

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 January 2012 (26.01.2012)

PCT

(10) International Publication Number
WO 2012/010854 A1

(51) International Patent Classification:

A61K 31/46 (2006.01) *A61K 45/06* (2006.01)
A61K 31/4704 (2006.01) *A61K 9/00* (2006.01)
A61K 31/56 (2006.01) *A61P 11/06* (2006.01)
A61K 31/573 (2006.01) *A61P 11/00* (2006.01)

(21) International Application Number:

PCT/GB2011/001114

(22) International Filing Date:

25 July 2011 (25.07.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2105/MUM/2010	23 July 2010 (23.07.2010)	IN
2219/MUM/2010	4 August 2010 (04.08.2010)	IN
2346/MUM/2010	20 August 2010 (20.08.2010)	IN
69/MUM/2011	10 January 2011 (10.01.2011)	IN

(71) Applicant (for all designated States except US): **CIPLA LIMITED** [IN/IN]; Mumbai Central, Mumbai 400 008 (IN).

(71) Applicant (for MW only): **CURTIS, Philip, Anthony** [GB/GB]; A.A. Thornton & Co, 235 High Holburn, London (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MALHOTRA, Geena** [IN/IN]; 4 Anderson House, Opposite Mazgaon Post Office, Mazgaon, Mumbai 400 010, Maharashtra (IN). **PURANDARE, Shrinivas, Madhukar** [IN/IN]; B/25, Naperol Towers, Opposite R.A. Kidwai Road, Oppo-

site Gyaneshwar Vidyalaya, Wadala, Mumbai 400 031, Maharashtra (IN). **LULLA, Amar** [IN/IN]; 131 Maker Towers "L", 13th Floor, Cuffe Parade, Colaba, Mumbai 400 005, Maharashtra (IN).

(74) Agent: **CURTIS, Philip, Anthony**; A A Thornton & Co, 235 High Holborn, London WC1V 7LW (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, 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, KM, 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, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

Published:

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

(54) Title: INHALATION FORMULATIONS COMPRISING CARMOTEROL IN COMBINATION WITH A CORTICOSTEROID

(57) Abstract: A pharmaceutical composition comprising carmoterol in combination with a corticosteroid selected from fluticasone, ciclesonide or mometasone, and, optionally, one or more pharmaceutically acceptable excipients.



WO 2012/010854 A1

INHALATION FORMULATIONS COMPRISING CARMOTEROL IN COMBINATION WITH A
CORTICOSTEROID

FIELD OF INVENTION:

- 5 The present invention relates to pharmaceutical compositions for inhalation. There is also provided a process for preparing the compositions and use thereof in the treatment and / or prevention of respiratory, inflammatory or obstructive airway disease.

BACKGROUND OF INVENTION:

10

Asthma and chronic obstructive pulmonary disease (COPD) are the very common conditions which affect many people. Airflow obstruction is the main characteristic feature in each of these airway diseases and the medications utilized in the treatment are also often similar.

- 15 Asthma is a chronic inflammatory disorder of the airways associated with airway hyper responsiveness, which leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are associated with variable airflow obstruction within the lung which is often reversible, either spontaneously or with treatment.

- 20 Chronic obstructive pulmonary disease (COPD) is a severe respiratory condition that is increasingly prevalent worldwide. In India, the estimated prevalence is about 12.36 million. It is currently the fourth leading cause of death in the UK & US, and predicted to rank third in the global impact of disease by the year 2020.

- 25 Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterized by air flow limitation that is not fully reversible. The airflow obstruction is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs it also produces significant systemic consequences. COPD is associated with mucus
30 hyper secretion, emphysema, bronchiolitis.

Therapy for the treatment and/or prevention of asthma and chronic obstructive pulmonary disease (COPD) currently includes the use of bronchodilators such as beta₂-agonists, anticholinergics and steroids.

More specifically asthma, COPD and other related disorders have been known to be treated with beta₂-agonist as they provide a bronchodilator effect, resulting in relief from the symptoms of breathlessness. Beta₂-agonists can be short acting for immediate relief, or long acting for long term prevention of asthma symptoms.

5

Long acting β₂-agonists improve lung function, reduce symptoms and protect against exercise-induced dyspnea in patients with asthma and COPD. Long acting β₂-agonists induce bronchodilation by causing prolonged relaxation of airway smooth muscle. In addition to prolonged bronchodilation, long acting β₂-agonists (LABAs) exert other effects such as
10 inhibition of airway smooth-muscle cell proliferation and inflammatory mediator release, as well as non smooth-muscle effects, such as stimulation of mucociliary transport, cytoprotection of the respiratory mucosa and attenuation of neutrophil recruitment and activation.

15 Further, use of a long acting β₂-agonist reduces the frequency of drug administration.

Currently available long acting beta₂-agonists (LABAs) include salmeterol and formoterol.

Even though it is known that beta₂-agonists provide a symptomatic relief in
20 bronchoconstriction, another component of asthma, which is inflammation, requires separate treatment such as steroid. Most of the inhaled corticosteroids need to be administered in multiple dosage regimens.

Inhaled corticosteroids (ICS) are the mainstay of asthma management and are used in almost
25 all patients with persistent asthma. Many patients with persistent asthma can be controlled with the use of regular inhaled corticosteroids (ICS) therapy. Corticosteroids are known to exhibit inhibitory effect on inflammatory cells as well as inflammatory mediators involved in the pathogenesis of respiratory disorders.

30 However, a considerable proportion of patients treated with inhaled corticosteroids (ICS) have been found to remain symptomatic, despite the use of low to moderate doses of inhaled corticosteroids (ICS).

Also, use of these corticosteroids, especially in children, has been limited due to their potential side effects. In children and teenagers, these medicines can prohibit or slow down growth and may affect the function of adrenal glands. Another possible problem in children is that these corticosteroids may cause infections such as chickenpox and measles.

Other side effects that are always feared with the use of these corticosteroids are that they cause suppression of the Hypothalamic-Pituitary-Adrenal (HPA) axis, produces adverse effects on the bone growth in children and on the bone density in the elderly, ocular complications (cataract formation and glaucoma) and skin atrophy. In elderly people, corticosteroids may seem to increase the risk of high blood pressure and bone diseases. Bone associated diseases by using corticosteroids are especially more likely to occur in elderly females.

15

Thus the therapeutic options in the treatment of asthma chronic obstructive pulmonary disease (COPD) which are not adequately controlled by the use of low to moderate doses of ICS are either to increase the dose of the inhaled corticosteroid (ICS) or to combine the therapy of an inhaled corticosteroid (ICS) with bronchodilators such as beta₂-agonists and/or anticholinergics.

20

Currently available corticosteroids include beclomethasone, budesonide, fluticasone, mometasone, ciclesonide and triamcinolone.

Anticholinergic agents also act as bronchodilators and are potential alternatives to beta agonists. However, anticholinergics can also be administered along with beta₂-agonists (LABAs) for the management of asthma. Anticholinergics act by competing with acetylcholine for the receptor sites at vagus nerve or nerve-muscle junctions. This prevents the transmission of reflexes that are induced by asthma stimuli.

30

Use of anticholinergics provides an advantage in elderly patients as the responsiveness of β_2 -agonists declines with old age. Further it would be advantageous to use in patients who are intolerant to the use of beta₂-agonists.

Further, anticholinergics can also be used in patients suffering from nocturnal asthma, chronic asthma with concurrent fixed way obstruction, intrinsic asthma and also in patients with asthma of longer duration.

5

Although combination therapy of a bronchodilator with an inhaled corticosteroid improves pulmonary efficiency, reduces inflammatory response and provides symptomatic relief as compared to higher doses of inhaled corticosteroid alone in patients affected by respiratory disorders such as asthma, the selection of a specific bronchodilator and inhaled corticosteroid
10 plays a very important role in formulation of fixed dose combinations.

Additionally, it simplifies the therapy, reduces the cost and also provides control of respiratory disorders. Reducing the dose frequency to the minimum is a main step in simplifying asthma management for improving patient adherence to the therapy.

15

Currently, there are several approved combinations of long-acting beta agonist (LABA) and inhaled corticosteroid (ICS). Some of these approved combinations for the treatment of asthma and chronic obstructive pulmonary disease (COPD) are salmeterol / fluticasone propionate (Advair diskus, Advair HFA), and formoterol fumarate dihydrate / budesonide
20 (Symbicort).

Most of the available combinations of a long-acting beta agonist (LABA) with inhaled corticosteroid (ICS) have to be administered twice daily.

