active microgranules have a molecular ratio of salmeterol component to budesonide component comprised between 0.5 and 1.5 times the average molecular ratio, advantageously between 0.7 and 1.3 times the average molecular ratio, preferably between 0.85 and 1.15 times the average molecular ratio.

19. A process for the preparation of a composition for treating by inhalation a patient suffering asthma or other inflammatory respiratory disorders, in which effective amounts of salmeterol or a physiologically salt of salmeterol or a solvate thereof, and budesonide or a therapeutically salt of budesonide or a solvate thereof are mixed together with a pharmaceutically

acceptable carrier and are processed in a form for substantially simultaneous administration to the human in need with a molecular ratio of the salmeterol component to the budesonide component is in the range 1:2 to 1:50

5

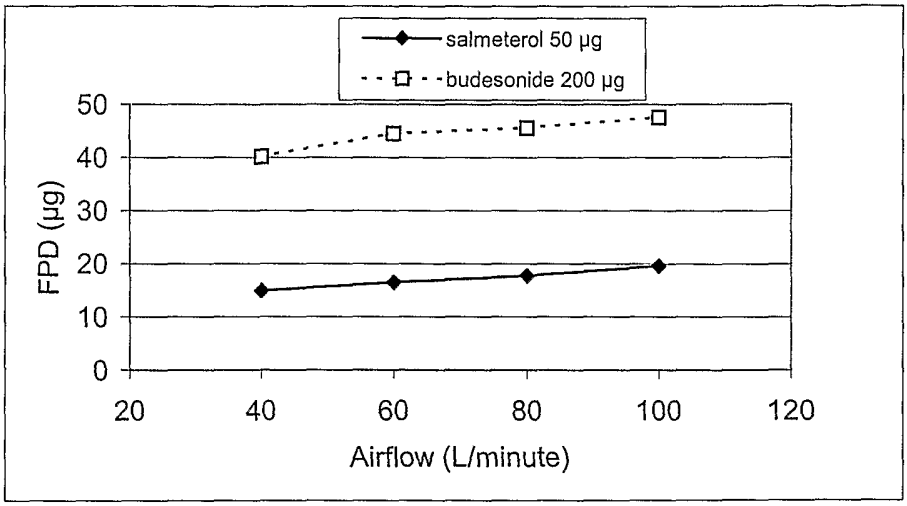
salmeterol 50 µg
budesonide 200 µg
FPD (µg)
50
40
30
20
10
0
20
40
60
80
100
120
Airflow (L/minute)

Fig. 1

INTERNATIONAL SEARCH REPORT

In al Application No
PCT/BE 02/00132

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/58 A61P11/06 //(A61K31/58,31:135)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	V.MANCINI, L.PINTO: "Fluticasone propionate or budesonide with salmeterol in bronchial severe asthma in pediatric age" ALLERGY, vol. 53, no. suppl.43, 1998, page 185 XP001013216 page 185 ---	1,4,14, 15,19
X	N.VAITKIENE E.A.: "Optimal inhaled steroids dose determination for asthma patients using monotherapy or combining it with salmeterol" EUROPEAN RESPIRATORY JOURNAL SUPPLEMENT, vol. 10, no. 25, 1997, page 105S XP001013222 page 105S ---	1,4,14, 15,19

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[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2002	26/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Peeters, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	J.FERRES E.A.: "Budesonide combined with salmeterolin the treatment of asthma in children" EUROPEAN RESPIRATORY JOURNAL, vol. 12, no. suppl.29, 1998, page 69s XP001013401 page 69S	1,4,14, 15,19
X	P.ODEBACK: "Is the addition of salmeterol more effective than doubling the dose of budesonide in mild asthma?" EUROPEAN RESPIRATORY JOURNAL, vol. 12, no. suppl.28, 1998, page 38s XP001008684 page 38S	1,4, 13-15,19
X	G.FUGLSANG E.A.: "Effect of salmeterol treatment on nitric oxide level in exhaled air and dose-response to terbutaline in children with mild asthma" PEDIATRIC PULMONOLOGY, vol. 25, no. 5, 1998, pages 314-321, XP001073773 page 314 page 315, column 2 page 319	1,3-5, 14,15,19
X	D.H.YATES E.A.: "An inhaled glucocorticoid does not prevent tolerance to the bronchoprotective effect of a long-acting inhaled beta2-agonist" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, vol. 154, no. 6 part 1, 1996, pages 1603-1607, XP001073766 page 1603 page 1604, column 1 page 1605, column 1	1,3,4, 12,14, 15,19
X	D.H.YATES: "Effect of short- and long-acting inhaled beta2-agonists on exhaled nitric oxide in asthmatic patients" EUROPEAN RESPIRATORY JOURNAL, vol. 10, no. 7, 1997, pages 1483-1488, XP001073772 page 1483 page 1485, column 1	1,3,4, 14,15,19

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	L.P.NIELSEN E.A.: "Salmeterol reduces the need for inhaled corticosteroid in steroid-dependent asthmatics" RESPIRATORY MEDICINE, vol. 93, no. 12, 1999, pages 863-868, XP001073799 page 863 page 864, column 1 -----	1,4,5, 13-15,19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BE 02/00132

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 15-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy