

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

(19) World Intellectual Property
Organization
International Bureau



WIPO | PCT



(10) International Publication Number
WO 2013/178742 A1

(43) International Publication Date
5 December 2013 (05.12.2013)

(51) International Patent Classification:

A61K 9/14 (2006.01) A61P 11/08 (2006.01)
A61K 31/4706 (2006.01) A61P 11/06 (2006.01)
A61K 9/00 (2006.01)

(21) International Application Number:

PCT/EP2013/061181

(22) International Filing Date:

30 May 2013 (30.05.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

12382221.5 31 May 2012 (31.05.2012) EP
61/660,003 15 June 2012 (15.06.2012) US

(71) Applicant: **ALMIRALL, S.A.** [ES/ES]; Ronda del General Mitre 151, E-08022 Barcelona (ES).

(72) Inventors: **ALLAIN RUIZ, Sandrine**; C/O Laureà Miró 408-410, Sant Feliu de Llobregat, E-08980 Barcelona (ES). **SEOANE NUNEZ, Beatriz**; C/O Laureà Miró 408-410, Sant Feliu de Llobregat, E-08980 Barcelona (ES). **DE MIQUEL SERRA, Gonzalo**; C/O Laureà Miró 408-410, Sant Feliu de Llobregat, E-08980 Barcelona (ES).

(74) Agent: **SRINIVASAN, Ravi Chandran**; 14 South Square, Gray's Inn, London Greater London WC1R 5JJ (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: NOVEL DOSAGE FORM AND FORMULATION OF ABEDITEROL

(57) Abstract: The present invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 1.25 or about 2.5 micrograms of free base abediterol administered with the Gen-uair® inhaler. The present invention also provides said pharmaceutical composition for use in the treatment of respiratory disease such as asthma and chronic obstructive pulmonary disease COPD.



WO 2013/178742 A1

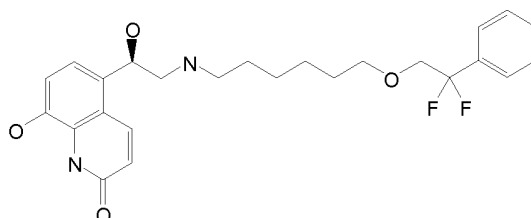
NOVEL DOSAGE FORM AND FORMULATION OF ABEDITEROL

Field of the Invention

- 5 The present invention relates to a novel dosage for abediterol and to novel methods and formulations for the treatment of respiratory disease in a mammal, especially asthma and chronic obstructive pulmonary disease (COPD), using abediterol.

Background of the Invention

- 10 Abediterol [5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1(R)-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one] is described in WO 2006/122788, WO 2008 /095720 and WO 2010/072354 . It has the structure shown below.



(I)

- 15 Abediterol is a potent, long acting and selective β_2 adrenergic receptor agonist intended for administration by inhalation for treatment of respiratory diseases, especially asthma and COPD, currently in clinical trials.
- 20 Dry powder inhalers are well known devices for administering pharmaceutically active agents to the respiratory tract. They are particularly suitable for the administration of active agents in the treatment of respiratory diseases such as asthma, COPD, emphysema or the like.
- 25 The Genuair® inhaler is a novel, breath-actuated multidose, dry powder inhaler designed for the effective delivery of various types of inhaled drugs (Greguletz et al., Am. J. Respir. Crit. Care Med., 2009, 179,;A4578). This inhaler, which has been developed from the Novolizer® inhaler (WO 97/000703) incorporates a number of technological

advances including improved fluid and particle dynamics to ensure powder entrainment during inhalation and affective deagglomeration of the inhalation powder into a suitable aerosol even at low inhalation flow rate and volume (WO 03/000325 and WO2006/008027). In addition the Genuair® inhaler has been used in clinical trials to

5 reliably deliver various types of drugs as both monotherapy and combination therapy (H. Chrystyn et al., Int. J. Clinical Practice, 66, 3, 309-317, 2012, H. Magnussen et al. *Respiratory Medicine* (2009) 103, 1832-1837.).

Summary of the Invention

10 It has now been discovered that for the treatment of respiratory disorders in humans, particularly asthma and COPD, abediterol is most effective upon inhalation of a dosage equivalent to about 1.25 or to about 2.5 micrograms metered nominal dose of the free base administered with the Genuair® inhaler.

15 When administered with the Genuair® inhaler a metered nominal dose of about 1.25 micrograms of free base abediterol is equivalent to about 1.1 micrograms delivered dose and to about 0.45 micrograms fine particle dose.

In a similar way a metered nominal dose of about 2.5 micrograms of free base abediterol

20 administered with the Genuair® inhaler is equivalent to about 2.3 micrograms delivered dose and to about 1.0 micrograms fine particle dose.

The invention thus provides in a first embodiment a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically

25 acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 1.25 or about 2.5 micrograms of free base abediterol administered with the Genuair® inhaler.

In another embodiment, the invention also provides a pharmaceutical composition in the

30 form of a dry powder for inhalation comprising abediterol or a pharmaceutically

acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing a metered nominal dose of about 1.25 or about 2.5 micrograms of free base abediterol.

- 5 This pharmaceutical composition can be provided as a single dose formulation or as a multidose formulation. In both cases the inhaler devices are calibrated to provide a dose equivalent to a metered nominal dose of about 1.25 or about 2.5 micrograms of free base abediterol administered with the Genuair® inhaler. This composition can be administered one or more times per day, preferably once or twice a day, most preferably once a day.
- 10 The invention also provides a method of treating a respiratory condition, e.g., selected from asthma and chronic obstructive pulmonary disease, in a patient in need of such treatment, comprising administering a pharmaceutical composition, according to the previous paragraph and providing a dose of abediterol equivalent to a metered nominal dose of about 1.25 or about 2.5 micrograms of free base abediterol administered with the
- 15 Genuair® inhaler. The invention further provides the use of abediterol in the manufacture of a pharmaceutical composition as described in the preceding paragraph, for use in such a method.

- Abediterol may be administered as monotherapy, or in combination with one or more
- 20 additional anti-inflammatory and/or bronchodilating agents, e.g., corticosteroids, such as budesonide, mometasone or fluticasone, PDE IV inhibitors, such as roflumilast or cilomilast and M3 antimuscarinic agents, such as, glycopyrronium, tiotropium or aclidinium. The invention thus also provides pharmaceutical compositions as described above further comprising such an additional agent, as well as methods of treating
- 25 respiratory disorders comprising administering these compositions.

Detailed description of the invention

- Typically, the present invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt
- 30 thereof in admixture with a pharmaceutically acceptable carrier, providing upon

inhalation a dose equivalent to a metered nominal dose of about 1.25 micrograms of free base abediterol administered with the Genuair® inhaler.

Typically, the present invention also provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 2.5 micrograms of free base abediterol administered with the Genuair® inhaler.

The term "therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

The term "metered nominal dose" refers to the quantity of drug substance contained in the metering chamber of the delivery device and is normally expressed as quantity per inhalation.

Upon actuation, the drug substance leaves the device and becomes available to the patient as a so-called "delivered dose" (also known as "emitted dose"), which is normally smaller than the metered nominal dose, due to the mechanics of the device. Thus, the delivered dose is the amount of the drug which is available at the mouth for inhalation. The delivered dose can be measured using standard techniques known to those skilled in the art.

The term "fine particle dose" refers to the quantity of drug substance in the delivered dose below a cut off aerodynamic threshold of 5 micrometer, i.e. the delivered dose with an aerodynamic particle diameter less than 5 micrograms that is available for deposition in the lungs. The fine particle dose can be measured using standard techniques known to those skilled in the art.

In the context of dosage of an active agent, “about” as used herein means within the normal limits of acceptable variations as defined by the European and US Pharmacopeia of plus/minus 35% or preferably acceptable variations as defined by the current most stringent requirement, the US FDA draft guidance for inhaler of plus/minus 25% or the
5 acceptable variations defined by the CHMP Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products of plus/minus 15%.

Thus the delivered dose of “about 1.1 micrograms” is meant a target delivered dose ranging from 0.71 to 1.49 micrograms, preferably from 0.82 to 1.38 micrograms, more
10 preferably from 0.93 to 1.27 micrograms. Similarly the delivered dose of “about 2.3 micrograms” is meant a target delivered dose ranging from 1.49 to 3.11 micrograms, preferably from 1.72 to 2.88, more preferably from 1.95 to 2.65.

Similarly, the fine particle dose is also subjected to the same variation and proportional to
15 the delivered dose. Thus a delivered dose of “about 1.1 micrograms” corresponds to a fine particle dose of “about 0.45 micrograms” i.e. ranging from 0.29 to 0.61 micrograms, preferably from 0.33 to 0.57 micrograms, more preferably from 0.38 to 0.52 micrograms. The delivered dose of “about 2.3 micrograms” corresponds to a fine particle dose of about 1.0 micrograms, i.e. ranging from 0.65 to 1.35 micrograms, preferably from 0.75 to
20 1.25 micrograms, more preferably from 0.85 to 1.15 micrograms.

In the same way, a metered nominal dose of “about 2.5 micrograms” is meant a target nominal dose ranging from 1.62 to 3.38 micrograms, preferably from 1.87 to 3.13 micrograms, more preferably from 2.12 to 2.88 micrograms. Similarly the metered
25 nominal dose of “about 1.25 micrograms” meant a target nominal dose ranging from 0.81 to 1.69 micrograms, preferably from 0.93 to 1.57 micrograms, more preferably from 1.06-1.44 micrograms.

The invention thus provides in a further embodiment a pharmaceutical composition in the
30 form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing

upon inhalation a delivered dose ranging from 0.71 to 1.49 micrograms, preferably from 0.82 to 1.38 micrograms, more preferably from 0.93 to 1.27 micrograms of free base abediterol.

5 In another embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 1.49 to 3.11 micrograms, preferably from 1.72 to 2.88, more preferably from 1.95 to 2.65 of free base abediterol.

10

In a still another embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.29 to 0.61 micrograms, preferably,
15 from 0.33 to 0.57 micrograms being most preferably from 0.38 to 0.52 micrograms of free base abediterol.

The invention also provides in a further embodiment a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing
20 upon inhalation a fine particle dose ranging from 0.65 to 1.35 micrograms, preferably, from 0.75 to 1.25 micrograms being most preferably from 0.85 to 1.15 micrograms of free base abediterol.

25 In another embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 0.81 to 1.69 micrograms, preferably from 0.93 to 1.57 micrograms, more preferably from 1.06 to 1.44 micrograms of free
30 base abediterol.

The invention also provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 1.62 to 3.38 micrograms, preferably from 1.87 to 3.13 micrograms, more preferably from 2.12 to 2.88 micrograms of free base abediterol.

In a further embodiment, the present invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 0.625 micrograms of free base abediterol administered with the Genuair® inhaler. A dose of 0.625g abediterol has surprisingly been found to be the minimum dose having similar therapeutic effect to other β_2 adrenergic receptor agonist compounds, such as salbutamol and indacaterol.

In a still further embodiment, the present invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing a metered nominal dose of about 0.625 micrograms of free base abediterol.

When administered with the Genuair® inhaler a metered nominal dose of about 0.625 micrograms of free base abediterol is equivalent to about 0.562 micrograms delivered dose and to about 0.22 micrograms fine particle dose.

As mentioned before, the delivered dose is subjected within the normal limits of acceptable variations as defined above. Thus the delivered dose of “about 0.562 micrograms” is meant a target delivered dose ranging from 0.365 to 0.759 micrograms, preferably from 0.421 to 0.703 micrograms, more preferably from 0.477 to 0.647 micrograms.

Similarly, the fine particle dose of “about 0.22 micrograms” is meant a target dose ranging from 0.14 to 0.30 micrograms, preferably from 0.16 to 0.28 micrograms, more preferably from 0.18 to 0.26 micrograms.

- 5 Similarly a metered nominal dose of “about 0.625 micrograms” is also subjected to the same variation limits as defined above and thus the metered nominal dose of “about 0.625 micrograms” is meant a target nominal dose ranging from 0.406 to 0.844 micrograms, preferably from 0.468 to 0.782 micrograms, more preferably from 0.531 to 0.719 micrograms.

10

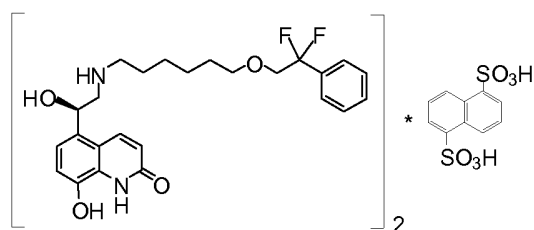
- The invention thus provides in a further embodiment a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 0.365 to 0.759 micrograms, preferably
15 from 0.421 to 0.703 micrograms, more preferably from 0.477 to 0.647 micrograms of free base abediterol.

- In another embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable
20 salt thereof in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.14 to 0.30 micrograms, preferably from 0.16 to 0.28 micrograms, more preferably from 0.18 to 0.26 micrograms of free base abediterol.

- 25 In a still another embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a nominal dose ranging from 0.406 to 0.844 micrograms, preferably from 0.468 to 0.782 micrograms, more preferably from 0.531 to 0.719 micrograms of free base
30 abediterol.

These pharmaceutical compositions can be provided as a single dose formulation or as a multidose formulation. In both cases the inhaler devices are calibrated to provide a dose of free base abediterol as defined above administered with the Genuair® inhaler.

- 5 The term "treatment" as used herein refers to the treatment of a disease or medical condition in a patient which includes:
- (a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient;
 - (b) ameliorating the disease or medical condition, i.e., causing regression of the disease
 - 10 or medical condition in a patient;
 - (c) suppressing the disease or medical condition, i.e., slowing the development of the disease or medical condition in a patient; or
 - (d) alleviating the symptoms of the disease or medical condition in a patient.
- 15 Typically, abediterol is administered in the form a salt derived from pharmaceutically-acceptable acids include acetic, benzenesulphonic, benzoic, camphosulphonic, citric, ethanesulphonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, lactic, maleic, malic, mandelic, methanesulphonic, mucic, naphthalene-1,5-disulphonic acid (napadisylate), nitric, pantothenic, phosphoric, succinic, sulphuric, tartaric, p-
- 20 toluenesulphonic, xinafoic (1-hydroxy-2-naphthoic acid). Particularly preferred are salts derived from fumaric, hydrobromic, hydrochloric, acetic, sulphuric, methanesulphonic, naphthalene-1,5-disulphonic, xinafoic, and tartaric acids. Most preferred are salts derived from methanesulphonic and naphthalene-1,5-disulphonic acids.
- 25 Salts derived from naphthalene-1,5-disulphonic acid are typically mononapadisylate or heminaadisylate salts and pharmaceutically acceptable solvates thereof. Abediterol is preferably administered in the form of heminaadisylate salt having the following chemical structure:



It is to be understood that all dose values of abediterol described in the present invention are related to the dose of abediterol as free base and thus the amount of the corresponding salt should be taken into account. Therefore, in the case that the salt used is the heminapadisylate, the metered nominal dose of 1.25 micrograms of abediterol free base as defined herein above will correspond to a metered nominal dose of about 1.64 micrograms of abediterol heminapadisylate. In the same way, the metered nominal dose of 2.5 micrograms as defined herein above will correspond to a metered nominal dose of about 3.28 micrograms of abediterol heminapadisylate and the metered nominal dose of 0.625 micrograms as defined herein above will correspond to a metered nominal dose of about 0.82 micrograms of abediterol heminapadisylate.

In case that the salt used is the mesylate, the metered nominal dose of 1.25 micrograms as defined herein above will correspond to a metered nominal dose of about 1.51 micrograms of abediterol mesylate. In the same way, the metered nominal dose of 2.5 micrograms as defined herein above will correspond to a metered nominal dose of about 3.02 micrograms of abediterol mesylate and the metered nominal dose of 0.625 micrograms as defined herein above will correspond to a metered nominal dose of about 0.755 micrograms of abediterol mesylate.

Abediterol is preferably administered in the form of a dry powder of a pharmaceutically acceptable salt, in admixture with a carrier, such as lactose powder, suitable for inhalation. For example, the abediterol is abediterol heminapadisylate in admixture with lactose powder.

The respiratory disease or condition to be treated with the formulations and methods of the present invention is typically asthma, acute or chronic bronchitis, emphysema,

chronic obstructive pulmonary disease (COPD), bronchial hyperreactivity or rhinitis, in particular asthma or chronic obstructive pulmonary disease (COPD).

Typically, the pharmaceutical compositions of the present invention is suitable for
5 administration by inhalation and may further comprise a therapeutically effective amount of one or more other therapeutic agents, as defined herein. However, any other form of topical, parenteral or oral application is possible. The application of inhaled dosage forms embodies the preferred application form, especially in the therapy of diseases or disorders of the lung.

10

The pharmaceutical composition of the present invention may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient(s) into association with the carrier. In general the pharmaceutical compositions are prepared by uniformly and intimately bringing into association the
15 active ingredient(s) with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired form.

20

The carrier for a pharmaceutical composition in the form of a dry powder is typically chosen from starch or a pharmaceutically acceptable sugar, such as lactose or glucose. Lactose is preferred.

Additional suitable carriers can be found in Remington: The Science and Practice of Pharmacy, 20th Edition, Lippincott Williams & Wilkins, Philadelphia, Pa., 2000.

25

The pharmaceutical compositions for inhalation are delivered with the help of inhalers, such as dry powder inhalers, aerosols or nebulisers. The inhaler is typically configured to deliver, upon actuation, a therapeutically effective amount of one or more other therapeutic agents, as defined herein.

30

Packaging of the compound of the invention in the inhaler may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the compound of the invention

can be pre-metered or metered in use. Dry powder inhalers are classified into three groups: (a) single dose, (b) multiple unit dose and (c) multi dose devices.

For inhalers of the first type (a), single doses have been weighed by the manufacturer into
5 small containers, which are mostly hard gelatine capsules. A capsule has to be taken from a separate box or container and inserted into a receptacle area of the inhaler. Next, the capsule has to be opened or perforated with pins or cutting blades in order to allow part of the inspiratory air stream to pass through the capsule for powder entrainment or to discharge the powder from the capsule through these perforations by means of centrifugal
10 force during inhalation. After inhalation, the emptied capsule has to be removed from the inhaler again. Mostly, disassembling of the inhaler is necessary for inserting and removing the capsule, which is an operation that can be difficult and burdensome for some patients. Other drawbacks related to the use of hard gelatine capsules for inhalation powders are (a) poor protection against moisture uptake from the ambient air, (b)
15 problems with opening or perforation after the capsules have been exposed previously to extreme relative humidity, which causes fragmentation or indenture, and (c) possible inhalation of capsule fragments. Moreover, for a number of capsule inhalers, incomplete expulsion has been reported.

20 Some capsule inhalers have a magazine from which individual capsules can be transferred to a receiving chamber, in which perforation and emptying takes place, as described in WO 92/03175. Other capsule inhalers have revolving magazines with capsule chambers that can be brought in line with the air conduit for dose discharge (e. g. WO 91/02558 and GB 2242134). They comprise the type of multiple unit dose inhalers
25 (b) together with blister inhalers, which have a limited number of unit doses in supply on a disk or on a strip.

Blister inhalers provide better moisture protection of the medicament than capsule inhalers. Access to the powder is obtained by perforating the cover as well as the blister
30 foil, or by peeling off the cover foil. When a blister strip is used instead of a disk, the number of doses can be increased, but it is inconvenient for the patient to replace an

empty strip. Therefore, such devices are often disposable with the incorporated dose system, including the technique used to transport the strip and open the blister pockets.

Multi-dose devices (c) do not contain pre-measured quantities of the medicament containing powder. They consist of a relatively large container and a dose measuring principle that has to be operated by the patient. The container bears multiple doses that are isolated individually from the bulk of powder by volumetric displacement. Various dose measuring principles exist, including rotatable membranes (e.g. EP0069715) or disks (e.g. GB 2041763; EP 0424790; DE 4239402 and EP 0674533), rotatable cylinders (e.g. EP 0166294; GB 2165159 and WO 92/09322) and rotatable frustums (e.g. WO 92/00771), all having cavities which have to be filled with powder from the container. Other multi dose devices have measuring plungers with a local or circumferential recess to displace a certain volume of powder from the container to a delivery chamber or an air conduit (e.g. EP 0505321, WO 92/04068 and WO 92/04928), or measuring slides such as the Novolizer SD2FL (ex. Sofotec), also known as Genuair®, are described above.

Reproducible dose measuring is one of the major concerns for multi dose devices. The powder formulation has to exhibit good and stable flow properties, because filling of the dose measuring cups or cavities is mostly under the influence of the force of gravity. For reloaded single dose and multiple unit dose inhalers, the dose measuring accuracy and reproducibility can be guaranteed by the manufacturer. Multi dose inhalers on the other hand, can contain a much higher number of doses, whereas the number of handlings to prime a dose is generally lower.

Because the inspiratory air stream in multi-dose devices is often straight across the dose measuring cavity, and because the massive and rigid dose measuring systems of multi dose inhalers can not be agitated by this inspiratory air stream, the powder mass is simply entrained from the cavity and little de-agglomeration is obtained during discharge.

Consequently, separate disintegration means are necessary. However in practice, they are not always part of the inhaler design. Because of the high number of doses in multi-dose

devices, powder adhesion onto the inner walls of the air conduits and the de-agglomeration means must be minimized and/or regular cleaning of these parts must be possible, without affecting the residual doses in the device. Some multi dose inhalers have disposable drug containers that can be replaced after the prescribed number of doses
5 has been taken (e.g. WO 97/000703). For such semi-permanent multi dose inhalers with disposable drug containers, the requirements to prevent drug accumulation are even stricter.

In another embodiment, abediterol can also be administered via single dose dry powder
10 inhalers such as the devices described in WO 2005/113042 or in EP1270034. These devices are low resistance unit dosage form inhalers. The unit dosage form of the dry powder formulation are capsules typically made of gelatin or a synthetic polymer, preferably hydroxypropyl methyl cellulose (HPMC) , also known as hypromellose. The hypromellose capsules are preferably packaged in a blister. The blister is preferably a
15 peel foil blister that allows patients to remove capsules stored therein without damaging them and optimizes product stability.

Apart from applications through dry powder inhalers the compositions of the invention can be administered in aerosols which operate via propellant gases or by means of so-called atomisers or nebulizers, via which solutions or suspensions of pharmacologically-
20 active substances can be sprayed under high pressure so that a mist of inhalable particles results.

Medicaments for administration by inhalation desirably have a controlled particle size.
25 The optimum particle size for inhalation into the bronchial system is usually 1-10 μ m, preferably 2-5 μ m. Particles having a size above 20 μ m are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means, for example, by micronisation or supercritical fluid techniques. The desired fraction may be separated
30 out by air classification or sieving. Preferably, the particles will be crystalline.

Achieving a high dose reproducibility with micronised powders is difficult because of their poor flowability and extreme agglomeration tendency. To improve the efficiency of dry powder compositions, the particles should be large while in the inhaler, but small when discharged into the respiratory tract. Thus, an excipient, for example a mono-, di-
5 or polysaccharide or sugar alcohol, such as lactose, mannitol or glucose is generally employed. The particle size of the excipient will usually be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as lactose particles, preferably crystalline alpha lactose monohydrate, e.g., having an average particle size range of 20-1000 μm , preferably in the range of 90-150
10 μm . The average particle size can be measured using standard techniques known to those skilled in the art.

The median particle size approximately corresponds to the average and is the diameter where 50 mass-% of the particles have a larger equivalent diameter, and the other 50
15 mass-% have a smaller equivalent diameter. Hence the average particle size is generally referred to in the art as equivalent d50. The distribution of particle size around may affect flow properties, bulk density, etc. Hence to characterize a particle size diameter, other equivalent diameters can be used in addition to d50, such as d10 and d90. d10 is the equivalent diameter where 10 mass-% of the particles have a smaller diameter (and hence
20 the remaining 90% is coarser). d90 is the equivalent diameter where 90 mass-% of the particles have a smaller diameter. In one embodiment, the lactose particles for use in formulations of the invention have a d10 of 90 - 160 μm , a d50 of 170 – 270 μm , and d90 of 290 – 400 μm . The d10, d50 and d90 values can be measured using standard
techniques known to those skilled in the art.

25 Suitable lactose materials for use in the present invention are commercially available, e.g., from DMV International (Respitose GR-001, Respitose SV-001, Respitose SV-003 or a mixture thereof), Meggle (Capsulac 60, Inhalac 70, Inhalac 120, Inhalac 230, Capsulac 60 INH, Sorbolac 400, or a mixture thereof), and Borculo Domo (Lactohale
30 100-200, Lactohale 200-300 and Lactohale 100-300, or a mixture thereof).

In another embodiment, the carrier used may be in the form of a mixture of different types of carrier having different particles sizes. For example, a mixture of a fine carrier and a coarse carrier may be present in the formulation, wherein the average particle size of the fine carrier is lower than the average particle size of the coarse carrier. Preferably the fine carrier may have an average particle size range of 1 - 50 μm , preferably 2 - 20 μm , more preferably, 5 - 15 μm . The coarse carrier may have an average particle size range of 20 - 1000 μm , preferably 50-500 μm , more preferably 90-400 μm , being most preferably, 150-300 μm . The content of the fine carrier with respect to the coarse carrier may vary from 1% to 10%, preferably, from 3% to 6%, e.g., 5%, by weight of the total coarse carrier.

In one embodiment lactose particles for use in formulations of the invention is a mixture of a coarse lactose having a d10 of 90 - 160 μm , a d50 of 170 - 270 μm , and d90 of 290 - 400 μm and a fine lactose having a d10 of 2 - 4 μm , a d50 of 7 - 10 μm , and d90 of 15 - 24 μm .

The ratio by weight between the lactose particles and the abediterol, will depend on the inhaler device used, but is typically, e.g., 1000:1 to 40000:1, for example 2000:1 to 20000:1, e.g., 4000-10000:1.

In a preferred embodiment, the abediterol is administered in the form of a dry powder of a pharmaceutically acceptable salt in admixture with lactose, in a ratio by weight of the active ingredient to lactose of 1:20000 to 1:2000, suitable for administration via a dry powder inhaler, wherein the active ingredient particles have an average particle size of from 1.5 to 5 μm in diameter, e.g., less than 3 μm in diameter, and the lactose particles have a d10 of 90 - 160 μm , a d50 of 170 - 270 μm , and d90 of 290 - 400 μm . Said lactose particles are optionally mixed with a fine lactose having a particle size d10 of 2 - 4 μm , a d50 of 7 - 10 μm , and d90 of 15 - 24 μm .

Additional active agents such as M3 antagonists (anticholinergics), PDE IV inhibitors, corticosteroids, leukotriene D4 antagonists, inhibitors of egfr-kinase, p38 kinase inhibitors or NK1 receptor agonists may be utilized in the methods and formulations of the inventions. For example, the invention provides abediterol formulations as described
 5 herein further comprising an effective amount of such additional active agents, e.g. further comprising an effective amount of a M3 antagonist, a PDE IV inhibitor, or a corticosteroid. The invention also provides methods for treating respiratory conditions as herein before described, e.g., asthma or COPD, comprising administering an abediterol formulation as described herein and further comprising administering simultaneously
 10 effective amount of such additional active agents, e.g. further comprising an effective amount of a M3 antagonist, a PDE IV inhibitor, or a corticosteroid.

Examples of suitable M3 antagonists (anticholinergics) that can be combined with abediterol are tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts,
 15 glycopyrronium salts, trospium salts, zamifenacin, revatropate, espatropate, darotropium bromide, CI-923, NPC-14695, BEA-2108, 3-[2-Hydroxy-2,2-bis(2-thienyl)acetoxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane salts (in particular acridinium salts, more preferably acridinium bromide), 1-(2-Phenylethyl)-3-(9H-xanthen-9-ylcarbonyloxy)-1-azoniabicyclo[2.2.2]octane salts, 2-oxo-1,2,3,4-tetrahydroquinazoline-3-carboxylic acid
 20 endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester salts (DAU-5884), 3-(4-Benzylpiperazin-1-yl)-1-cyclobutyl-1-hydroxy-1-phenylpropan-2-one (NPC-14695), N-[1-(6-Aminopyridin-2-ylmethyl)piperidin-4-yl]-2(R)-[3,3-difluoro-1(R)-cyclopentyl]-2-hydroxy-2-phenylacetamide (J-104135), 2(R)-Cyclopentyl-2-hydroxy-N-[1-[4(S)-methylhexyl]piperidin-4-yl]-2-phenylacetamide (J-106366), 2(R)-Cyclopentyl-2-
 25 hydroxy-N-[1-(4-methyl-3-pentenyl)-4-piperidinyl]-2-phenylacetamide (J-104129), 1-[4-(2-Aminoethyl)piperidin-1-yl]-2(R)-[3,3-difluorocyclopent-1(R)-yl]-2-hydroxy-2-phenylethan-1-one (Banyu-280634), N-[N-[2-[N-[1-(Cyclohexylmethyl)piperidin-3(R)-ylmethyl]carbamoyl]ethyl]carbamoylmethyl]-3,3,3-triphenylpropionamide (Banyu CPTP), 2(R)-Cyclopentyl-2-hydroxy-2-phenylacetic acid 4-(3-azabicyclo[3.1.0]hex-3-
 30 yl)-2-butynyl ester (Ranbaxy 364057), 3(R)-[4,4-Bis(4-fluorophenyl)-2-oxoimidazolidin-1-yl]-1-methyl-1-[2-oxo-2-(3-thienyl)ethyl]pyrrolidinium iodide, N-[1-(3-

- Hydroxybenzyl)-1-methylpiperidinium-3(S)-yl]-N-[N-[4-(isopropoxycarbonyl)phenyl]carbamoyl]-L-tyrosinamide trifluoroacetate, UCB-101333, Merck's OrM3, 7-endo-(2-hydroxy-2,2-diphenylacetoxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0(2,4)]nonane salts, 3(R)-[4,4-Bis(4-fluorophenyl)-2-oxoimidazolidin-1-yl]-1-methyl-1-(2-phenylethyl)pyrrolidinium iodide, trans-4-[2-[Hydroxy-2,2-(dithien-2-yl)acetoxy]-1-methyl-1-(2-phenoxyethyl)piperidinium bromide from Novartis (412682), 7-(2,2-diphenylpropionyloxy)-7,9,9-trimethyl-3-oxa-9-azoniatricyclo[3.3.1.0*2,4*]nonane salts, 7-hydroxy-7,9,9-trimethyl-3-oxa-9-azoniatricyclo[3.3.1.0*2,4*]nonane 9-methyl-9H-fluorene-9-carboxylic acid ester salts, all of them optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally in the form of their pharmacologically-compatible acid addition salts. Among the salts chlorides, bromides, iodides and methanesulphonates are preferred.
- Examples of suitable corticosteroids and glucocorticoids that can be combined with abediterol are prednisolone, methylprednisolone, dexamethasone, dexamethasone acetate, dexamethasone cipeclate, naflocort, deflazacort, halopredone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, fluocinolone acetonide, fluocinonide, clocortolone pivalate, methylprednisolone aceponate, dexamethasone palmitoate, tipredane, hydrocortisone aceponate, prednicarbate, alclometasone dipropionate, halometasone, methylprednisolone suleptanate, mometasone, mometasone furoate, rimexolone, prednisolone farnesylate, ciclesonide, butixocort propionate, RS-85095, CGP-13774, GW-250495, deltacortisone, NO-Prednisolone, NO-Budesonide, etiprednol dicloacetate, QAE-397, 7beta-OH-EPIA, RPR-106541, deprodone propionate, fluticasone, fluticasone propionate, fluticasone furoate, halobetasol propionate, loteprednol etabonate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate, triamcinolone, betamethasone 17-valerate, betamethasone, betamethasone dipropionate, 21-Chloro-11beta-hydroxy-17alpha-[2-(methylsulfonyl)acetoxy]-4-pregnene-3,20-dione, desisobutyrylciclesonide, hydrocortisone acetate, hydrocortisone sodium succinate, prednisolone sodium phosphate

and hydrocortisone probutate, prednisolone sodium metasulfobenzoate and clobetasol propionate.

Examples of suitable PDE4 inhibitors that can be combined with abediterol are

- 5 benafentrine dimaleate, etazolate, denbufylline, rolipram, cipamfylline, zardaverine, arofylline, filaminast, tielukast, tofomilast, piclamilast, tolafentrine, mesopram, drotaverine hydrochloride, lirimilast, roflumilast, cilomilast, oglemilast, apremilast, tetomilast, revamilast, ronomilast, (R)-(+)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine (CDP-840), N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-
- 10 hydroxy-1H-indol-3-yl]-2-oxoacetamide (GSK-842470), 9-(2-Fluorobenzyl)-N6-methyl-2-(trifluoromethyl)adenine (NCS-613), N-(3,5-Dichloro-4-pyridinyl)-8-methoxyquinoline-5-carboxamide (D-4418), 3-[3-(Cyclopentyloxy)-4-methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride (V-11294A), 6-[3-(N,N-Dimethylcarbamoyl)phenylsulfonyl]-4-(3-methoxyphenylamino)-8-methylquinoline-3-
- 15 carboxamide hydrochloride (GSK-256066), 4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)naphthalen-1-yl]-1-(2-methoxyethyl)pyridin-2(1H)-one (T-440), (-)-trans-2-[3'-[3-(N-Cyclopropylcarbamoyl)-4-oxo-1,4-dihydro-1,8-naphthyridin-1-yl]-3-fluorobiphenyl-4-yl]cyclopropanecarboxylic acid, MK-0873, CDC-801, GSK-356278, TA-7906, CP-80633, RPL-554, NIK-616, GPD-1116, D4396, UK-500001, BLX-914, 2-
- 20 carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, *cis* [4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol, 5(S)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(S)-(3-methylbenzyl)piperidin-2-one (IPL-455903), ONO-6126 (Eur Respir J 2003, 22(Suppl. 45): Abst 2557) and the compounds claimed in the PCT patent applications number WO 03/097613, WO
- 25 2004/058729, WO 2005/049581, WO 2005/123693, WO 2005/123692, and WO 2010/069504.

Particularly preferred additional therapeutic agents are selected from the group consisting of tiotropium, glycopyrronium, aclidinium, 1-(2-Phenylethyl)-3-(9H-xanthen-9-

- 30 ylcarbonyloxy)-1-azoniabicyclo[2.2.2]octane, mometasone, fluticasone, budesonide, rolipram, roflumilast and cilomilast, more preferably, tiotropium, aclidinium,

mometasone, fluticasone and roflumilast, in free or pharmaceutically acceptable salt form.

For example, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 1.25 or about 2.5 micrograms of free base abediterol together with a dose equivalent to a metered nominal dose of about 50-900 µg (e.g. 50, 70, 80, 85, 100, 110, 150, 170, 200, 220, 300, 330, 340, 350, 400, 440, 800, 880 or 900 µg) of mometasone in free or pharmaceutically acceptable salt form, administered with the Genuair® inhaler. Preferably the mometasone is mometasone furoate.

Thus in a preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 1.25 micrograms of free base abediterol together with a dose equivalent to a metered nominal dose of about 85 micrograms of mometasone furoate administered with the Genuair® inhaler.

The present invention also provides, in a preferred embodiment, a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 1.25 micrograms of free base abediterol together with a dose equivalent to a metered nominal dose of about 170 micrograms of mometasone furoate administered with the Genuair® inhaler.

In another preferred embodiment, the present invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a

pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 1.25 micrograms of free base abediterol together with a dose equivalent to a metered nominal dose of about 340 micrograms of mometasone furoate administered with the Genuair® inhaler.

Similarly, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 2.5 micrograms of free base abediterol together with a dose equivalent to a metered nominal dose of about 85 micrograms of mometasone furoate administered with the Genuair® inhaler.

The present invention also provides, in a preferred embodiment, a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 2.5 micrograms of free base abediterol together with a dose equivalent to a metered nominal dose of about 170 micrograms of mometasone furoate administered with the Genuair® inhaler.

In another preferred embodiment, the present invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 2.5 micrograms of free base abediterol together with a dose equivalent to a metered nominal dose of about 340 micrograms of mometasone furoate administered with the Genuair® inhaler.

When administered with the Genuair® inhaler a metered nominal dose of about 85 micrograms of mometasone furoate is equivalent to about 76 micrograms delivered dose and to about 30 micrograms fine particle dose. In a similar way a metered nominal dose of about 170 micrograms of mometasone furoate administered with the Genuair® inhaler is equivalent to about 150 micrograms delivered dose and to about 65 micrograms fine particle dose. Finally, a metered nominal dose of about 340 micrograms of mometasone furoate administered with the Genuair® inhaler is equivalent to about 300 micrograms delivered dose and to about 130 micrograms fine particle dose.

As mentioned before, the delivered dose of mometasone furoate is also subjected to the same acceptable variation limits as defined by the European and US pharmacopeia. Thus the delivered dose of “about 76 micrograms” is meant a target delivered dose ranging from 49.40 to 102.60 micrograms (plus/minus 35%), preferably from 57 to 95 micrograms (plus/minus 25%), more preferably from 64.6 to 87.4 micrograms (plus/minus 15%). In the same way, the delivered dose of “about 150 micrograms” is meant a target delivered dose ranging from 97.50 to 202.50 micrograms, preferably from 112.50 to 187.50 micrograms, more preferably from 127.50 to 172.50 micrograms. Similarly the delivered dose of “about 300 micrograms” is meant a target delivered dose ranging from 195 to 405 micrograms, preferably from 225 to 375 micrograms, more preferably from 255 to 345 micrograms.

As mentioned before the fine particle dose is the amount of drug substance in the delivered dose below a cut off aerodynamic threshold of 5 micrometer and thus is also subjected to the same acceptable variation limits and proportional to the delivered dose as defined by the European and US pharmacopeia.

Thus the fine particle dose of “30 micrograms” is meant a target fine particle dose ranging from 19.50 to 40.5 micrograms, preferably from 22.5 to 37.5 micrograms, more preferably from 25.5 to 34.5 micrograms. In the same way, the fine particle dose of “about 65 micrograms” is meant a target delivered dose ranging from 42.25 to 87.75 micrograms, preferably from 48.75 to 81.25 micrograms, more preferably from 55.25 to

74.75 micrograms. Similarly the fine particle dose of “about 130 micrograms” is meant a target delivered dose ranging from 84.5 to 175.5 micrograms, preferably from 97.5 to 162.5 micrograms, more preferably 110.5 to 149.50 micrograms.

- 5 In the same way, the metered nominal dose of “about 85 micrograms” is meant a target metered nominal dose ranging from 55.25 to 114.75 micrograms, preferably from 63.75 to 106.25 micrograms, more preferably from 72.25 to 97.75 micrograms. Similarly, the metered nominal dose of “about 170 micrograms” is meant a target metered nominal dose ranging from 110.50 to 229.50 micrograms, preferably from 127.50 to 212.50
- 10 micrograms, more preferably from 144.50 to 195.50 micrograms. Similarly the metered nominal dose of “about 340 micrograms” is meant a target metered nominal dose ranging from 221 to 459 micrograms, preferably from 255 to 425 micrograms, more preferably from 289 to 391 micrograms.
- 15 Thus in a preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 0.365 to 0.759 micrograms of free base abediterol together with a delivered dose ranging from
- 20 49.40 to 102.60 micrograms of mometasone furoate, preferably a delivered dose ranging from 0.421 to 0.703 micrograms of free base abediterol together with a delivered dose ranging from 57 to 95 micrograms of mometasone furoate, more preferably a delivered dose ranging from 0.477 to 0.647 micrograms of free base abediterol together with a delivered dose ranging from 64.6 to 87.4 micrograms of mometasone furoate.
- 25 Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 0.365 to 0.759 micrograms of
- 30 free base abediterol together with a delivered dose ranging from 97.50 to 202.50 micrograms of mometasone furoate, preferably a delivered dose ranging from 0.421 to

0.703 micrograms of free base abediterol together with a delivered dose ranging from 112.50 to 187.50 micrograms of mometasone furoate, more preferably a delivered dose ranging from 0.477 to 0.647 micrograms of free base abediterol together with a delivered dose ranging from 127.50 to 172.50 micrograms of mometasone furoate.

5

Typically, the invention also provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 0.365 to 0.759 micrograms of free base abediterol together with a delivered dose ranging from 195 to 405 micrograms of mometasone furoate, preferably a delivered dose ranging from 0.421 to 0.703 micrograms of free base abediterol together with a delivered dose ranging from 225 to 375 micrograms of mometasone furoate, more preferably a delivered dose ranging from 0.477 to 0.647 micrograms of free base abediterol together with a delivered dose ranging from 255 to 345 micrograms of mometasone furoate.

In a preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 0.71 to 1.49 micrograms of free base abediterol together with a delivered dose ranging from 49.40 to 102.60 micrograms of mometasone furoate, preferably a delivered dose ranging from 0.82 to 1.38 micrograms of free base abediterol together with a delivered dose ranging from 57 to 95 micrograms of mometasone furoate, more preferably a delivered dose ranging from 0.93 to 1.27 micrograms of free base abediterol together with a delivered dose ranging from 64.6 to 87.4 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 0.71 to 1.49 micrograms of free

base abediterol together with a delivered dose ranging from 97.50 to 202.50 micrograms of mometasone furoate, preferably a delivered dose ranging from 0.82 to 1.38 micrograms of free base abediterol together with a delivered dose ranging from 112.50 to 187.50 micrograms of mometasone furoate, more preferably a delivered dose ranging from 0.93 to 1.27 micrograms of free base abediterol together with a delivered dose ranging from 127.50 to 172.50 micrograms of mometasone furoate.

Typically, the invention also provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 0.71 to 1.49 micrograms of free base abediterol together with a delivered dose ranging from 195 to 405 micrograms of mometasone furoate, preferably a delivered dose ranging from 0.82 to 1.38 micrograms of free base abediterol together with a delivered dose ranging from 225 to 375 micrograms of mometasone furoate, more preferably a delivered dose ranging from 0.93 to 1.27 micrograms of free base abediterol together with a delivered dose ranging from 255 to 345 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 1.49 to 3.11 micrograms of free base abediterol together with a delivered dose ranging from 49.40 to 102.60 micrograms of mometasone furoate, preferably a delivered dose ranging from 1.72 to 2.88 micrograms of free base abediterol together with a delivered dose ranging from 57 to 95 micrograms of mometasone furoate, more preferably a delivered dose ranging from 1.95 to 2.65 micrograms of free base abediterol together with a delivered dose ranging from 64.6 to 87.4 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof

- and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 1.49 to 3.11 micrograms of free base abediterol together with a delivered dose ranging from 97.50 to 202.50 micrograms of mometasone furoate, preferably a delivered dose ranging from 1.72 to 2.88
- 5 micrograms of free base abediterol together with a delivered dose ranging from 112.50 to 187.50 micrograms of mometasone furoate, more preferably a delivered dose ranging from 1.95 to 2.65 micrograms of free base abediterol together with a delivered dose ranging from 127.50 to 172.50 micrograms of mometasone furoate.
- 10 Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 1.49 to 3.11 micrograms of free
- 15 base abediterol together with a delivered dose ranging from 195 to 405 micrograms of mometasone furoate, preferably a delivered dose ranging from 1.72 to 2.88 micrograms of free base abediterol together with a delivered dose ranging from 225 to 375 micrograms of mometasone furoate, more preferably a delivered dose ranging from 1.95 to 2.65 micrograms of free base abediterol together with a delivered dose ranging from 255 to 345 micrograms of mometasone furoate.
- 20
- In another preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.14 to
- 25 0.30 micrograms of free base abediterol together with a fine particle dose ranging from 19.50 to 40.5 micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.16 to 0.28 micrograms of free base abediterol together with a fine particle dose ranging from 22.5 to 37.5 micrograms of mometasone furoate, more preferably a fine particle dose ranging from 0.18 to 0.26 micrograms of free base abediterol together with
- 30 a fine particle dose ranging from 25.5 to 34.5 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.14 to 0.30 micrograms of free base abediterol together with a fine particle dose ranging from 42.25 to 87.75 micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.16 to 0.28 micrograms of free base abediterol together with a fine particle dose ranging from 48.75 to 81.25 micrograms of mometasone furoate, more preferably a fine particle dose ranging from 0.18 to 0.26 micrograms of free base abediterol together with a fine particle dose ranging from 55.25 to 74.75 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.14 to 0.30 micrograms of free base abediterol together with a fine particle dose ranging from 84.5 to 175.5 micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.16 to 0.28 micrograms of free base abediterol together with a fine particle dose ranging from 97.5 to 162.5 micrograms of mometasone furoate, more preferably a fine particle dose ranging from 0.18 to 0.26 micrograms of free base abediterol together with a fine particle dose ranging from 110.5 to 149.50 micrograms of mometasone furoate.

In another preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.29 to 0.61 micrograms of free base abediterol together with a fine particle dose ranging from 19.50 to 40.5 micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.33 to 0.57 micrograms of free base abediterol together with a fine particle dose ranging from 22.5 to 37.5 micrograms of mometasone furoate, more preferably a fine

particle dose ranging from 0.38 to 0.52 micrograms of free base abediterol together with a fine particle dose ranging from 25.5 to 34.5 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry
5 powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof
and mometasone furoate in admixture with a pharmaceutically acceptable carrier,
providing upon inhalation a fine particle dose ranging from 0.29 to 0.61 micrograms of
free base abediterol together with a fine particle dose ranging from 42.25 to 87.75
micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.33 to
10 0.57 micrograms of free base abediterol together with a fine particle dose ranging from
48.75 to 81.25 micrograms of mometasone furoate, more preferably a fine particle dose
ranging from 0.38 to 0.52 micrograms of free base abediterol together with a fine particle
dose ranging from 55.25 to 74.75 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry
15 powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof
and mometasone furoate in admixture with a pharmaceutically acceptable carrier,
providing upon inhalation a fine particle dose ranging from 0.29 to 0.61 micrograms of
free base abediterol together with a fine particle dose ranging from 84.5 to 175.5
20 micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.33 to
0.57 micrograms of free base abediterol together with a fine particle dose ranging from
97.5 to 162.5 micrograms of mometasone furoate, more preferably a fine particle dose
ranging from 0.38 to 0.52 micrograms of free base abediterol together with a fine particle
dose ranging from 110.5 to 149.50 micrograms of mometasone furoate.

25 Typically, the invention provides a pharmaceutical composition in the form of a dry
powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof
and mometasone furoate in admixture with a pharmaceutically acceptable carrier,
providing upon inhalation a fine particle dose ranging from 0.65 to 1.35 micrograms of
30 free base abediterol together with a fine particle dose ranging from 19.50 to 40.5
micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.75 to

1.25 micrograms of free base abediterol together with a fine particle dose ranging from 22.5 to 37.5 micrograms of mometasone furoate, more preferably a fine particle dose ranging from 0.85 to 1.15 micrograms of free base abediterol together with a fine particle dose ranging from 25.5 to 34.5 micrograms of mometasone furoate.

5

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.65 to 1.35 micrograms of free base abediterol together with a fine particle dose ranging from 42.25 to 87.75 micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.75 to 1.25 micrograms of free base abediterol together with a fine particle dose ranging from 48.75 to 81.25 micrograms of mometasone furoate, more preferably a fine particle dose ranging from 0.85 to 1.15 micrograms of free base abediterol together with a fine particle dose ranging from 55.25 to 74.75 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.65 to 1.35 micrograms of free base abediterol together with a fine particle dose ranging from 84.5 to 175.5 micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.75 to 1.25 micrograms of free base abediterol together with a fine particle dose ranging from 97.5 to 162.5 micrograms of mometasone furoate, more preferably a fine particle dose ranging from 0.85 to 1.15 micrograms of free base abediterol together with a fine particle dose ranging from 110.5 to 149.50 micrograms of mometasone furoate.

In another preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 0.406

to 0.844 micrograms of free base abediterol together with a metered nominal dose ranging from 55.25 to 114.75 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 0.468 to 0.782 micrograms of free base abediterol together with a metered nominal dose ranging from 63.75 to 106.25 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 0.531 to 0.719 micrograms of free base abediterol together with a metered nominal dose ranging from 72.25 to 97.75 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 0.406 to 0.844 micrograms of free base abediterol together with a metered nominal dose ranging from 110.50 to 229.50 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 0.468 to 0.782 micrograms of free base abediterol together with a metered nominal dose ranging from 127.50 to 212.50 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 0.531 to 0.719 micrograms of free base abediterol together with a metered nominal dose ranging from 144.50 to 195.50 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 0.406 to 0.844 micrograms of free base abediterol together with a metered nominal dose ranging from 221 to 459 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 0.468 to 0.782 micrograms of free base abediterol together with a metered nominal dose ranging from 255 to 425 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 0.531 to 0.719 micrograms of free base abediterol together with a metered nominal dose ranging from 289 to 391 micrograms of mometasone furoate.

In another preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 0.71 to 1.49 micrograms of free base abediterol together with a metered nominal dose ranging from 55.25 to 114.75 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 0.93 to 1.57 micrograms of free base abediterol together with a metered nominal dose ranging from 63.75 to 106.25 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 1.06 to 1.44 micrograms of free base abediterol together with a metered nominal dose ranging from 72.25 to 97.75 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 0.81 to 1.69 micrograms of free base abediterol together with a metered nominal dose ranging from 110.50 to 229.50 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 0.93 to 1.57 micrograms of free base abediterol together with a metered nominal dose ranging from 127.50 to 212.50 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 1.06 to 1.44 micrograms of free base abediterol together with a metered nominal dose ranging from 144.50 to 195.50 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 0.81 to 1.69 micrograms of free base abediterol together with a metered nominal dose ranging from 221 to 459 micrograms of mometasone furoate, preferably a metered nominal dose ranging from

0.93 to 1.57 micrograms of free base abediterol together with a metered nominal dose ranging from 255 to 425 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 1.06 to 1.44 micrograms of free base abediterol together with a metered nominal dose ranging from 289 to 391 micrograms of mometasone furoate.

5

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 1.62 to 3.38 micrograms of free base abediterol together with a metered nominal dose ranging from 55.25 to 114.75 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 1.87 to 3.13 micrograms of free base abediterol together with a metered nominal dose ranging from 63.75 to 106.25 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 2.12 to 2.88 micrograms of free base abediterol together with a metered nominal dose ranging from 72.25 to 97.75 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 1.62 to 3.38 micrograms of free base abediterol together with a metered nominal dose ranging from 110.50 to 229.50 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 1.87 to 3.13 micrograms of free base abediterol together with a metered nominal dose ranging from 127.50 to 212.50 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 2.12 to 2.87 micrograms of free base abediterol together with a metered nominal dose ranging from 144.50 to 195.50 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof

and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 1.62 to 3.38 micrograms of free base abediterol together with a metered nominal dose ranging from 110.50 to 229.50 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 1.87 to 3.13 micrograms of free base abediterol together with a metered nominal dose ranging from 127.50 to 212.50 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 2.12 to 2.87 micrograms of free base abediterol together with a metered nominal dose ranging from 144.50 to 195.50 micrograms of mometasone furoate.

10

In another embodiment, the invention also provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 1.25 micrograms of free base abediterol together with a dose equivalent to a metered nominal dose of about 70 micrograms of mometasone furoate administered with the Genuair® inhaler. The invention also provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 2.5 micrograms of free base abediterol together with a dose equivalent to a metered nominal dose of about 70 micrograms of mometasone furoate administered with the Genuair® inhaler. The invention also provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal dose of about 0.625 micrograms of free base abediterol together with a dose equivalent to a metered nominal dose of about 70 micrograms of mometasone furoate administered with the Genuair® inhaler.

30

When administered with the Genuair® inhaler a metered nominal dose of about 70 micrograms of mometasone furoate is equivalent to about 62 micrograms delivered dose and to about 22 micrograms fine particle dose.

- 5 As mentioned before, the doses of mometasone furoate are also subjected to the same acceptable variation limits as defined by the European and US pharmacopeia. Thus the delivered dose of “about 62 micrograms” is meant a target delivered dose ranging from 40.3 to 83.7 micrograms (plus/minus 35%), preferably from 46.5 to 77.5 micrograms (plus/minus 25%), more preferably from 52.7 to 71.3 micrograms (plus/minus 15%).
- 10 Thus, the fine particle dose of “27 micrograms” is meant a target fine particle dose ranging from 14.3 to 29.7 micrograms, preferably from 16.5 to 27.5 micrograms, more preferably from 18.7 to 25.3 micrograms. In the same way, the metered nominal dose of “about 70 micrograms” is meant a target metered nominal dose ranging from 45.5 to 94.5 micrograms, preferably from 52.5 to 87.5 micrograms, more preferably from 59.5 to 80.5
- 15 micrograms.

- Thus in a preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a delivered dose ranging from 0.365 to
- 20 0.759 micrograms of free base abediterol together with a delivered dose ranging from 40.3 to 83.7 micrograms of mometasone furoate, preferably a delivered dose ranging from 0.421 to 0.703 micrograms of free base abediterol together with a delivered dose ranging from 46.5 to 77.5 micrograms of mometasone furoate, more preferably a delivered dose ranging from 0.477 to 0.647 micrograms of free base abediterol together
- 25 with a delivered dose ranging from 52.7 to 71.3 micrograms of mometasone furoate.

- In a further preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically
- 30 acceptable carrier, providing upon inhalation a delivered dose ranging from 0.71 to 1.49 micrograms of free base abediterol together with a delivered dose ranging from 40.3 to

83.7 micrograms of mometasone furoate, preferably a delivered dose ranging from 0.82 to 1.38 micrograms of free base abediterol together with a delivered dose ranging from 46.5 to 77.5 micrograms of mometasone furoate, more preferably a delivered dose ranging from 0.93 to 1.27 micrograms of free base abediterol together with a delivered
5 dose ranging from 52.7 to 71.3 micrograms of mometasone furoate.

In a further preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically
10 acceptable carrier, providing upon inhalation a delivered dose ranging from 1.49 to 3.11 micrograms of free base abediterol together with a delivered dose ranging from 40.3 to 83.7 micrograms of mometasone furoate, preferably a delivered dose ranging from 1.72 to 2.88 micrograms of free base abediterol together with a delivered dose ranging from 46.5 to 77.5 micrograms of mometasone furoate, more preferably a delivered dose
15 ranging from 1.95 to 2.65 micrograms of free base abediterol together with a delivered dose ranging from 52.7 to 71.3 micrograms of mometasone furoate.

In another preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically
20 acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.14 to 0.30 micrograms of free base abediterol together with a fine particle dose ranging from 14.3 to 29.7 micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.16 to 0.28 micrograms of free base abediterol together with a fine particle dose ranging from 16.5 to 27.5 micrograms of mometasone furoate, more preferably a fine
25 particle dose ranging from 0.18 to 0.26 micrograms of free base abediterol together with a fine particle dose ranging from 18.7 to 25.3 micrograms of mometasone furoate.

In another preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically
30 acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically

acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.29 to 0.61 micrograms of free base abediterol together with a fine particle dose ranging from 14.3 to 29.7 micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.33 to 0.57 micrograms of free base abediterol together with a fine particle dose ranging from 16.5 to 27.5 micrograms of mometasone furoate, more preferably a fine particle dose ranging from 0.38 to 0.52 micrograms of free base abediterol together with a fine particle dose ranging from 18.7 to 25.3 micrograms of mometasone furoate.

In another preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.65 to 1.35 micrograms of free base abediterol together with a fine particle dose ranging from 14.3 to 29.7 micrograms of mometasone furoate, preferably a fine particle dose ranging from 0.75 to 1.25 micrograms of free base abediterol together with a fine particle dose ranging from 16.5 to 27.5 micrograms of mometasone furoate, more preferably a fine particle dose ranging from 0.85 to 1.15 micrograms of free base abediterol together with a fine particle dose ranging from 18.7 to 25.3 micrograms of mometasone furoate.

In another preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 0.406 to 0.844 micrograms of free base abediterol together with a metered nominal dose ranging from 45.5 to 94.5 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 0.468 to 0.782 micrograms of free base abediterol together with a metered nominal dose ranging from 52.5 to 87.5 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 0.531 to 0.719 micrograms of free base abediterol together with a metered nominal dose ranging from 59.6 to 80.5 micrograms of mometasone furoate.

In another preferred embodiment, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 0.71 to 1.49 micrograms of free base abediterol together with a metered nominal dose ranging from 45.5 to 94.5 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 0.93 to 1.57 micrograms of free base abediterol together with a metered nominal dose ranging from 52.5 to 87.5 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 1.06 to 1.44 micrograms of free base abediterol together with a metered nominal dose ranging from 59.6 to 80.5 micrograms of mometasone furoate.

Typically, the invention provides a pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt thereof and mometasone furoate in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a metered nominal dose ranging from 1.62 to 3.38 micrograms of free base abediterol together with a metered nominal dose ranging from 45.5 to 94.5 micrograms of mometasone furoate, preferably a metered nominal dose ranging from 1.87 to 3.13 micrograms of free base abediterol together with a metered nominal dose ranging from 52.5 to 87.5 micrograms of mometasone furoate, more preferably a metered nominal dose ranging from 2.12 to 2.88 micrograms of free base abediterol together with a metered nominal dose ranging from 59.6 to 80.5 micrograms of mometasone furoate.

Typically, in these embodiments, the pharmaceutical composition is administered once daily. The once daily dose can be administered either in the morning or in the evening, preferably in the morning.

The invention also provides a pharmaceutical composition comprising abediterol, a corticosteroid as defined above and an anticholinergic, as defined above. Most preferred corticosteroid is mometasone furoate as defined above. Most preferred anticholinergic is

acridinium bromide as defined above. These triple combinations are suitable for administration once or twice a day, preferably once a day.

Examples

5

Example 1

Pharmaceutical composition for inhalation comprising abediterol heminapadisylate and a carrier.

The following equipment were used to prepare the inhalable powder formulations according to the present invention:

10

Mixing Container: Bohle Mixer LM 40 & Bohle bin 10L (2 31 rpm)
Turbula Mixer & Glas bottle 3000 mL (33 rpm)

Sieving Equipment: Bohle Turbo-sieve BTS 100 (800 rpm).

15

The process for manufacturing the pharmaceutical composition in a batch size of 3 kg comprising abediterol heminapadisylate and alpha-lactose monohydrate (having for example, a d_{10} : 90-160 μm , d_{50} : 170-270 μm , d_{90} : 290-400 μm) as a carrier is as follows:

20

1. 20% by weight of lactose used as a carrier was blended with abediterol heminapadisylate. The resulting mixture was sieved and mixed again.
2. The remaining 80% by weight of lactose was sieved and added to the mixture of Step 1. The whole mixture was blended, sieved and blended again resulting in the final inhalation powder blend.

25

When two different types of lactose, for example having a coarse lactose as defined above and a fine lactose (having for example a d_{10} of 2 - 4 μm , a d_{50} of 7 - 10 μm , and d_{90} of 15 - 24 μm), are used, these lactose types are previously mixed together and blended before adding abediterol heminapadisylate as described above.

For preparing 1.25 µg of abediterol free base per dose (i.e. 1.641 µg abediterol heminapadisylate), the following amount of the ingredients are used:

Substance	Dosis [µg] per shot)	Dosis [g] per batch
Abediterol (as heminapadisylate)	1.641	410
CapsuLac 60 INH	11998.358	2849
Total	12000.000	3000

- 5 Similarly, for preparing 2.5 µg of abediterol free base per dose (i.e. 3.283 µg abediterol heminapadisylate), the following amount of the ingredients are used:

Substance	Dosis [µg] per shot	Dosis [g]pro Ansatz (dose [g] per batch)
Abediterol (as heminapadisylate)	3.283	0.821
CapsuLac 60 INH	11996.717	2999
Total	12000.000	3000

- Genuair® (H. Chrystyn et al., 2009) cartridges were filled with the composition. The Genuair® cartridge is calibrated to provide 30 or 60 metered doses. Each actuation of the
- 10 Genuair® provides a metered dose of 12 mg of the composition.

Example 1.2. measurement of the delivered dose.

- The measurement of the delivered dose is carried out based on Ph. Eur. Chapter 2.9.18 and USP <601> using "collection tube" apparatus (CT). For this, the Genuair® inhaler is
- 15 fitted to the Collection Tube via an adapter, the dosage key of the Genuair® inhaler is pressed and released and then 2L or 4L of air are sucked through the inhaler and the Collection Tube (the inspiratory flow rate through the inhaler was approx. 65L/min at a pressure drop of 4KPa). Subsequently, the inhalation powder delivered to the Collection Tube is extracted with solvent and analyzed using High Performance Liquid
- 20 chromatography equipment (HPLC).

According to the invention, for a nominal dose of 2.5 micrograms of abediterol free base is delivered about 2.3 micrograms of abediterol free base per dose. The acceptance variance defined by the CHMP guideline on the Pharmaceutical Quality on inhalation and Nasal Products was 1.95-2.65 micrograms abediterol free base.

5

Similarly, for a nominal dose of 1.25 micrograms of abediterol free base is delivered about 1.1 micrograms of abediterol free base per dose. The acceptance variance defined by the CHMP guideline on the Pharmaceutical Quality on inhalation and Nasal Products was 0.93-1.26 micrograms abediterol free base.

10

Example 1.3. Measurement of the Fine Particle dose (FPD).

The test on the aerodynamic assessment of the fine particles (FPD <5 µm) of the inhalation powder composition is carried out in combination with the Genuair[®] inhaler. The Fine Particle Fraction of abediterol free base was calculated on basis of the principles of the aerodynamic assessment of fine particles according to the Current European pharmacopoeia (Ph. Eur. Chapter 2.9.18) and USP <601> by the aid of aerodynamic impactor analyses using a modified Anderson Cascade Impactor (ACI), 60 L/min-configuration including pre-separator, stage -1, -0, and stage 1-7 (filter stage). The content of the active ingredient on each stage of the impactor is determined by means of HPLC.

20

The fine particle dose (FPD <5 µm) is calculated based on Ph. Eur. Chapter 2.9.18 and USP <601> by point to point interpolation per dosage. Linear point to point interpolation is done between the stages with a corresponding effective cut-off diameter which enclose the 5 µm mark.

25

To obtain the Fine Particle Dose, the cumulative percent value (y-value) at which the line of data plot crosses 5 µm mark is determined. The found cumulative percent must be multiplied by the sum of mass of the active ingredient per dosage on stage -1 –stage 7 (Filter) to obtain the fine particle dose, < 5µm, in µg.

$$\text{FPD } [\mu\text{g}] = y_{\text{FPD}} \cdot F / 100\%$$

FPD = Fine particle dose < 5 µm of the active ingredient per dosage [µg].

y_{FPD} = y-value of cumulative percentage of mass at a particle size of 5 µm
evaluated by linear point to point interpolation [%].

F = sum of mass on stage -1 –stage 7 (filter) per dosage [µg].

5

According to the invention, a nominal dose of 2.5 micrograms of abediterol free base provides about 1.0 micrograms FPD per dose. The acceptance variance defined by the CHMP guideline on the Pharmaceutical Quality on inhalation and Nasal Products was 0.85-1.15 micrograms abediterol free base.

10

Similarly, for a nominal dose of 1.25 micrograms of abediterol free base is delivered about 0.45 micrograms per dose. The acceptance variance defined by the CHMP guideline on the Pharmaceutical Quality on inhalation and Nasal Products was 0.38-0.52 micrograms abediterol free base.

15

Example 2

Clinical phase IIa study: A randomised, single dose, double-blind, double-dummy, 6 way complete cross-over, placebo and active comparator controlled, assesses the efficacy, safety and tolerability of single doses of abediterol administered once daily by inhalation compared to placebo and active comparator in persistent asthmatic patients.

20

Methods: 62 patients (Adult men and women aged 18-70 years) with a clinical diagnosis of persistent asthma, as defined by the 2011 GINA guideline, for at least 6 months prior to screening and with a FEV₁ 61-85% of the predicted normal values (according to Quanjer et al. 1993) were randomised to treatment sequences comprising a single-dose administration of abediterol (at metered nominal doses of 0.313, 0.625, 1.25 and 2.5 micrograms in the Genuair® device), one administration of salbutamol (at a metered nominal dose of 400 micrograms (100 micrograms x 4 puffs) in the Ventolin Evohaler® device) and placebo (administered in both Genuair® and Ventolin Evohaler®)

25

administered all of them by means of a dry powder inhaler. The washout period between each administration was at least 7 days.

Results: Time to peak FEV₁ at day 1 was achieved within the 4h post-dose for all
 5 abediterol doses. Abediterol dose-dependently increased peak FEV₁ on Day 1 (table 1).

Table 1: Change from baseline in peak FEV₁ on Day 1

	Abediterol				Salbutamol	Placebo
	0.313 µg (n=60)	0.625 µg (n=60)	1.25 µg (n=60)	2.5 µg (n=61)	400 µg (n=58)	(n=59)
ml	477*	524*	573**	608***	555**	202

*p < 0.001 vs placebo, ** p < 0.05 vs 0.313 µg & placebo.

*** p < 0.05 vs 0.625 & 0.313 µg & placebo

10

At all doses, abediterol clearly increases the average peak FEV₁ compared with placebo. At doses of 1.25 and 2.5 micrograms, abediterol increased bronchodilatory effect compared with salbutamol. In addition, abediterol was well tolerated, with no dose-dependent effect on ECG, laboratory parameters or adverse events.

15

Example 3

Clinical phase IIa study: A randomised, single dose, double-blind, double-dummy, 6 way complete cross-over, placebo and active comparator controlled, assesses the efficacy, safety and tolerability of single doses of abediterol administered once daily by inhalation
 20 compared to placebo and active comparator in patients with stable moderate to severe chronic obstructive pulmonary disease (COPD).

Methods: 63 patients (men and women aged ≥ 40 years) with a clinical diagnosis of stable moderate to severe COPD, as defined by the 2011 GOLD guideline, with no signs
 25 of an exacerbation within 6 weeks prior to the screening visit and with a FEV₁ 30-80% of the predicted normal values (according to Quanjer et al. 1993) were randomised to

- treatment sequences comprising a single-dose administration of abediterol (at a metered nominal dose of 0.625, 2.5, 5 and 10 micrograms in the Genuair® device), one administration of indacaterol (at a metered nominal dose of 150 micrograms once daily in the Onbrez Breezhaler® device) and placebo (administered in both Genuair® and Onbrez Breezhaler®). The washout period between each administration was at least 7 days. Lung function measurements included (by spirometry) trough FEV₁. Trough FEV₁ is defined as a main FEV₁ value between 23 and 24h after Investigational Medicinal Product (IMP) administration.
- 10 Results: Abediterol dose-dependently increased trough FEV₁ on Day 1 (table 2).

Table 2: Change from baseline in morning pre-dose (trough) FEV₁ at Day 2.

	Abediterol				Indacaterol	Placebo
	0.625 µg (n=67)	2.5 µg (n=66)	5 µg (n=)	10 µg (n=)	150 µg (n=68)	(n=68)
ml	66*	168**	198**	223***	76*	-35

*p < 0.001 vs placebo . ** p < 0.001 vs 0.625 µg & indacaterol & placebo

*** p < 0.05 vs 2.5 µg & 0.625 µg & indacaterol & placebo

- 15 Abediterol significantly increases the average trough FEV₁ compared with placebo. The increase in FEV₁ is statistically significant at 24h for all doses. At doses of 2.5, 5 and 10 micrograms, abediterol produces greater trough FEV₁ than with indacaterol 150 micrograms dose. Strikingly, the increase in trough FEV₁ is statistically significant
- 20 compared with indacaterol. At all these doses, abediterol was well tolerated, with no dose-dependent effect on ECG, laboratory parameters or adverse events. The 2.5 micrograms dose was selected to be the minimum therapeutic effective dose producing higher bronchodilatory effects when compared with indacaterol 150 micrograms.
- 25 **Conclusion:** Abediterol provides a sustained bronchodilation over time with effect lasting more than 24h for all dose levels tested. At a dose of 0.625 micrograms, abediterol achieves a similar level of bronchodilatory effect as salbutamol and indacaterol. At a

dose of 1.25 and 2.5 micrograms, abediterol shows increased bronchodilatory effects when compared with salbutamol. In addition at a dose of 2.5 micrograms, abediterol has higher bronchodilatory effects when compared with indacaterol 150 micrograms.

Abediterol provides good safety and tolerability profile at all doses tested with no overall clinically relevant changes on safety outcomes (HR, QTcF, glucose and potassium).

Based on the efficacy and tolerability data, Abediterol 1.25 and 2.5 micrograms were selected as the investigational dose for a future long-term clinical trial for asthmatic and COPD patients. A dose of 0.625 micrograms abediterol is also of interest since it is the minimum dose having similar therapeutic effect to salbutamol and indacaterol.