25 Even from the patient compliance point of view, the treatment calls for the patient to comply with different dosage regimens, different frequencies of administration, etc.

Efforts to improve compliance have always been aimed at by, simplifying the medication packaging, providing effective medication reminders, improving patient education, and
30 limiting the number of medications prescribed simultaneously.

US20050059643 discloses a composition of a steroid and a betamimetic such as carmoterol.

5.

EP1787639 discloses an aerosol solution of a beta-agonist of the phenylalkylamino class and a steroid.

EP1452179 discloses a combination preparation of carmoterol and a corticosteroid.

5

EP1834643 discloses a combined preparation of carmoterol and an active ingredient for simultaneous, sequential or separate use in the treatment of inflammatory or obstructive airway disease.

10 EP1603565 discloses a composition of carmoterol and budesonide with a weight ratio from 1:1000 to 1:50.

US2009088408 discloses pharmaceutical compositions of anticholinergics, corticosteroids and betamimetics and their use in the treatment of respiratory diseases.

15

US2005042174 discloses a combination of doses of a beta₂-agonist, an anticholinergic agent and an anti-inflammatory steroid.

WO2006105401 discloses anticholinergic in combination with a corticosteroid, and a long
20 acting beta agonist, for simultaneous or sequential administration in the prevention or treatment of a respiratory, inflammatory or obstructive airway disease.

Further selecting a combination of a long-acting beta₂ agonist (LABA) and an inhaled corticosteroid (ICS) is critical since both drugs should be capable of being administered once
25 daily. A treatment method where a long-acting beta₂ agonist (LABA) is required to be administered once daily and an inhaled corticosteroid (ICS) is required to be administered twice daily or vice versa will not be useful since the purpose of once a day treatment is defeated.

30 However, none of the above prior art specifically discloses the combination of carmoterol with fluticasone furoate or carmoterol with ciclesonide or carmoterol with mometasone furoate or carmoterol with fluticasone furoate and tiotropium. Moreover, none of these mention or disclose that the combination of carmoterol with fluticasone furoate or carmoterol

with ciclesonide or carmoterol with mometasone furoate or carmoterol with fluticasone furoate and tiotropium can be administered once daily for the prevention or treatment of respiratory, inflammatory or obstructive airway disease.

- 5 There remains a need to formulate a pharmaceutical composition which simplifies the dosage regimen, preferably by administering a once a day, composition for the treatment of these respiratory disorders.

OBJECT OF THE INVENTION:

10

The object of the present invention is to provide a pharmaceutical composition comprising one or more bronchodilators and one or more inhaled corticosteroids (ICS) for administration in the prevention or treatment of respiratory, inflammatory or obstructive airway disease.

- 15 Another object of the present invention is to provide such a pharmaceutical composition for once daily administration for the prevention or treatment of respiratory, inflammatory or obstructive airway disease.

- Yet another object of the present invention is to provide a process for preparing the
20 pharmaceutical composition comprising one or more bronchodilators and one or more inhaled corticosteroids (ICS) for administration in the prevention or treatment of respiratory, inflammatory or obstructive airway disease.

- A further object of the present invention is to provide a method for prophylaxis or treatment
25 of asthma, COPD or a related respiratory disorder which comprises administering a pharmaceutical composition comprising one or more bronchodilators and one or more inhaled corticosteroids (ICS).

SUMMARY OF THE INVENTION:

30

According to a first aspect of the present invention, there is provided a pharmaceutical composition comprising one or more bronchodilators and one or more inhaled corticosteroids (ICS). Preferably the composition further comprises one or more anticholinergics.

According to a second aspect of the present invention, there is provided a process for preparing pharmaceutical composition comprising carmoterol and fluticasone, especially an ester of fluticasone, in particular fluticasone furoate.

5

According to a third aspect of the present invention, there is provided a pharmaceutical composition comprising carmoterol and ciclesonide.

According to a fourth aspect of the present invention, there is provided a pharmaceutical
10 composition comprising carmoterol and mometasone.

According to a fifth aspect of the present invention, there is provided a pharmaceutical composition comprising carmoterol, tiotropium and fluticasone, especially an ester of fluticasone, in particular fluticasone furoate .

15

According to a sixth aspect of the present invention, there is provided a process for preparing the pharmaceutical compositions described above.

According to a seventh aspect of the present invention, there is provided a method for
20 prophylaxis or treatment of asthma, COPD or a related respiratory disorder which comprises administering a pharmaceutical compositions described above.

According to a eighth aspect of the present invention there is provided the use of the pharmaceutical compositions described above in treating disorders or conditions that respond
25 to, or are prevented, ameliorated or eliminated by, the administration of a long-acting beta agonist (LABA) and inhaled corticosteroid (ICS).

DETAILED DESCRIPTION OF THE INVENTION:

30 Drug therapy with a long-acting beta agonist (LABA) and inhaled corticosteroid (ICS) has been recommended for the prevention or treatment of respiratory, inflammatory or obstructive airway disease such as asthma and chronic obstructive pulmonary disease (COPD).

Further, there is a need to formulate a composition which can be administered once daily for the prevention of conditions that respond to, or are prevented, ameliorated or eliminated by, the administration of a long-acting beta agonist (LABA) and inhaled corticosteroid (ICS).

5

Preferably the bronchodilator includes one or more long acting beta agonists (LABA). Preferably the bronchodilator further includes one or more anticholinergics.

It is a particular feature of the invention to provide a pharmaceutical composition comprising
10 carmoterol in combination with one or more corticosteroids, wherein the corticosteroid is selected from fluticasone, mometasone and ciclesonide, along with one or more optional pharmaceutically acceptable excipients.

It is an advantageous feature of the present invention to provide the composition with an anti-
15 cholinergic, which is preferably tiotropium.

Specific pharmaceutical compositions according to the invention include:

- A corticosteroid comprising fluticasone in combination with a beta2-agonist comprising
20 carmoterol.

- A corticosteroid consisting of fluticasone in combination with a beta2-agonist consisting of carmoterol.

25 - A corticosteroid comprising fluticasone in combination with a beta2-agonist comprising carmoterol and an anti-cholinergic comprising tiotropium.

- A corticosteroid consisting of fluticasone in combination with a beta2-agonist consisting of carmoterol and an anti-cholinergic consisting of tiotropium.

30

- A corticosteroid comprising ciclesonide in combination with a beta2-agonist comprising carmoterol.

- A corticosteroid consisting of ciclesonide in combination with a beta2-agonist consisting of carmoterol.

- A corticosteroid comprising mometasone in combination with a beta2-agonist comprising
5 carmoterol.

- A corticosteroid consisting of mometasone in combination with a beta2-agonist consisting of carmoterol.

10 In the above compositions, the fluticasone may be provided as the ester of fluticasone, in particular the furoate or the valerate or propionate.

The invention also encompasses methods of preparing the pharmaceutical compositions according to the invention and their use in respiratory, inflammatory or obstructive airway
15 diseases.

It has been surprisingly found that carmoterol in combination with fluticasone furoate provides relief from respiratory disorders, while simultaneously reducing the frequency of dosage administration.

20

The present invention thus provides a novel combination for inhalation comprising carmoterol in combination with fluticasone furoate for the prevention or treatment of respiratory, inflammatory or obstructive airway disease while simultaneously reducing the frequency of dosage administration.

25

In this specification, the term "carmoterol" is used in a broad sense to include not only "carmoterol" *per se* but also any pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable
30 polymorphs, and pharmaceutically acceptable prodrugs thereof. For example, the carmoterol may be carmoterol hydrochloride.

Carmoterol, chemically known as 8-hydroxy-5 - (1-hydroxy-2-(N-(2-(4-methoxy:phenyl) -1-methyl:ethyl) amino)ethyl)-2 (1H)-quinolinone hydrochloride salt is a long acting beta₂-agonist characterized by having a rapid onset of action, similar to that of salbutamol and formoterol, prolonged duration of action up to 30 hours, and also having a high selectivity
5 towards the beta₂ adrenoreceptor. Further more carmoterol is more potent than other long acting β₂-agonists such as formoterol, and salmeterol.

In this specification, the term “fluticasone” is used in a broad sense to include not only “fluticasone” per se but also any pharmaceutically acceptable salts, pharmaceutically
10 available esters, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs, and pharmaceutically acceptable prodrugs thereof. Further, the term and “fluticasone furoate” is used in a broad sense to include not only “fluticasone furoate” per se but also any pharmaceutically acceptable salts, pharmaceutically
15 acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs, and pharmaceutically acceptable prodrugs thereof.

