

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 November 2007 (01.11.2007)

PCT

(10) International Publication Number
WO 2007/121913 A2

(51) International Patent Classification:

A61K 31/57 (2006.01) A61K 9/00 (2006.01)
A61K 31/58 (2006.01)

(21) International Application Number:

PCT/EP2007/003420

(22) International Filing Date: 19 April 2007 (19.04.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

11/408,026 21 April 2006 (21.04.2006) US

(71) Applicant (for all designated States except US): **CHIESI FARMACEUTICI S.P.A.** [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LEWIS, David, Andrew** [GB/IT]; Via Palermo 26/A, I-43100 Parma (IT). **MEAKIN, Brian, John** [GB/GB]; Sussex Lodge, 6, Oakley, Claverton Down, Bath BA2 6D5 (GB). **BRAMBILLA, Gaetano** [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).

(74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.r.l., Via Plinio, 63, I-20129 Milano (IT).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL SOLUTION FORMULATIONS FOR PRESSURISED METERED DOSE INHALERS

(57) Abstract: The invention relates to the use a solution formulation for pressurized metered dose inhalers able of providing therapeutical doses of two or more active drug substances to the lung for the manufacture of a medicament for the prevention or treatment of a severe broncho-pulmonary disease, wherein all the active drug substances are fully dissolved in the formulation as well as the two or more active drug substances are delivered with substantially the same particle size distribution.

WO 2007/121913 A2

**PHARMACEUTICAL SOLUTION FORMULATIONS FOR
PRESSURISED METERED DOSE INHALERS**

FIELD OF THE INVENTION

The invention relates to the use of a solution formulation for pressurized metered dose inhalers (pMDIs) able of providing therapeutic doses of two or more active drug substances to the lung for the manufacture of a medicament for the prevention or treatment of a severe broncho-pulmonary disease wherein substantially all of the liquid particles emitted on actuation of said inhaler contain said two or more active drug substances in a ratio which is substantially the same as said predetermined ratio of said two or more active drug substances in said medicament as well as the two or more active drug substances are delivered with substantially the same particle size distribution.

BACKGROUND OF THE INVENTION

Treatment of broncho-pulmonary diseases such as asthma and COPD with inhaled aerosol drugs offers advantages over systemic therapy, including a more rapid onset and reduced adverse effects, because of direct targeting of the lungs.

Pressurised metered dose inhalers (pMDIs) are well known devices for administering pharmaceutical products to the respiratory tract by inhalation. MDI uses a propellant to expel droplets containing the pharmaceutical product to the respiratory tract as an aerosol. Formulations for aerosol administration via MDIs can be solutions or suspensions. Solution formulations offer the advantage of being homogeneous with the active ingredient and excipients completely dissolved in the propellant vehicle or its mixture with suitable co-solvents such as ethanol. Solution formulations also obviate physical stability problems associated with suspension formulations so assuring more consistent uniform dosage administration.

Drugs commonly delivered by inhalation for treating broncho-

pulmonary diseases include short-acting and long-acting β_2 -agonists, anticholinergics/antimuscarinic agents, and corticosteroids in hydrofluoroalkanes propellant (HFA).

5 In particular, long-acting β_2 -agonists (LABAs) such as formoterol and salmeterol and antimuscarinic agents, such as selective muscarinic receptors 3M antagonists, in combination with inhaled corticosteroids (ICS), have been proposed for the prevention and/or treatment of said diseases.

10 However, despite of modern maintenance treatment, some patients are still under treated particularly when the broncho-pulmonary disease is in a severe form.

Hence there is still an unmet need for more efficacious medicaments for the prevention or treatments of severe forms of broncho-pulmonary diseases, in particular of severe forms of asthma and COPD. As explained in details hereinafter, more efficacious medicaments are obtained by providing 15 pressurized solution formulations of two or more drug substances that, upon actuation of the inhaler, deliver the active drug substances in a ratio which is substantially the same as the predetermined ratio of said active drug substances in the medicament and the active drug substances are delivered with substantially the same particle size distribution.