CLAIMS

1. A pharmaceutical composition in the form of a dry powder for inhalation comprising
abediterol or a pharmaceutically acceptable salt in admixture with a pharmaceutically
5 acceptable carrier, providing upon inhalation a dose equivalent to a metered nominal
dose of about 1.25 or about 2.5 micrograms of free base abediterol administered with
the Genuair® inhaler.
2. A pharmaceutical composition in the form of a dry powder for inhalation comprising
abediterol or a pharmaceutically acceptable salt in admixture with a pharmaceutically
10 acceptable carrier, providing upon inhalation a metered nominal dose ranging from
0.81 to 1.69 micrograms, preferably from 0.93 to 1.57 micrograms, more preferably
from 1.06 to 1.44 micrograms of free base abediterol.
3. A pharmaceutical composition in the form of a dry powder for inhalation comprising
abediterol or a pharmaceutically acceptable salt in admixture with a pharmaceutically
15 acceptable carrier, providing upon inhalation a metered nominal dose ranging from
1.62 to 3.38 micrograms, preferably from 1.87 to 3.13 micrograms, more preferably
from 2.12 to 2.88 micrograms of free base abediterol.
4. A pharmaceutical composition in the form of a dry powder for inhalation comprising
abediterol or a pharmaceutically acceptable salt in admixture with a pharmaceutically
20 acceptable carrier, providing upon inhalation a delivered dose ranging from 0.71 to
1.49 micrograms, preferably from 0.82 to 1.38 micrograms, more preferably from
0.93 to 1.27 micrograms of free base abediterol.
5. A pharmaceutical composition in the form of a dry powder for inhalation comprising
abediterol or a pharmaceutically acceptable salt in admixture with a pharmaceutically
25 acceptable carrier, providing upon inhalation a delivered dose ranging from 1.49 to
3.11 micrograms, preferably from 1.72 to 2.88, more preferably from 1.95 to 2.65 of
free base abediterol.
6. A pharmaceutical composition in the form of a dry powder for inhalation comprising
abediterol or a pharmaceutically acceptable salt in admixture with a pharmaceutically
30 acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.29 to

- 0.61 micrograms, preferably, from 0.33 to 0.57 micrograms being most preferably from 0.38 to 0.52 micrograms of free base abediterol.
7. A pharmaceutical composition in the form of a dry powder for inhalation comprising abediterol or a pharmaceutically acceptable salt in admixture with a pharmaceutically acceptable carrier, providing upon inhalation a fine particle dose ranging from 0.65 to 1.35 micrograms, preferably, from 0.75 to 1.25 micrograms being most preferably from 0.85 to 1.15 micrograms of free base abediterol.
8. The pharmaceutical composition according to any of the preceding claims, in the form of a single-dose dry powder formulation comprising a single dose of free base abediterol as defined in any one of claims 1 to 7.
9. The pharmaceutical composition according to any of the preceding claims in the form of a multi-dose dry powder formulation for administration in a mutlidose dry powder inhaler device calibrated to provide a dose of free base abediterol as defined in any one of claims 1 to 7.
10. The pharmaceutical composition according to any of the preceding claims, wherein the pharmaceutically acceptable salt is heminapadisylate.
11. The pharmaceutical composition according to any of the preceding claims wherein the pharmaceutically acceptable carrier is lactose particles.
12. The pharmaceutical composition according to any of the preceding claims wherein the ratio by weight of abediterol to carrier is from 1:1000 to 1:40000.
13. The pharmaceutical composition according to claim 12 wherein the ratio by weight of abediterol to carrier is from 1:2000 to 1:20000.
14. The pharmaceutical composition according to any of the preceding claims wherein the average particle diameter of abediterol heminapadisylate is within 1.5-5 μm .
15. The pharmaceutical composition according to any of the preceding claims wherein the carrier particles have a d10 of 90 - 160 μm , a d50 of 170 – 270 μm , and d90 of 290 – 400 μm .
16. The pharmaceutical composition according to claim 15, wherein the carrier particles are admixed with a additional particles of lactose having a d10 of 2 - 4 μm , a d50 of 7 – 10 μm , and d90 of 15 – 24 μm .

17. The pharmaceutical composition according to any of the preceding claims further comprising an effective amount of one or more additional active agents selected from M3 antagonists, PDE IV inhibitors, and corticosteroids.
18. The pharmaceutical composition according to claim 17 wherein the additional active agent is selected from tiotropium, aclidinium, mometasone, fluticasone and roflumilast, in free or pharmaceutically acceptable salt form.
19. The pharmaceutical composition according to claim 1, wherein the additional active ingredient is mometasone furoate in a dose equivalent to a metered nominal dose of about 50-900 micrograms administered with the Genuair® inhaler.
20. The pharmaceutical composition according to claim 19, wherein the mometasone furoate is present in an amount of about 70 micrograms per metered nominal dose.
21. The pharmaceutical composition according to claim 19, wherein the mometasone furoate is present in an amount of about 85 micrograms per metered nominal dose.
22. The pharmaceutical composition according to claim 19, wherein the mometasone furoate is present in an amount of about 170 micrograms per metered nominal dose.
23. The pharmaceutical composition according to claim 19, wherein the mometasone furoate is present in an amount of about 340 micrograms per metered nominal dose.
24. A method of treating a respiratory condition selected from asthma and chronic obstructive pulmonary disease in a patient in need of such treatment, comprising administering a dose of free base abediterol as defined in any one of claims 1 to 16.
25. The method according to claim 24, further comprising an effective amount of one or more additional active agents as defined in any of claims 17 to 23.
26. The use of abediterol in the manufacture of a medicament for administration in accordance with the method of claim 24 or 25.
27. The use of abediterol in the manufacture of a pharmaceutical composition according to any of claims 1-23.
28. Abediterol in free or pharmaceutically acceptable salt form for use in any of the methods of claim 24 or 25.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/061181

A. CLASSIFICATION OF SUBJECT MATTER		
INV. A61K9/14	A61K31/4706	A61K9/00 A61P11/08 A61P11/06
ADD.		
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)		
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 practicable, search terms used)		
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/095720 A1 (ALMIRALL LAB [ES]; PUIG DURAN CARLOS [ES]; MOYES VALLS ENRIQUE [ES]) 14 August 2008 (2008-08-14) cited in the application examples 1-5 page 11, line 11 - line 28 page 13, line 29 - page 18, line 2 claims 6-19	1-7, 9-11, 14-28
X	WO 2010/072354 A1 (ALMIRALL SA [ES]; CARRERA CARRERA FRANCESC [ES]; PUIG DURAN CARLOS [ES]) 1 July 2010 (2010-07-01) cited in the application examples 3,4 page 10, line 21 - line 28 claims 6-15	1-9, 11-13, 17-28
----- -/-		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family 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 application or patent 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
24 July 2013		01/08/2013
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/061181

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/094484 A1 (ALMIRALL SA [ES]; RUF THORSTEN [ES]; MASSANA MONTEJO ERIC [ES]) 26 August 2010 (2010-08-26) claims page 22, line 6 - line 13 page 7, line 11 - page 11, line 30 -----	1-28
A	H. CHRYSTYN ET AL: "The Genuair inhaler: a novel, multidose dry powder inhaler", INTERNATIONAL JOURNAL OF CLINICAL PRACTICE, vol. 66, no. 3, 16 February 2012 (2012-02-16), pages 309-317, XP055039099, ISSN: 1368-5031, DOI: 10.1111/j.1742-1241.2011.02832.x the whole document -----	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/061181

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008095720 A1	14-08-2008	AR 065247 A1 AT 551323 T AU 2008213109 A1 BR PI0806391 A2 CA 2677610 A1 CL 4042008 A1 CN 101679269 A CO 6231025 A2 DK 2121615 T3 EC SP099557 A EP 2121615 A1 ES 2306595 A1 ES 2384905 T3 HK 1133011 A1 HR P20120456 T1 JP 2010518038 A NZ 578412 A PE 15212012 A1 PE 17522008 A1 PL 2121615 T3 PT 2121615 E RS 52302 B RU 2009133442 A SI 2121615 T1 TW 200902001 A US 2010093681 A1 WO 2008095720 A1 ZA 200904851 A	27-05-2009 15-04-2012 14-08-2008 06-09-2011 14-08-2008 18-08-2008 24-03-2010 20-12-2010 02-07-2012 29-09-2009 25-11-2009 01-11-2008 13-07-2012 10-08-2012 30-06-2012 27-05-2010 25-02-2011 26-11-2012 06-12-2008 30-11-2012 25-06-2012 31-12-2012 20-03-2011 31-08-2012 16-01-2009 15-04-2010 14-08-2008 28-04-2010
WO 2010072354 A1	01-07-2010	AR 074792 A1 AU 2009331961 A1 CA 2748105 A1 CN 102264703 A CO 6390056 A2 DK 2367796 T3 EA 201100970 A1 EP 2367796 A1 ES 2397209 T3 HK 1156318 A1 HR P20120941 T1 JP 2012513424 A KR 20110103397 A NZ 592797 A PE 09292011 A1 PT 2367796 E SG 171992 A1 SI 2367796 T1 SM T201300001 B TW 201024265 A US 2011251234 A1 UY 32297 A WO 2010072354 A1	09-02-2011 30-06-2011 01-07-2010 30-11-2011 29-02-2012 17-12-2012 30-12-2011 28-09-2011 05-03-2013 01-02-2013 31-12-2012 14-06-2012 20-09-2011 31-08-2012 29-12-2011 23-01-2013 28-07-2011 31-12-2012 08-03-2013 01-07-2010 13-10-2011 31-05-2010 01-07-2010
WO 2010094484 A1	26-08-2010	AR 075769 A1 AU 2010214855 A1 CA 2749045 A1 CN 102317264 A CO 6361996 A2	27-04-2011 21-07-2011 26-08-2010 11-01-2012 20-01-2012

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/061181

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		EA 201101211 A1	30-03-2012
		EC SP11011337 A	31-10-2011
		EP 2221297 A1	25-08-2010
		EP 2398772 A1	28-12-2011
		JP 2012518020 A	09-08-2012
		KR 20110123740 A	15-11-2011
		PE 04202012 A1	09-05-2012
		SG 173092 A1	29-08-2011
		TW 201031409 A	01-09-2010
		US 2012040941 A1	16-02-2012
		UY 32435 A	31-05-2010
		WO 2010094484 A1	26-08-2010

摘要

本發明提供了一種供吸入的乾粉形式的藥物組合物，其包括與藥學上可接受的載體混合的阿貝特羅(abediterol)或藥學上可接受的鹽，在吸入時提供的劑量相當於採用 Genuair®吸入器給予的約 1.25 或約 2.5 微克阿貝特羅游離碱的定量標稱劑量。本發明還提供所述藥物組合物用於在呼吸系統疾病的治療中使用，例如用於哮喘和慢性阻塞性肺病 COPD。