Fluticasone is currently commercially available as a furoate salt and a propionate salt.
20 Fluticasone furoate is a corticosteroid which substantially overcomes the potential side effects that are generally produced by the use of conventional corticosteroids. Moreover fluticasone furoate exhibits a 1.7 times higher binding affinity for the human glucocorticoid receptor as compared to that of fluticasone propionate and also provides prolonged protection up to 26 hours against airway hyperresponsiveness as compared to fluticasone propionate.

25

Fluticasone furoate has a longer duration of action with an elimination half life of 15.1 hrs.

Fluticasone furoate is a synthetic fluorinated corticosteroid that has been developed as an intranasal treatment for patients with symptoms of rhinitis and has an enhanced affinity
30 towards the glucocorticoid receptor.

Fluticasone furoate and carmoterol mainly act on two different components of asthma exhibiting a complimentary action. Chronic inflammation which is commonly associated

with asthma is managed by fluticasone furoate while other aspects of asthma, such as abnormalities in bronchial smooth muscle are improved, by carmoterol.

Further, fluticasone furoate has greater potency than other clinically used corticosteroids for the glucocorticoid receptor and against the proinflammatory transcription factors nuclear factor κ B (NF- κ B), activation protein-1, and tumor necrosis factor- induced interleukin-8 cytokine production.

As noted above, fluticasone furoate has a longer duration of action with an elimination half life of 15.1 hrs. Carmoterol has a longer duration of action up to 30 hrs.

Hence, the combination of fluticasone furoate with carmoterol provides a novel combination which has the convenience of once daily administration for patients of asthma and COPD.

Although carmoterol is administered once daily and fluticasone propionate is administered twice daily it may be possible to use half dose of carmoterol along with Fluticasone propionate.

Thus another embodiment of the present invention provides a novel combination for inhalation comprising carmoterol in combination with fluticasone propionate, wherein the combination is administered twice daily.

Yet another embodiment of the present invention provides a novel combination for inhalation comprising carmoterol in combination with an ester of fluticasone, wherein the combination is administered once daily.

Further, combination of fluticasone furoate and carmoterol exhibits a synergistic activity, in which fluticasone furoate helps in increasing the activity of carmoterol; at the same time carmoterol helps in improving the efficacy of fluticasone furoate.

According to the present invention, carmoterol may be present in the in the amount of about 0.5mcg to 10mcg.

According to the present invention, an ester of fluticasone may be present in the in the amount of about 0.5 mcg to 800mcg.

According to one embodiment of the present invention the pharmaceutical composition may
5 comprise carmoterol and fluticasone furoate with one or more pharmaceutically acceptable excipients.

It has further been surprisingly found that carmoterol in combination with ciclesonide provides relief from respiratory disorders, while simultaneously reducing the frequency of
10 dosage administration.

The present invention thus provides a novel combination for inhalation comprising carmoterol in combination with ciclesonide for the prevention or treatment of respiratory, inflammatory or obstructive airway disease while simultaneously reducing the frequency of
15 dosage administration.

In this specification, the term “ciclesonide” are used in a broad sense to include not only “ciclesonide” per se but also any pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable
20 enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs, and pharmaceutically acceptable prodrugs thereof.

Ciclesonide, a non halogenated corticosteroid is a prodrug which is hydrolysed enzymatically by esterases to form its active metabolite desisobutyl ciclesonide in the lung. Further
25 ciclesonide has negligible systemic effects and therefore exhibits a better safety profile.

Ciclesonide and carmoterol mainly act on two different components of asthma exhibiting a complimentary action. Chronic inflammation which is commonly associated with asthma is managed by ciclesonide while other aspects of asthma, such as abnormalities in bronchial
30 smooth muscle are improved, by carmoterol.

Ciclesonide exhibits a longer duration of action due to its lipophilic nature and lipid conjugation property. Carmoterol has a longer duration of action up to 30 hrs.

Hence, the combination of ciclesonide with carmoterol provides a novel combination which has the convenience of once daily administration for patients of asthma and COPD.

- 5 Further, combination of ciclesonide and carmoterol exhibits a synergistic activity, in which ciclesonide helps in increasing the activity of carmoterol; at the same time carmoterol helps in improving the efficacy of ciclesonide.

According to the present invention, carmoterol may be present in the in the amount of about
10 05mcg to 10mcg.

According to the present invention, ciclesonide may be present in the in the amount of about 20mcg to 800mcg.

- 15 According to one embodiment of the present invention the pharmaceutical composition may comprise carmoterol and ciclesonide with one or more pharmaceutically acceptable excipients.

It has further been surprisingly found that carmoterol in combination with mometasone
20 provides relief from respiratory disorders, while simultaneously reducing the frequency of dosage administration.

The present invention thus provides a novel combination for inhalation comprising carmoterol in combination with mometasone for the prevention or treatment of respiratory,
25 inflammatory or obstructive airway disease while simultaneously reducing the frequency of dosage administration.

In this specification, the term “mometasone” is used in a broad sense to include not only “mometasone” *per se* but also any pharmaceutically acceptable salts, pharmaceutically
30 acceptable esters, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs, and pharmaceutically acceptable prodrugs thereof. For example, the mometasone may be mometasone furoate.

Mometasone is a potent synthetic corticosteroid which exhibits a greater binding affinity towards the corticosteroid receptor.

- 5 Mometasone and carmoterol mainly act on two different components of asthma exhibiting a complimentary action. Chronic inflammation which is commonly associated with asthma is managed by mometasone, while, other aspects of asthma, such as abnormalities in bronchial smooth muscle are improved, by carmoterol.
- 10 Hence, the combination of mometasone with carmoterol provides a novel combination which has the convenience of once daily administration for patients of asthma and COPD.

Further, a rapid onset of action of the combination due to carmoterol may increase in patient's confidence in the treatment and subsequently improve compliance to therapy.

15

The combination of mometasone and carmoterol exhibits a synergistic activity, in which mometasone helps in increasing the activity of carmoterol; at the same time carmoterol helps in improving the efficacy of mometasone.

- 20 According to the present invention, carmoterol may be present in the amount of about 1mcg to 4mcg.

According to the present invention, mometasone may be present in the amount of about 50mcg to 800mcg.

25

According to one embodiment of the present invention, the pharmaceutical composition may comprise carmoterol and mometasone with one or more pharmaceutically acceptable excipients.

- 30 As discussed above, the selection of a specific β_2 -agonist, anticholinergic agent and inhaled corticosteroid (ICS) plays a very important role in formulation of fixed dose combinations.

We have also found that a combination therapy of fluticasone furoate, carmoterol and tiotropium is effective for treating inflammatory and/or obstructive diseases of the respiratory tract, particularly asthma or chronic obstructive pulmonary disease (COPD).

- 5 Furthermore, the combination of fluticasone furoate, carmoterol and tiotropium provides a rapid onset of action and improved control of obstructive or inflammatory airway diseases, or reduction in the exacerbations of the diseases.

Another advantage of the combination is that it facilitates the treatment of an obstructive and
10 inflammatory airway disease with a single medicament.

Further, this combination therapy provides for administration by the use of a single inhaler for patients who currently have to make use of multiple inhalers. This is because Fluticasone Furoate can be administered once daily along with Tiotropium as compared to Fluticasone
15 Propionate which is to be administered twice daily. This is particularly important in case of elderly patients who may get confused between the inhalers and who also suffer from several other medical conditions such as heart disease, arthritis etc. and are receiving multiple other medications.

- 20 Thus the present invention provides a pharmaceutical composition comprising fluticasone furoate, carmoterol and tiotropium for once daily administration.

According to another embodiment the present invention provides a pharmaceutical composition comprising fluticasone propionate, carmoterol and tiotropium, preferably for
25 twice daily administration.

According to yet another embodiment the present invention provides a pharmaceutical composition comprising an ester of fluticasone, carmoterol and tiotropium, preferably for once daily administration.

30

Chronic inflammation which is commonly associated with asthma is managed by fluticasone

The anticholinergic used according to the present invention is preferably tiotropium, especially tiotropium bromide, and particularly tiotropium bromide monohydrate.

Tiotropium bromide is an anticholinergic bronchodilator that antagonises muscarinic M1, M2
5 and M3 receptors. Tiotropium, is chemically described as (1 α , 2 β , 4 β , 5 α , 7 β)-7-[(Hydroxydi-
2-thienylacetyl) oxy]-9, 9-dimethyl-3-oxa-9-azoniatricyclo [3.3.1.0^{2,4}] nonane bromide
monohydrate. Tiotropium has a longer duration of action of up to 32 hours. Also tiotropium
exhibits an improvement in dyspnea and ceases the need for rescue therapy.