20 In this way a co-deposition within the lung of the combination of the active drug substances is obtained which results in a clinical response of lung function that is greater than the sum of the response of the individual drugs administered.

SUMMARY OF THE INVENTION

25 It is one object of the present invention to provide the use of a pressurized solution formulation for metered dose inhalers containing two or more active drug substances in a predetermined ratio dissolved in an HFA propellant and ethanol as a co-solvent for the manufacture of a medicament

for the prevention and/or treatment of a severe broncho-pulmonary diseases, wherein substantially all of the liquid particles emitted on actuation of said inhaler contain said two or more active drug substances in a ratio which is substantially the same as said predetermined ratio of said two or more active
5 drug substances in said medicament wherein substantially all of the liquid particles emitted on actuation of said inhaler contain said two or more active drug substances in a ratio which is substantially the same as said predetermined ratio of said two or more active drug substances in said medicament and the two or more active drug substances are delivered with
10 substantially the same particle size distribution.

The invention is also directed to a method of preventing or treating a severe broncho-pulmonary disease, said method comprising the administration of a combination of two or more active drug substances to the lung region tract of said subject by actuation of a pressurized single metered dose inhaler
15 containing said two or more active drug substances in a predetermined ratio and dissolved in an HFA propellant and ethanol as a co-solvent, wherein substantially all of the liquid particles emitted on actuation of said inhaler contain said two or more active drug substances in a ratio which is substantially the same as said predetermined ratio of said two or more active
20 drug substances in said medicament and said two or more active drug substances are delivered with substantially the same particle size distribution.

The invention is further directed to the use of a pressurized solution formulation for metered dose inhalers containing two or more active drug substances in a predetermined ratio dissolved in an HFA propellant and not
25 more than 20% w/w ethanol as a co-solvent wherein substantially all of the liquid particles emitted on actuation of said inhaler contain said two or more active drug substances in a ratio which is substantially the same as said predetermined ratio of said two or more active drugs as well as the two or

more active drug substances are delivered with substantially the same particle size for improving the co-deposition of said drugs in the lung tract of a patient and therefore their synergistic interaction.

Preferably, the active drug substances comprise a bronchodilating
5 and/or anti-inflammatory compound, more preferably a long acting
beta₂-agonist and an inhaled corticosteroid.

DEFINITION

As used herein the expression 'substantially all of the liquid particles emitted on actuation of said inhaler contain said two or more active drug
10 substances in a ratio which is substantially the same as said predetermined ratio of said two or more active drug substances in said medicament' means that the relative standard deviation (RSD) of the ratio of the amounts of drugs measured along the stages of an Andersen Cascade Impactor (ACI) is less than 5.0%, preferably 3.5%, more preferably less than 2.0% when at least one of
15 the active ingredient is delivered at a dose comprised between 4 and 16 µg, while is less than 15%, preferably less than 12% when at least one of the active ingredient is delivered at a dose higher than 0.5 but lower than 4 µg.

The relative standard deviation (RDS) is calculated by the formula:
(SD/mean)*100.

20 As used herein the expression 'the two or more active drug substances are delivered with substantially the same particle size' means that the particle size distribution of the drugs determined along the stages of the Andersen Cascade Impactor (ACI) is not statistically significantly different ($p < 0.05$).

As used herein the term "dose" means the amount of active ingredient
25 delivered by a single actuation of the inhaler.

As used herein, the expression '% w/w' means the weight percentage of the component in respect to the total weight of the composition.

According to the Global Initiative for Asthma (GINA), severe persistent

asthma is defined as a form characterized by daily symptoms, frequent exacerbations, frequent nocturnal asthma symptoms, limitation of physical activities, forced expiratory volume in one second (FEV₁) equal to or less than 60% predicted and with a variability higher than 30%.

5 According to the Global initiative for chronic Obstructive Pulmonary Disease (GOLD) guidelines, severe COPD is a form characterized by a ratio between FEV₁ and the Forced Vital Capacity (FVC) lower than 0.7 and FEV₁ between 30% and 50% predicted. The very severe form is further characterized by chronic respiratory failure.

10 The particle size distribution (PSD) data of the pMDI formulations have been obtained using an Andersen Cascade Impactor (ACI) in accordance with the European Pharmacopoeia 5th Edition 2007, part 2.9.18, page 3109 and in particular according to the procedure described in details in Example 1.

 The level of co-deposition may be monitored by a scintigraphic study
15 which allows to evaluate the distribution of the active substances along the various lung areas, i.e. from the central to the peripheral airways.

 Formulations, which upon actuation of the pressurized metered dose inhaler, on evaporation of the propellant mixture, feature an average particle size of the two active ingredients equal or below 1.1 micrometer are also
20 referred herewith as extrafine.

BRIEF DESCRIPTION OF THE DRAWINGS

 Figure 1 shows the cumulative % undersize BDP and FF mass distributions for the sample as determined in Example 1; and

 Figure 2 shows the percentage (of metered dose) ACI stage by stage
25 deposition of LABA and ICS (bars represents Mean $\pm$ SD; (n=6)) as measured in Example 2.

DETAILED DESCRIPTION OF THE INVENTION

 The medicaments of the present invention are obtained by providing

solution formulations of two or more drug substances to be used with pressurized metered dose inhalers (pMDIs) that, upon actuation of the inhaler, deliver the active drug substances in a ratio which is substantially the same as the predetermined ratio of said active drug substances in the medicament and the active drug substances are delivered with substantially the same particle size distribution at stages. In fact this allows achieving a co-deposition within the lung of the combination of the active drug substances which results in a clinical response of lung function that is greater than the sum of the response of the individual drugs administered. Co-deposition in the same lung region indeed maximizes the synergistic effects, with a great improvement in the lung function of the patients.

The solution formulations to be used with pMDIs of the present invention (hereinafter pressurized solution formulations), comprise an ethanol/HFA propellant based solution formulation for aerosol administration containing a combination of two or more active drug substances, wherein said active drug substances are fully dissolved in the formulation, each liquid particle generated during the MDIs atomisation process contains drug concentrations consistent with the liquid properties of the product's solution formulation. This consistency is maintained for the residual particles following excipient evaporation.

Moreover, it has been found that each droplet of the aerosol cloud emitted on actuation of the inhaler containing a solution of different active drug substances dries to give particles of the active materials with identical size distributions in the correct ratio.

This characteristic is maintained through the life of the inhaler device.

It has now surprisingly been found that the formulations described above are particularly useful for the prevention and/or treatment of a severe broncho-pulmonary disease, especially severe persistent asthma and severe

COPD.

It is preferred that the solution formulation be suitable for delivering the therapeutic daily doses of the active ingredients in one or two actuations.

Advantageously, the solution formulation is suitable for delivering at least one of the active ingredients at a dose lower than 20 μg . In particular, in certain embodiments, the dose of at least one of the active ingredient to be delivered shall be comprised between 4 and 16 μg , preferably 6 or 12 μg , more preferably 6 μg . In other embodiments, the dose of at least one of the active ingredient shall be higher than 0.5 but lower than 4 μg , preferably 1 or 2 μg , more preferably 1 μg .

Active ingredients which may be used in the aerosol formulations of the invention are short- and long-acting β_2 -adrenergic agonists, preferably long-acting β_2 -adrenergic agonists such as formoterol, salmeterol, indacaterol, carmoterol and salts thereof and their combinations with other active ingredients, preferably selected from the group of inhaled corticosteroids (ICS) or anticholinergic atropine-like derivatives, antimuscarinic M3 inhibitors or phosphodiesterase 4 (PDE4) inhibitors.