10 Tiotropium in combination with pulmonary rehabilitation (PR) associated with an increased
exercise endurance time produces clinically meaningful improvements in dyspnea and health
status as compared to pulmonary rehabilitation (PR alone in COPD patients).

Further, tiotropium is more potent than ipratropium in the treatment of patients with COPD in
15 terms of the effect of lung function, dyspnea, exacerbation rates and health status.

Thus the present invention provides a pharmaceutical composition comprising fluticasone
furoate, tiotropium and carmoterol.

20 According to the present invention, an ester of fluticasone may be present in the in the
amount of about 0.5 mcg to 800mcg.

According to the present invention, tiotropium (particularly tiotropium bromide) may be
present in the in the amount of about 2.25mcg to 30mcg.

25

According to the present invention, carmoterol (particularly carmoterol hydrochloride) may
be present in the in the amount of about 0.5mcg to 10mcg.

According to one embodiment of the present invention the pharmaceutical composition may
30 comprise carmoterol and fluticasone furoate, indacaterol and tiotropium with one or more
pharmaceutically acceptable excipients.

The pharmaceutical compositions of the present invention may be administered by any suitable methods used for delivery of the drugs to the respiratory tract. The composition of the present invention may thus be administered as metered dose inhalers (MDI), dry powder inhalers (DPI), nebuliser, nasal spray, nasal drops, insufflation powders.

5

The various dosage forms according to the present invention may comprise one or more pharmaceutically acceptable carriers/excipients suitable for formulating the same.

The metered dose inhalers, according to the present invention may comprise one or more
10 pharmaceutically acceptable excipients such as but not limited to HFC/HFA propellants, co-solvents, bulking agents, non volatile component, buffers/pH adjusting agents, surface active agents, preservatives, complexing agents, or combinations thereof.

Propellants are those which, when mixed with the cosolvent(s), form a homogeneous
15 propellant system in which a therapeutically effective amount of the medicament can be dissolved. The HFC/HFA propellant must be toxicologically safe and must have a vapor pressure which is suitable to enable the medicament to be administered via a pressurized MDI.

20 According to the present invention the HFC/HFA propellants may comprise, one or more of 1,1,1,2-tetrafluoroethane (HFA-134(a)) and 1,1,1,2,3,3,3-heptafluoropropane (HFA-227), difluoromethane (HFC-32), 1,1,1-trifluoroethane HFC-143(a)), 1,1,2,2-tetrafluoroethane HFC-134), and 1,1-difluoroethane HFC-152(a)) and such other propellants which may be known to the person skilled in the art.

25

Co-solvent is any solvent which is miscible in the formulation in the amount desired and which, when added, provides a formulation in which the medicament can be dissolved. The function of the cosolvent is to increase the solubility of the medicament and the excipients in the formulation.

30 According to the present invention the co-solvent may comprise one or more of, C₂-C₆ aliphatic alcohols, such as but not limited, to ethyl alcohol and isopropyl alcohol; glycols such as but not limited to propylene glycol, polyethylene glycols, polypropylene glycols,

glycol ethers, and block copolymers of oxyethylene and oxypropylene; and other substances, such as, but not limited to glycerol, polyoxyethylene alcohols, and polyoxyethylene fatty acid esters; hydrocarbons such as, but not limited to, n-propane, n-butane, isobutane, n-pentane, iso-pentane, neo-pentane, and n-hexane; and ethers such as but not limited to diethyl ether.

- 5 Suitable surfactants may be employed in the aerosol solution formulation meant for administration through metered dose inhalers of the present invention which may serve to stabilize the solution formulation and improve the performance of valve systems of the metered dose inhaler.
- 10 According to the present invention the surfactant may comprise one or more ionic and/or non-ionic surfactant, but not limited to, salts of stearic acids such as magnesium stearate or esters such, as ascorbyl palmitate, isopropyl myristate and tocopherol esters oleic acid, sorbitan trioleate, lecithin, isopropylmyristate, tyloxapol, polyvinylpyrrolidone, polysorbates such as polysorbate 80, Polysorbate 20, Polysorbate 40, vitamin E-TPGS, and macrogol
- 15 hydroxystearates such as macrogol-15-hydroxystearate, acetylated monoglycerides like Myvacet 9-45 and Myvacet 9-08, Polyoxyethylene ethers, ethyloleate, glyceryl trioleate, glyceryl monolaurate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetylalcohol, sterylalcohol, cetylpyridinium chloride, block polymers, natural oils, polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan
- 20 fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides and polyethoxylated fatty alcohols.
- 25 The surfactants may also be selected from the vast class known in the art like oils such as, but not limited to, corn oil, olive oil, cottonseed oil and sunflower seed oil, mineral oils like liquid paraffin, oleic acid and also phospholipids such as lecithin, or sorbitan fatty acid esters like sorbitan trioleate or Tween 20, Tween 60, Tween 80, PEG - 25 Glyceryl trioleate, PVP, citric acid, PFDA (per fluoro-n-decanoic acid).

30

Non- volatile component is all the suspended or dissolved constituents that would be left after evaporation of the solvent.

According to the present invention, the non-volatile component may comprise one or more of monosaccharides such as, but not limited to, glucose, arabinose; disaccharides such as but not limited to lactose, maltose; oligosaccharides and polysaccharides such as, but not limited to, dextran; polyalcohol such, as but not limited to, glycerol, sorbitol, mannitol, xylitol; salts such as but not limited to potassium chloride, magnesium chloride, magnesium sulphate, sodium chloride, sodium citrate, sodium phosphate, sodium hydrogen phosphate, sodium hydrogen carbonate, potassium citrate, potassium phosphate, potassium hydrogen phosphate, potassium hydrogen carbonate, calcium carbonate and calcium chloride.

10

Suitable bulking agents may be employed in metered dose inhalation formulation of the present invention.

According to the present invention, the bulking agent may comprise one or more of saccharides, including monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose, glucose, fructose, ribose, mannose, sucrose, terhalose, lactose, maltose, starches, dextran or mannitol.

Suitable buffers or pH adjusting agents may be employed in the metered dose inhalation formulation of the present invention.

According to the present invention, the buffer or the pH adjusting agent may comprise one or more of organic or inorganic acids such as, but not limited to, citric acid, ascorbic acid, hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid.

25

Suitable preservatives may be employed in the aerosol solution formulation of the present invention to protect the formulation from contamination with pathogenic bacteria.

According to the present invention, the preservative may comprise one or more of benzalkonium chloride, benzoic acid, benzoates such as sodium benzoate and such other preservatives which may be known to the person skilled in the art.

30

Suitable complexing agents may be employed in the aerosol solution formulation of the present invention which is capable of forming complex bonds.

According to the present invention, the complexing agent may comprise one or more of, but
5 not limited to, sodium EDTA or disodium EDTA.

The pharmaceutical composition of the present invention may be administered by a dry powder inhaler (DPI).

10 The pharmaceutically acceptable excipients suitable for dry powder inhalation according to the present invention may be selected from suitable carriers which may comprise one or more of, but not limited to, sugars such as glucose, saccharose, lactose and fructose, starches or starch derivatives, oligosaccharides such as dextrans, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for
15 example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate, etc. lactose, lactitol, dextrates, dextrose, maltodextrin, saccharides including monosaccharides, disaccharides, polysaccharides; sugar alcohols such as arabinose, ribose, mannose, sucrose, trehalose, maltose, dextran.

The pharmaceutical composition of the present invention may be administered by
20 nebulization.

Nebulisation therapy has an advantage over other inhalation therapy, since it is easy to use and does not require co-ordination or much effort .It also works much more rapidly than medicines taken by mouth.

For nebulisers, the composition according to the present invention may comprise suitable
25 excipients such as tonicity agents, pH regulators, chelating agents, tonicity adjusting agents, surfactants, buffer agents in a suitable vehicle.

Isotonicity-adjusting agents, which may be used, may comprise one or more of, but not limited to, sodium chloride, potassium chloride, zinc chloride, calcium chloride and mixtures thereof. Other isotonicity-adjusting agents may also include, but are not limited to, mannitol,
30 glycerol, and dextrose and mixtures thereof.

The pH may be adjusted by the addition of pharmacologically acceptable acids. Pharmacologically acceptable inorganic acids or organic acids may be used for this purpose. Examples of preferred inorganic acids which may be used include one or more of, but not limited to, hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and phosphoric acid or combinations thereof. Examples of particularly suitable organic acids which may be used include one or more of, but not limited to, ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and propionic acid or combinations thereof. Examples of preferred bases which may be used include one or more of, but not limited to, aqueous ammonia solution, ammonium carbonate, sodium borate, sodium carbonate, and sodium hydroxide or combinations thereof..

Complexing/chelating agents according to the present invention may comprise one or more of, but not limited to, editic acid (EDTA) or one of the known salts thereof, e.g. sodium EDTA or disodium EDTA dihydrate (sodium edetate) or combinations thereof.

Suitable surfactants or wetting agents may also be used in the pharmaceutical compositions of the present invention. According to the present invention, surfactant may comprise one or more, but not limited to Polysorbates such as such as polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbate 65, polysorbate 85, sorbitan fatty acid esters such as Span 20, Span 40, Span 60 Span 80, Span 120; sodium lauryl sulfate; polyethoxylated castor oil; polyethoxylated hydrogenated castor oil, sodium dodecyl sulfate (sodium lauryl sulfate), Lauryl dimethyl amine oxide, Docusate sodium, Cetyl trimethyl ammonium bromide (CTAB) Polyethoxylated alcohols, Polyoxyethylene sorbitan, Octoxynol, N, N-dimethyldodecylamine-N-oxide, Hexadecyltrimethylammonium bromide, Polyoxyl 10 lauryl ether, Brij, Bile salts (sodium deoxycholate, sodium cholate), Polyoxyl castor oil, Nonylphenol ethoxylate, Cyclodextrins, Lecithin, Methylbenzethonium chloride. Carboxylates, Sulphonates, Petroleum sulphonates, alkylbenzenesulphonates, Naphthalenesulphonates, Olefin sulphonates, Alkyl sulphates, Sulphates, Sulphated natural oils & fats, Sulphated esters, Sulphated alkanolamides, Alkylphenols, ethoxylated & sulphated, Ethoxylated aliphatic alcohol, polyoxyethylene surfactants, carboxylic esters Polyethylene glycol esters, Anhydrosorbitol ester & it's ethoxylated derivatives, Glycol esters of fatty acids, Carboxylic amides, Monoalkanolamine condensates, Polyoxyethylene fatty acid amides, Quaternary ammonium salts, Amines with amide linkages,

Polyoxyethylene alkyl & alicyclic amines, N,N,N,N tetrakis substituted ethylenediamines 2-alkyl 1- hydroxyethyl 2-imidazolines, N -coco 3-aminopropionic acid/ sodium salt, N-tallow 3 -iminodipropionate disodium salt, N-carboxymethyl n dimethyl n-9 octadecenyl ammonium hydroxide, n-cocoamidethyl n-hydroxyethylglycine sodium salt etc.

5

According to the present invention, the buffer agents may comprise one or more of organic or inorganic acids such as but not limited to citric acid/sodium hydrogensulphate borate buffer, phosphates (sodium hydrogen orthophosphate, disodium hydrogenphosphate), trometamol, acetate buffer, citrate buffer, sodium citrate dehydrate, citric acid monohydrate, sodium
10 dihydrogen phosphate dehydrate, anhydrous disodium hydrogen phosphate or equivalent conventional buffers.

Anti-microbial preservative agent may be added for multi-dose packages.

The compositions according to the present invention may be provided in suitable containers with suitable means enabling the application of the contained formulation to the respiratory
15 tract.

The powder for inhalation intended for administration through DPI may either be encapsulated in capsules of gelatin or HPMC or in blisters or alternatively, the dry powder may be contained as a reservoir either in a single dose or multi-dose dry powder inhalation device.

20

Alternatively, the powder for inhalation intended to be used for DPI may be suspended in a suitable liquid vehicle and packed in an aerosol container along with suitable propellants or mixtures thereof.

Further, the powder for inhalation intended to be used for DPI may also be dispersed in a
25 suitable gas stream to form an aerosol composition.

The MDI composition according to the present invention may be packed in plain aluminium cans or SS (stainless steel) cans. Some aerosol drugs tend to adhere to the inner surfaces, i.e., walls of the cans and valves, of the MDI. This can lead to the patient getting significantly less than the prescribed amount of the active agent upon each activation of the MDI. Coating the

inner surface of the container with a suitable polymer can reduce this adhesion problem. Suitable coatings include fluorocarbon copolymers such as FEP-PES (fluorinated ethylene propylene and polyethersulphone) and PFA-PES (perfluoroalkoxyalkane and polyethersulphone), epoxy and ethylene. Alternatively, the inner surfaces of the cans may be
5 anodized, plasma treated or plasma coated.

It may be well acknowledged to a person skilled in the art that the said pharmaceutical composition, according to the present invention, may further comprise one or more active(s) selected from anticholinergics, antihistamines, antiallergics or leukotriene antagonist or their pharmaceutically acceptable salts, solvates, tautomers, derivatives, enantiomers, isomers,
10 hydrates, prodrugs or polymorphs thereof.

The present invention also provides a process to manufacture the compositions according to the present invention.

15 The present invention provides a process of preparing a metered dose inhalation compositions which process comprises admixing of a pharmaceutically acceptable carrier or excipient with the actives and the propellant and providing the compositions in precrimped cans.

20 The present invention provides a process of preparing a dry powder inhalation compositions which process comprises admixing of a pharmaceutically acceptable carrier or excipient with the actives and providing the compositions to be administered through a dry powder inhaler.

The present invention also provides a process of preparing an inhalation solution/suspension
25 which process comprises dissolving/dispersing the drugs, optionally chelating agents, osmotic agents and any other suitable ingredients in the vehicle and adjusting the pH using a suitable pH adjusting agent.

30 The present invention also provides a method for the treatment in a mammal, such as a human, for treating chronic obstructive pulmonary disease and asthma, which method comprises administration of a therapeutically effective amount of pharmaceutical

compositions according to the present invention. The method of treatment may be characterized in that the pharmaceutical compositions according to the present invention are administered once a day in therapeutically effective amounts.

- 5 The present invention provides a pharmaceutical composition comprising one or more bronchodilators (such as a long-acting beta agonist (LABA)) and an inhaled corticosteroid (ICS) for use in treating disorders or conditions that respond to, or are prevented, ameliorated or eliminated by, the administration of one or more bronchodilators (such as a long-acting beta agonist (LABA)) and inhaled corticosteroid (ICS).

10

The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the present invention.

Example 1

15

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2
2.	Fluticasone furoate	100
3.	HFA227	q.s.

Process:

- 1) Carmoterol and Fluticasone furoate were homogenized with a part quantity of HFA.
- 2) The suspension obtained in step 1 was transferred to the mixing vessel where remaining
20 quantity of HFA was added.
- 3) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 2

25

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2
2.	Fluticasone furoate	100

3.	Lactose	100% of the drug
4.	HFA227	q.s.

Process:

- 1) Carmoterol and Fluticasone furoate were homogenized with lactose and a part quantity of HFA.
- 5 2) The suspension obtained in step 1 was transferred to the mixing vessel where remaining quantity of HFA was added.
- 3) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

10 Example 3

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Fluticasone furoate	100 mcg
3.	PEG400/1000	0.3% of total formulation
4.	PVP K 25	0.001% of total formulation
5.	HFA227	q.s.

Process:

- 1) PVP was dissolved in PEG and part quantity of HFA
- 15 2) The solution obtained in Step 1 was transferred to a mixing vessel.
- 3) Carmoterol and Fluticasone furoate were homogenized with a part quantity of HFA.
- 4) The suspension obtained in step 3 was transferred to the mixing vessel where remaining quantity of HFA was added.
- 5) The resulting total suspension was mixed, recirculated and filled in into pre-crimped
- 20 aluminum cans.

Example 4

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Fluticasone furoate	100 mcg
3.	Ethanol	15-20% of total formulation
4.	Glycerol	1% of total formulation
5.	HCL (0.08N)	pH 2.5 – 3.5
6.	HFA134a	q.s.

Process:

- 1) Glycerol was dissolved in ethanol and required quantity of HCl was added.
- 2) Carmoterol and Fluticasone furoate were dissolved in the solution obtained in step 1.
- 5 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 5

10

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Fluticasone furoate	100 mcg
3.	Ethanol	15-20% of total formulation
4.	HCL (0.08N)	pH 2.5-3.5
5.	HFA134a	q.s.