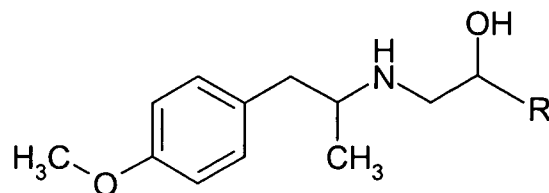
Preferred ICS are beclomethasone dipropionate, budesonide and its 22R-epimer, rofleponide, ciclesonide, fluticasone propionate, mometasone furoate or triamcinolone and its ester such as triamcinolone acetonide. In a preferred embodiment the ICS is budesonide or an epimer thereof. In another preferred embodiment the ICS is beclomethasone dipropionate.

Preferred anticholinergic atropine-like derivatives are ipratropium bromide, oxitropium bromide, tiotropium bromide or glycopyrronium bromide.

Preferred long acting β_2 -agonists are formoterol, carmoterol and salmeterol and salts thereof.

More preferably, the first active ingredient is a long acting

beta₂-agonists belonging to the formula sketched below



wherein R is 1-formylamino-2-hydroxy-phen-5-yl (formoterol) or 8-hydroxy-2(1H)-quinolinon-5-yl (TA 2005) or one of their salts, solvates,
5 solvates of the salts or stereoisomers.

In a particular embodiment, the solution formulation will be suitable for delivering 6 or 12 µg/dose of formoterol fumarate, more preferably 6 µg, either alone or in combination. In another embodiment, the solution formulation will be advantageously suitable for delivering 0.5 to 4 µg/dose,
10 preferably 0.5 to 2 µg/dose, more preferably 1 µg/dose of carmoterol hydrochloride (TA 2005) either alone or in combination.

The ratios in which the beta₂-agonist and the other active drug substance may be used in the solution formulation are variable. Depending on the choice of the active drug substance, the ratios by weight which may be
15 used within the scope of the present invention vary on the basis of the different molecular weights of the various substances and their different potencies.

Advantageously, the pressurized solutions according to the invention may contain the beta₂-agonist and the other active drug substance in ratios by
20 weight ranging from 1:2 to 1:3200.

In certain embodiments wherein the other active substance is an ICS, if the beta₂-agonist is delivered at a dose comprised between 4 and 16 µg, the ratio shall range between 1:3 and 1:100, preferably between 1:8 and 1:40.

In other embodiments, if the beta₂-agonist is delivered at a dose higher
25 than 0.5 but lower than 4 µg, the ratio by weight shall range between 1:12.5

and 1:800, preferably between 1:25 and 1:400.

When the other active drug substance present in the solution formulation is budesonide, said formulation will be suitable for delivering 50 to 400 µg/dose, preferably 100 to 200 µg/dose, more preferably 100 or 200 µg/dose of said drug substance.

When the other active drug substance is beclomethasone dipropionate, the formulation will be suitable for delivering 50 to 200 µg/dose, preferably 100 or 200 µg/dose.

The hydrofluorocarbon propellant is preferably selected from the group of HFA 134a, HFA 227 and mixtures thereof.

Advantageously, the amount of ethanol in the solution formulation is comprised between 5% and 20% w/w, more advantageously between 6% and 18% w/w, preferably comprised between 8 and 16% w/w, more preferably the amount of ethanol is 12% or 15%.

The solution formulation of the invention may further contain small amounts of a mineral acid to adjust the apparent pH to between 2.5 and 5.0 wherein apparent is defined in EP 1157689.

Preferably, the solution formulation of the present invention are able of delivering, on actuation of the inhaler, an average fraction of particles of the active ingredients equal to or less than 1.1 micron, allowing the drugs to reach the small peripheral airways region where they exercise their pharmacological effects. The formulations featuring these characteristics will be herein defined as extrafine.