Process:

- 1) Required quantity of HCl was added to ethanol.
- 2) Carmoterol and Fluticasone furoate were dissolved in the solution obtained in step 1.
- 15 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 6

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Fluticasone furoate	100 mcg
3.	Ethanol	15-20% of total formulation
4.	Citric acid	pH 3 – 4
5.	HFA134a	q.s.

Process:

- 1) Required quantity of citric acid was added to ethanol.
- 2) Carmoterol and Fluticasone furoate were dissolved in the solution obtained in step 1.
- 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

10

Example 7

Sr. No.	Ingredients	Qty / Unit (mg)
1.	Carmoterol Hydrochloride	0.002
2.	Fluticasone Furoate	0.200
3.	Lactose monohydrate IP/Ph.Eur/NF	24.798
	Total	25.000

Process:

- 1) Sifted lactose was co-sifted with carmoterol and fluticasone furoate.
- 2) The mixture obtained in step (1) was blended.

Example 8

Sr. No.	Ingredients	Qty / Unit (mg)
1.	Carmoterol Hydrochloride	0.004

2.	Fluticasone Furoate	0.800
3.	Lactose monohydrate IP/Ph.Eur/NF	24.196
	Total	25.0000

Process:

- 1) Sifted lactose was co-sifted with carmoterol and fluticasone furoate.
- 2) The mixture obtained in step (1) was blended.

5

Example 9

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Ciclesonide	80/160mcg
3.	HFA227	q.s.

Process:

- 10 1) Carmoterol and Ciclesonide were homogenized with a part quantity of HFA.
- 2) The suspension obtained in step 1 was transferred to the mixing vessel where remaining quantity of HFA was added.
- 3) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

15

Example 10

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Ciclesonide	80/160 mcg
3.	Lactose	100% of the drug
4.	HFA227	q.s.

20 **Process:**

- 1) Carmoterol and Ciclesonide were homogenized with lactose and a part quantity of HFA.
 - 2) The suspension obtained in step 1 was transferred to the mixing vessel where remaining quantity of HFA was added.
 - 3) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum
- 5 cans.

Example 11

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Ciclesonide	80/160 mcg
3.	PEG400/1000	0.3% of total formulation
4.	PVP K 25	0.001% of total formulation
5.	HFA227	q.s.

10 Process:

- 1) PVP was dissolved in PEG and part quantity of HFA
 - 2) The solution obtained in Step 1 was transferred to a mixing vessel.
 - 3) Carmoterol and Ciclesonide were homogenized with a part quantity of HFA.
 - 4) The suspension obtained in step 3 was transferred to the mixing vessel where remaining
- 15 quantity of HFA was added.
- 5) The resulting total suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 12

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Ciclesonide	80/160 mcg
3.	Ethanol	15-20% of total formulation
4.	Glycerol	1% of total formulation

5.	HCL (0.08N)	pH 2.5 – 3.5
6.	HFA134a	q.s.

Process:

- 1) Glycerol was dissolved in ethanol and required quantity of HCl was added.
- 2) Carmoterol and Ciclesonide were dissolved in the solution obtained in step 1.
- 5 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 13

10

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Ciclesonide	80/160 mcg
3.	Ethanol	15-20% of total formulation
4.	HCL (0.08N)	pH 2.5-3.5
5.	HFA134a	q.s.

Process:

- 1) Required quantity of HCl was added to ethanol.
- 2) Carmoterol and Ciclesonide were dissolved in the solution obtained in step 1.
- 15 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 14

20

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Ciclesonide	80/160 mcg
3.	Ethanol	15-20% of total

		formulation
4.	Citric acid	pH 3 – 4
5.	HFA134a	q.s.

Process:

- 1) Required quantity of citric acid was added to ethanol.
- 2) Carmoterol and Ciclesonide were dissolved in the solution obtained in step 1.
- 5 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 15

10

Sr. No.	Ingredients	Qty / Unit (mg)
1.	Carmoterol Hydrochloride	0.001
2.	Ciclesonide	0.050
3.	Lactose monohydrate IP/Ph.Eur/NF	24.949
	Total	25.000

Process:

- 1) Sifted lactose was co-sifted with carmoterol and ciclesonide
- 2) The mixture obtained in step (1) was blended.

15

Example 16

Sr. No.	Ingredients	Qty / Unit (mg)
1.	Carmoterol Hydrochloride	0.002
2.	Ciclesonide	0.200
3.	Lactose monohydrate IP/Ph.Eur/NF	24.798
	Total	25.0000

Process:

- 20 1) Sifted lactose was co-sifted with carmoterol and ciclesonide

2) The mixture obtained in step (1) was blended.

Example 17

Sr. No.	Ingredients	Qty / Unit (mg)
1.	Carmoterol Hydrochloride	0.004
2.	Ciclesonide	0.800
3.	Lactose monohydrate IP/Ph.Eur/NF	24.196
	Total	25.0000

5

Process:

- 1) Sifted lactose was co-sifted with carmoterol and ciclesonide
- 2) The mixture obtained in step (1) was blended.

10 Example 18

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Mometasone furoate	100 mcg
3.	HFA227	q.s.

Process:

- 1) Carmoterol and Mometasone were homogenized with a part quantity of HFA.
- 15 2) The suspension obtained in step 1 was transferred to the mixing vessel where remaining quantity of HFA was added.
- 3) The resulting suspension was mixed, recirculated and filled into pre-crimped aluminum cans.

20 Example 19

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg

2.	Mometasone furoate	100 mcg
3.	Lactose	100% of the drug
4.	HFA227	q.s.

Process:

- 1) Carmoterol and Mometasone were homogenized with lactose and a part quantity of HFA.
- 2) The suspension obtained in step 1 was transferred to the mixing vessel where remaining
- 5 quantity of HFA was added.
- 3) The resulting suspension was mixed, recirculated and filled into pre-crimped aluminum cans.

Example 20

10

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Mometasone furoate	100 mcg
3.	PEG400/1000	0.3% of total formulation
4.	PVP K 25	0.001% of total formulation
5.	HFA227	q.s.

Process:

- 1) PVP was dissolved in PEG and part quantity of HFA
- 2) The solution obtained in Step 1 was transferred to a mixing vessel.
- 15 3) Carmoterol and Mometasone were homogenized with a part quantity of HFA.
- 4) The suspension obtained in step 3 was transferred to the mixing vessel where remaining quantity of HFA was added.
- 5) The resulting total suspension was mixed, recirculated and filled into pre-crimped aluminum cans.

20

Example 21

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Mometasone furoate	100 mcg
3.	Ethanol	15-20% of total formulation
4.	Glycerol	1% of total formulation
5.	HCL (0.08N)	pH 2.5 – 3.5
6.	HFA134a	q.s.

Process:

- 1) Glycerol was dissolved in ethanol and required quantity of HCl was added.
- 2) Carmoterol and Mometasone were dissolved in the solution obtained in step 1.
- 5 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled into pre-crimped aluminum cans.

Example 22

10

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Mometasone furoate	100 mcg
3.	Ethanol	15-20% of total formulation
4.	HCL (0.08N)	pH 2.5-3.5
5.	HFA134a	q.s.

Process:

- 1) Required quantity of HCl was added to ethanol.
- 2) Carmoterol and Mometasone were dissolved in the solution obtained in step 1.
- 15 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled into pre-crimped aluminum cans.

Example 23

Sr. No.	Ingredients	Qty / Spray
1.	Carmoterol	2 mcg
2.	Mometasone furoate	100 mcg
3.	Ethanol	15-20% of total formulation
4.	Citric acid	pH 3 – 4
5.	HFA134a	q.s.

Process:

- 5 1) Required quantity of citric acid was added to ethanol.
- 2) Carmoterol and Mometasone were dissolved in the solution obtained in step 1.
- 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled into pre-crimped aluminum cans.

10

Example 24

Sr. No.	Ingredients	Qty / Unit (mg)
1.	Carmoterol	0.002
2.	Mometasone furoate	0.100
3.	Lactose monohydrate IP/Ph.Eur/NF	24.898
	Total	25.000

Process:

- 15 1) Pre-sifted lactose was co-sifted with carmoterol and mometasone
- 2) The mixture obtained in step (1) was blended.

Example 25

Sr. No.	Ingredients	Qty / Unit (mg)
1.	Carmoterol	0.002

36

2.	Mometasone furoate	0.200
3.	Lactose monohydrate IP/Ph.Eur/NF	24.798
	Total	25.0000

Process:

- 1) Pre-sifted lactose was co-sifted with carmoterol and mometasone
- 2) The mixture obtained in step (1) was blended.