The solution formulations of the invention may be contained in a pressurized MDI having part of all of the internal metallic surfaces made of anodised aluminium, stainless steel or lined with an inert organic coating. Examples of preferred coatings are epoxy-phenol resins, perfluoroalkoxyalkane, perfluoroalkoxyalkylene, perfluoroalkylenes such as

polytetrafluoroethylene, fluorinated-ethylene-propylene, polyether sulfone and a mixture of fluorinated-ethylene-propylene and polyether sulfone. Other suitable coatings could be polyamide, polyimide, polyamideimide, polyphenylene sulfide or their combinations.

5 According to a particular embodiment, the invention provides a pressurised MDI consisting of an aluminium container filled with a formulation consisting of an extrafine solution of formoterol fumarate in combination with beclomethasone dipropionate in HFA 134a as a propellant in turn containing 12% w/w ethanol as a co-solvent, the apparent pH of said
10 solution having been adjusted to between 3.0 and 5.0 by addition of a suitable amount of hydrochloric acid.

 According to a further particular embodiment the invention provides a pressurised MDI consisting of a coated container filled with a formulation consisting of an extrafine solution of 8-hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-
15 2-(4-methoxy-phenyl)-1-methylethyl] amino] ethyl]-2(1H)-quinolinone hydrochloride (TA 2005) in combination with budesonide in HFA 134a as a propellant in turn containing 15% w/w ethanol as a co-solvent, the apparent pH of said solution having been adjusted to between 3.0 and 5.0 by addition of a suitable amount of phosphoric acid.

20 Advantageously, all the pressurized solution formulations of the present invention are filled in a device, such as an aerosol inhaler, according to a method comprising the following steps:

- (a) preparing of a solution of one or more active ingredients in one or more co-solvents;
- 25 (b) filling of the device with said solution;
- (c) optionally adding a pre-determined amount of a strong mineral acid;
- (d) adding a propellant containing a hydrofluoroalkane (HFA); and
- (e) crimping with valves and gassing.

The formulation is actuated by a metering valve capable of delivering a volume of between 50:1 and 100:1.

Metering valves fitted with gaskets made of chloroprene-based rubbers can preferably be used to reduce the ingress of moisture which, as previously mentioned, can adversely affect the stability of the drug during storage. Optionally, further protection can be achieved by packaging the product in a sealed aluminium pouch.

The pressurized solution formulations having the features described in the present invention, in particular those comprising a long-acting β 2-agonist (LABA) bronchodilator and an inhaled corticosteroid (ICS) are useful in the prevention and/or treatment of a severe broncho-pulmonary disease, in particular severe persistent asthma and severe and very severe chronic obstructive pulmonary disease (COPD).

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Example 1. Particle size distribution for formoterol fumarate and beclomethasone dipropionate within an ethanol based solution HFA pMDI by Andersen Cascade Impactor (ACI).

The solution formulation contained BDP (100 μ g/dose) and FF (6 μ g/dose) in 50 μ l in HFA 134a propellant vehicle with 12%w/w ethanol as cosolvent and 0.024%w/w hydrochloric acid (1M) as stabiliser. The formulation was packed in cans fitted with 50 μ l valves and fired using a 0.30 mm actuator. Aerodynamic particle size assessments were conducted using an Andersen Cascade Impactor fitted with a USP induction port at the beginning and end of can-use life from each of two batches. Each determination was obtained by sampling 15 consecutive doses at a sampling

flow rate of 28.3l/min. For each can tested the delivered dose was determined using DUSA methodology (Dose Unit Spray Apparatus) at the beginning, middle and end of can-use life. Quantification of BDP and FF within test samples was performed using a HPLC method. Metered dose, delivered dose, fine particle dose, fine particle fraction, mass median aerodynamic diameter (MMAD), and geometric standard deviation (GSD) for each impactor measurement were calculated.

Aerosol performances derived from impactor measurements are summarised in Table 1. For BDP and FF respectively, the mean delivered dose values obtained from the impactor measurements were within 95 to 100% and 91 to 101% of the mean values obtained using DUSA methodology. The consistency in the fine particle fraction (both $\leq 5 \mu\text{m}$ and $\leq 1 \mu\text{m}$), MMAD and GSD for BDP and FF is a consequence of the similar particle size distributions of the two drugs as shown in Fig. 1 (not statistically significantly different).

Table 1: Summary of Aerosol Performances. Data represents Mean $\pm$ SD; (n = 4)

Drug	BDP	FF
Metered Dose, MD (μg)	94.5 $\pm$ 2.3	5.4 $\pm$ 0.3
Delivered Dose (μg)	87.0 $\pm$ 2.2	4.9 $\pm$ 0.3
Fine particle dose $\leq 5 \mu\text{m}$ (μg)	34.5 $\pm$ 1.1	1.9 $\pm$ < 0.1
Fine particle fraction $\leq 5 \mu\text{m}$ (%)	39.7 $\pm$ 2.2	38.6 $\pm$ 2.2
Fine particle dose $\leq 1 \mu\text{m}$ (μg)	11.1 $\pm$ 0.2	0.6 $\pm$ < 0.1
Fine particle fraction $\leq 1 \mu\text{m}$ (%)	12.8 $\pm$ 0.4	11.8 $\pm$ 0.5
MMAD (μm)	1.4 $\pm$ < 0.1	1.5 $\pm$ < 0.1
GSD	2.0 $\pm$ 0.1	2.0 $\pm$ 0.1
Shot Weight (mg)	54.0 $\pm$ 1.3	

Table 2 presents the mean drug deposition for samples containing > 5% of the metered dose, the total being representative of 94.5 $\pm$ 5.4% of the total

metered drug mass. The ratio of BDP to FF presented in Table 2, expressed as mean and standard deviation, is 17.6 ± 0.3 , which is consistent with the ratio of metered BDP and FF (17.6 ± 0.6). The consistent ratio of the drug masses over the size fractions implies that each particle generated during the atomisation process contains drug concentrations consistent with the liquid properties of the product's solution formulation, and that this consistency is maintained for the residual particles following excipient evaporation, such that the measured particle size distributions for both resident drugs are identical.

Table 2: ACI stage-by-stage deposition. Data represents Mean $\pm$ SD; (n = 4)

Deposition site	BDP (μ g)	FF (μ g)	Ratio: BDP/FF
Actuator	7.5 ± 0.3	0.43 ± 0.03	17.6
Induction Port	49.5 ± 3.2	2.89 ± 0.23	17.1
Stage 4 (2.1 – 3.3 μ m)	5.9 ± 0.3	0.33 ± 0.01	17.8
Stage 5 (1.1 – 2.1 μ m)	14.2 ± 0.8	0.80 ± 0.03	17.7
Stage 6 (0.65 – 1.1 μ m)	6.4 ± 0.3	0.36 ± 0.01	17.8
Total:	83.6 ± 4.9	4.82 ± 0.32	Mean $\pm$ SD: 17.6 ± 0.3

Example 2. Solution combination containing carmoterol hydrochloride (TA 2005) as LABA and budesonide (BUD) as ICS.

The LABA TA 2005 is present in the combination at a strength 1 μ g/dose per actuation while budesonide is present at 100 μ g /dose per actuation within an acidified ethanol solution pressurized with HFA 134a. Aerodynamic assessment of fine particles was performed by sampling 10 consecutive doses from each pMDI into an ACI. The impactor was fitted with a USP induction port and operated at a sampling flow rate of 28.3 l/min. Three pMDIs were tested (from the beginning, middle, and end of batch) and were

tested at the beginning and end of life. Drug deposition within the impactor was quantified using an HPLC assay. The fine particle dose (FPD) was determined by summation of the drug collected on the ACI stages between S3 and filter.