5

Example 26

Sr. No.	Ingredients	Qty / Unit (mg)
1.	Carmoterol	0.004
2.	Mometasone furoate	0.400
3.	Lactose monohydrate IP/Ph.Eur/NF	24.596
	Total	25.0000

Process:

- 10 1) Pre-sifted lactose was co-sifted with carmoterol and mometasone
- 2) The mixture obtained in step (1) was blended.

Example 27

Sr. No.	Ingredients	Qty / unit (mg)
1.	Carmoterol Hydrochloride	0.002
2.	Tiotropium bromide monohydrate	0.0225
3.	Fluticasone Furoate	0.100
4.	Lactose monohydrate IP/Ph.Eur/NF	24.8755
	Total	25.000

15

Process:

- 1) Fluticasone furoate, Carmoterol and Tiotropium bromide were sifted with a part quantity of lactose.

- 2) The cosift of step 1 was then sifted with the remaining quantity of lactose and blended.
- 3) The blend of step 2 was then filled in capsules.

Example 28

5

Sr. No.	Ingredients	Qty / unit (mg)
1.	Carmoterol Hydrochloride	0.002
2.	Tiotropium bromide monohydrate	0.0225
3.	Fluticasone Furoate	0.200
4.	Lactose monohydrate IP/Ph.Eur/NF	24.7755
	Total	25.0000

Process:

- 1) Fluticasone furoate, Carmoterol and Tiotropium bromide were sifted with a part quantity of lactose.
- 10 2) The cosift of step 1 was then sifted with the remaining quantity of lactose and blended.
- 3) The blend of step 2 was then filled in capsules.

Example 29

Sr. No.	Ingredients	Qty / unit (mg)
1.	Carmoterol hydrochloride	0.002
2.	Tiotropium bromide monohydrate	0.0225
3.	Fluticasone Furoate	0.400
4.	Lactose monohydrate IP/Ph.Eur/NF	24.5755
	Total	25.0000

15

Process:

- 1) Fluticasone furoate, Carmoterol and Tiotropium bromide were sifted with a part quantity of lactose.
- 2) The cosift of step 1 was then sifted with the remaining quantity of lactose and blended.
- 20 3) The blend of step 2 was then filled in capsules.

Example 30

Sr. No.	Ingredients	Qty /Spray
1.	Fluticasone Furoate	50 mcg
2.	Tiotropium	9 mcg
3.	Carmoterol	1 mcg
4.	HFA134A OR HFA227	q.s

5 Process:

- 1) Fluticasone furoate, Carmoterol and Tiotropium were homogenized with part quantity of HFA.
- 2) The suspension obtained in step 1 was transferred to the mixing vessel where remaining quantity of HFA was added.
- 10 3) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 31

Sr. No.	Ingredients	Qty /Spray
1.	Fluticasone Furoate	50 mcg
2.	Tiotropium	9 mcg
3.	Carmoterol	1 mcg
4.	Lactose	100% of the drug
5.	HFA134A OR HFA227	q.s.

15

Process:

- 1) Fluticasone furoate, Carmoterol and Tiotropium were homogenized with lactose and part quantity of HFA.
- 2) The suspension obtained in step 1 was transferred to the mixing vessel where remaining
- 20 quantity of HFA was added.

3) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 32

5

Sr. No.	Ingredients	Qty /Spray
1.	Fluticasone Furoate	50 mcg
2.	Tiotropium	9 mcg
3.	Carmoterol	1 mcg
4.	PEG400/1000	0.3% of total formulation
5.	PVP K 25	0.001% of total formulation
	HFA134A OR HFA227	q.s.

Process:

- 1) PVP was dissolved in PEG and part quantity of HFA134A or HFA227.
- 2) The solution obtained in Step 1 was transferred to a mixing vessel.
- 10 3) Fluticasone furoate, Carmoterol and Tiotropium were homogenized with a part quantity of HFA.
- 4) The suspension obtained in step 3 was transferred to the mixing vessel where remaining quantity of HFA was added.
- 5) The resulting total suspension was mixed, recirculated and filled in into pre-crimped
- 15 aluminum cans.

Example 32

Sr. No.	Ingredients	Qty /Spray
1.	Fluticasone Furoate	50 mcg
2.	Tiotropium	9 mcg
3.	Carmoterol	1 mcg
4.	Ethanol	15-20% of total formulation
5.	Glycerol	1% of total formulation

6.	HCL (0.08N)	pH 2.5 – 3.5
7.	HFA134a	q.s.

Process:

- 1) Glycerol was dissolved in ethanol and required quantity of HCl was added.
- 2) Fluticasone furoate, Carmoterol and Tiotropium were dissolved in the solution obtained in
5 step 1.
- 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

10 Example 33

Sr. No.	Ingredients	Qty /Spray
1.	Fluticasone Furoate	50 mcg
2.	Tiotropium	9 mcg
3.	Carmoterol	1 mcg
4.	Ethanol	15-20% of total formulation
5.	HCL (0.08N)	pH 2.5-3.5
6.	HFA134a	q.s.

Process:

- 1) Required quantity of HCl was added to ethanol.
- 15 2) Fluticasone furoate, Carmoterol and Tiotropium were dissolved in the solution obtained in step 1.
- 3) The resulting solution was transferred to the mixing vessel where HFA was added.
- 4) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

20

Example 34

Sr. No.	Ingredients	Qty /Spray
---------	-------------	------------

1.	Fluticasone Furoate	50 mcg
2.	Tiotropium	9 mcg
3.	Carmoterol	1 mcg
4.	Ethanol	15-20% of total formulation
5.	Glycerol	1% of total formulation
6.	Citric acid anhydrous	pH 2.5 – 3.5
7.	HFA134a	q.s.

Process:

- 1) Citric acid anhydrous and glycerol were dissolved in ethanol.
- 2) Fluticasone furoate, Carmoterol and Tiotropium were dissolved in the solution obtained in step (1).
- 3) The solution obtained in step (2) was transferred to the main mixing vessel where it was mixed with entire quantity of HFA134a.
- 4) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

10

Example 35

Sr. No.	Ingredients	Qty /Spray
1.	Fluticasone Furoate	50 mcg
2.	Tiotropium	9 mcg
3.	Carmoterol	1 mcg
4.	Ethanol	15-20% of total formulation
5.	Citric acid anhydrous	pH 2.5 – 3.5
6.	HFA134a	q.s.

Process:

- 1) Citric acid anhydrous was dissolved in ethanol.
- 2) Fluticasone furoate, Carmoterol and Tiotropium were dissolved in the solution obtained in step (1).

3) The solution obtained in step (2) was transferred to the main mixing vessel where it was mixed with entire quantity of HFA134a.

4) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

5

Example 36

Sr. No.	Ingredients	Qty /Spray
1.	Fluticasone Furoate	50 mcg
2.	Tiotropium	9 mcg
3.	Carmoterol	1 mcg
4.	Ethanol	1-2% of total formulation
5.	Lecithin	0.02 of the API
6.	HFA134a or HFA227	q.s.

Process:

10 1) Lecithin was dissolved in ethanol.

2) Tiotropium and Carmoterol were homogenized with part quantity of HFA and transferred to the mixing vessel.

3) Fluticasone furoate was homogenized with lecithin and ethanol.

4) The suspension obtained instep (3) was transferred to the main mixing vessel where the
15 remaining quantity of HFA was added.

5) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 37

20

Sr. No.	Ingredients	Qty /Spray
1.	Fluticasone Furoate	50 mcg
2.	Tiotropium	9 mcg
3.	Carmoterol	1 mcg
4.	Ethanol	1-2% of total

		formulation
5.	Oleic acid	0.02 – 5% of the API
6.	HFA134a or HFA227	q.s.

Process:

- 1) Oleic acid was dissolved in ethanol.
- 2) Tiotropium and Carmoterol were homogenized with part quantity of HFA and transferred
5 to the mixing vessel.
- 3) Fluticasone furoate was homogenized with oleic acid and ethanol.
- 4) The suspension obtained instep (3) was transferred to the main mixing vessel where the remaining quantity of HFA was added.
- 5) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum
10 cans.