5 Table 3 summarizes the deposition of TA 2005 and budesonide on the individual stages of the ACI, while Table 4 summarizes the aerosol performances.

The nominal dose of the combination pMDI was 1 μ g TA 2005: 100 μ g budesonide. Figure 2 summarizes these results expressed as the % metered
10 dose.

Table 3: ACI stage-by-stage deposition. Data represents Mean $\pm$ SD; (n=6)

Deposition site	TA 2005 (μ g)	BUD (μ g)		Ratio: BUD/TA 2005
Actuator	0.08 $\pm$ 0.02	6.68 $\pm$ 1.14		83.5
Induction port	0.40 $\pm$ 0.03	38.16 $\pm$ 2.29		95.4
Stage 4	0.05 $\pm$ 0.01	5.45 $\pm$ 0.83		109.0
Stage 5	0.18 $\pm$ 0.02	18.5 $\pm$ 1.83		102.8
Stage 6	0.11 $\pm$ 0.01	10.8 $\pm$ 0.75		98.2
			Mean $\pm$ SD:	97.8 $\pm$ 9.5

Table 4: Summary of Aerosol Performances. Data represents Mean
15 $\pm$ SD (n=6)

Drug	BUD	TA 2005
Delivered Dose (μ g)	89.7 $\pm$ 3.2	089 $\pm$ 0.03
Fine particle dose $\leq 5\mu$ m (μ g)	47.1 $\pm$ 2.7	0.45 $\pm$ 0.03
Fine particle fraction $\leq 5\mu$ m (%)	52.5 $\pm$ 2.3	51.0 $\pm$ 3.0

The results demonstrate that the solution combination of the example provides fine particle fractions for the two components which are not statistically significantly different (p<0.05), despite the significantly different

concentration of the two active drugs in the aerosol cloud. The ratio between the two active drugs is maintained in all the ACI stages allowing their co-deposition in the lungs, which could offer an increased opportunity for any synergistic interaction to occur.

- 5 Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that, within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

CLAIMS

1. Use of a pressurized solution formulation for metered dose inhalers containing two or more active drug substances in a predetermined ratio
5 dissolved in an HFA propellant and a co-solvent for the manufacture of a medicament for the prevention and/or treatment of a severe broncho-pulmonary disease wherein substantially all of the liquid particles emitted on actuation of said inhaler contain said two or more active drug substances in a ratio which is substantially the same as said predetermined ratio of said two or
10 more active drug substances in said medicament and the two or more active drug substances are delivered with substantially the same particle size distribution.
2. The use according to claim 1, wherein one of the active drug substance is a beta₂-agonist.
- 15 3. The use according to claim 2 wherein the beta₂-agonist is selected from the group consisting of formoterol, carmoterol, indacaterol, salmeterol, stereoisomers, a salt thereof, a solvate thereof, a solvate of a salt thereof, and mixtures thereof.
4. The use according to claim 3 wherein the beta₂-agonist is formoterol
20 fumarate.
5. The use according to claim 3 wherein the beta₂-agonist is carmoterol hydrochloride.
6. The use according to anyone of claims 1 to 5, wherein the medicament also comprises an inhaled corticosteroid.
- 25 7. The use according to claim 6, wherein said corticosteroid is selected from the group consisting of beclomethasone dipropionate, fluticasone propionate, budesonide, the 22R-epimer of budesonide, rofleponide, ciclesonide, mometasone furoate, triamcinolone, an ester of triamcinolone,

and mixtures thereof.

8. The use according to claim 7, wherein the corticosteroid is beclomethasone dipropionate or budesonide.

9. The use according to anyone of the preceding claims, wherein the
5 medicament also comprises an anticholinergic atropine-like derivative or an antimuscarinic M3 inhibitor.

10. The use according to claim 9, wherein the anticholinergic atropine-like derivative is at least one member selected from the group consisting of ipratropium bromide, oxitropium bromide, tiotropium bromide,
10 glycopyrronium bromide, and mixtures thereof.

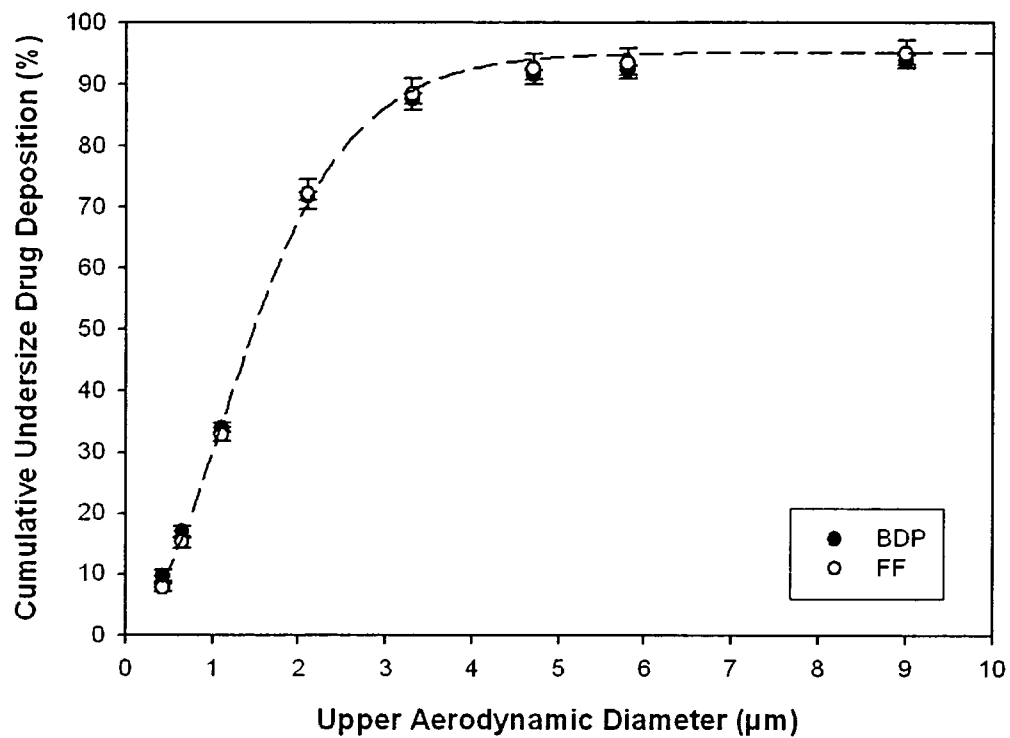
11. The use according to anyone of the preceding claims wherein the cosolvent is ethanol and its amount is comprised between 5% and 20% w/w.

12. The use according to anyone of the preceding claims wherein the broncho-pulmonary disease is severe persistent asthma

15 13. The use according to anyone of the claims 1 to 12 wherein the broncho-pulmonary disease is severe or very severe chronic obstructive pulmonary disease (COPD).

14. Use of a pressurized solution formulation for metered dose inhalers containing two or more active drug substances in a predetermined ratio
20 dissolved in an HFA propellant and not more than 20% w/w ethanol as a co-solvent wherein substantially all of the liquid particles emitted on actuation of said inhaler contain said two or more active drug substances in a ratio which is substantially the same as said predetermined ratio of said two or more active drugs as well as the two or more active drug substances are
25 delivered with substantially the same particle size for improving the co-deposition of said drugs in the lung tract of a patient.

Sheet 1/2

Figure 1: Cumulative % Undersize BDP and FF Mass Distributions

Sheet 2/2

Figure 2: Percentage (of Metered Dose) ACI Stage by Stage deposition of LABA and ICS. Bars represents Mean $\pm$ SD; (n=6)