Example 38

Sr.No.	Ingredients	Qty (% w/v)
1.	Tiotropium Bromide	0.001
2.	Carmoterol	0.0001
3.	Fluticasone Furoate	0.025
4.	Polysorbate 80	0.02
5.	Sodium Chloride	0.90
6.	Sodium Dihydrogen Phosphate Dihydrate	0.94
7.	Anhydrous Disodium Hydrogen Phosphate	0.175
8.	Disodium Edetate	0.01
9.	Water For Injection	q.s. to 100 ml

Process:

- 1) Sodium chloride, Disodium Edetate, Sodium Dihydrogen Phosphate Dihydrate, Anhydrous Disodium Hydrogen Phosphate and Tiotropium bromide were dissolved in WFI and filtered through sterilizing grade filter to obtain the main bulk.
- 2) Carmoterol , Fluticasone Furoate, Polysorbate 80 and WFI were collected in a pressure vessel and subjected to sterilization by autoclave to obtain slurry.
- 3) The slurry obtained in step (2) was added to the main bulk obtained in step (1).
- 4) Weight was made up with WFI and filled in 2.0ml in LDPE form fill seal ampoules.

Example 39

10

Sr.No.	Ingredients	Qty (% w/v)
1.	Tiotropium Bromide	0.001
2.	Carmoterol	0.0002
3.	Fluticasone Furoate	0.10
4.	Polysorbate 80	0.02
5.	Sodium Chloride	0.90
6.	Sodium Dihydrogen Phosphate Dihydrate	0.94
7.	Anhydrous Disodium Hydrogen Phosphate	0.175
8.	Disodium Edetate	0.01
9.	Water For Injection	q.s. to 100 ml

Process:

- 1) Sodium chloride, Disodium Edetate, Sodium Dihydrogen Phosphate Dihydrate, Anhydrous Disodium Hydrogen Phosphate and Tiotropium bromide were dissolved in WFI and filtered through sterilizing grade filter to obtain the main bulk.
- 2) Carmoterol , Fluticasone Furoate, Polysorbate 80 and WFI were collected in a pressure vessel and subjected to sterilization by autoclave to obtain slurry.
- 3) The slurry obtained in step (2) was added to the main bulk obtained in step (1).
- 4) Weight was made up with WFI and filled in 2.0ml in LDPE form fill seal ampoules.

Example 40

Sr.No.	Ingredients	Qty (% w/v)
1.	Mometasone Furoate	0.025
2.	Carmoterol	0.0001
3.	Polysorbate 80	0.02
4.	Sodium Chloride	0.80
5.	Disodium Edetate	0.01
5.	Citric Acid Monohydrate	0.20
6.	Sodium Citrate Dihydrate	0.28
8.	Water For Injection	q.s. to 100 ml

5

Process:

- 1) Sodium chloride, Disodium Edetate, Citric acid Monohydrate, Sodium Citrate dihydrate were dissolved in WFI and filtered through sterilizing grade filter to obtain the main bulk.
- 2) Carmoterol, Mometasone Furoate, Polysorbate 80 and WFI were collected in a pressure
10 vessel and subjected to sterilization by autoclave to obtain slurry.
- 3) The slurry obtained in step (2) was added to the main bulk obtained in step (1).
- 4) Weight was made up with WFI and filled in 2.0ml in LDPE form fill seal ampoules.

Example 41

15

Sr.No.	Ingredients	Qty (% w/v)
1.	Mometasone Furoate	0.05
2.	Carmoterol	0.0002
3.	Polysorbate 80	0.02
4.	Sodium Chloride	0.80
5.	Disodium Edetate	0.01
5.	Citric Acid Monohydrate	0.20

6.	Sodium Citrate Dihydrate	0.28
8.	Water For Injection	q.s. to 100 ml

Process:

- 1) Sodium chloride, Disodium Edetate, Citric acid Monohydrate, Sodium Citrate dihydrate
5 were dissolved in WFI and filtered through sterilizing grade filter to obtain the main bulk.
- 2) Carmoterol, Mometasone Furoate, Polysorbate 80 and WFI were collected in a pressure vessel and subjected to sterilization by autoclave to obtain slurry.
- 3) The slurry obtained in step (2) was added to the main bulk obtained in step (1).
- 4) Weight was made up with WFI and filled in 2.0ml in LDPE form fill seal ampoules.

10

Example 42

Sr.No.	Ingredients	Qty (% w/v)
1.	Carmoterol	0.0001
2.	Ciclesonide	0.025
3.	Polysorbate 80	0.02
4.	Sodium Chloride	0.80
5.	Disodium Edetate	0.01
5.	Citric Acid Monohydrate	0.12
6.	Sodium Citrate Dihydrate	0.40
7.	Sodium Hydroxide (1 % w/v solution / Hydrochloric acid (1 N Solution)	q.s. to pH
8.	Water For Injection	q.s. to 100 ml

15 Process:

- 1) Sodium chloride, Disodium Edetate, Citric acid Monohydrate, Sodium Citrate dihydrate were dissolved in WFI and filtered through sterilizing grade filter to obtain the main bulk.
- 2) Carmoterol, Ciclesonide, Polysorbate 80 and WFI were collected in a pressure vessel and subjected to sterilization by autoclave to obtain slurry.

- 3) The slurry obtained in step (2) was added to the main bulk obtained in step (1).
 4) Weight was made up with WFI and filled in 2.0ml in LDPE form fill seal ampoules.

Example 43

5

Sr.No.	Ingredients	Qty (% w/v)
1.	Carmoterol	0.0002
2.	Ciclesonide	0.05
3.	Polysorbate 80	0.02
4.	Sodium Chloride	0.80
5.	Disodium Edetate	0.01
5.	Citric Acid Monohydrate	0.12
6.	Sodium Citrate Dihydrate	0.40
7.	Sodium Hydroxide (1 % w/v solution / Hydrochloric acid (1 N Solution)	q.s. to pH
8.	Water For Injection	q.s. to 100 ml

Process:

- 1) Sodium chloride, Disodium Edetate, Citric acid Monohydrate, Sodium Citrate dihydrate
 10 were dissolved in WFI and filtered through sterilizing grade filter to obtain the main bulk.
 2) Carmoterol, Ciclesonide, Polysorbate 80 and WFI were collected in a pressure vessel and
 subjected to sterilization by autoclave to obtain slurry.
 3) The slurry obtained in step (2) was added to the main bulk obtained in step (1).
 4) Weight was made up with WFI and filled in 2.0ml in LDPE form fill seal ampoules.

15

Example 44

Sr.No.	Ingredients	Qty (% w/v)
1.	Carmoterol	0.0001
2.	Fluticasone Furoate	0.025

3.	Polysorbate 80	0.02
4.	Sodium Chloride	0.90
5.	Sodium Dihydrogen Phosphate Dihydrate	0.94
6.	Anhydrous Disodium Hydrogen Phosphate	0.175
7.	Disodium Edetate	0.01
8.	Water For Injection	q.s. to 100 ml

Process:

- 1) Sodium chloride, Disodium Edetate, Sodium Dihydrogen Phosphate Dihydrate, Anhydrous Disodium Hydrogen Phosphate were dissolved in WFI and filtered through
5 sterilizing grade filter to obtain the main bulk.
- 2) Carmoterol, Fluticasone furoate, Polysorbate 80 and WFI were collected in a pressure vessel and subjected to sterilization by autoclave to obtain slurry.
- 3) The slurry obtained in step (2) was added to the main bulk obtained in step (1).
- 4) Weight was made up with WFI and filled in 2.0ml in LDPE form fill seal ampoules.

10

Example 45

Sr.No.	Ingredients	Qty (% w/v)
1.	Carmoterol	0.0002
2.	Fluticasone Furoate	0.10
3.	Polysorbate 80	0.02
4.	Sodium Chloride	0.90
5.	Sodium Dihydrogen Phosphate Dihydrate	0.94
6.	Anhydrous Disodium Hydrogen Phosphate	0.175
7.	Disodium Edetate	0.01
8.	Water For Injection	q.s. to 100 ml

Process:

- 1) Sodium chloride, Disodium Edetate, Sodium Dihydrogen Phosphate Dihydrate, Anhydrous Disodium Hydrogen Phosphate were dissolved in WFI and filtered through
5 sterilizing grade filter to obtain the main bulk.
- 2) Carmoterol, Fluuticasone furoate, Polysorbate 80 and WFI were collected in a pressure vessel and subjected to sterilization by autoclave to obtain slurry.
- 3) The slurry obtained in step (2) was added to the main bulk obtained in step (1).
- 4) Weight was made up with WFI and filled in 2.0ml in LDPE form fill seal ampoules.

10

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and optional features, modification
15 and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or
20 "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates
25 otherwise. Thus, for example, reference to "an excipient" includes a single excipient as well as two or more different excipients, and the like.

CLAIMS:

1. A pharmaceutical composition comprising carmoterol in combination with a corticosteroid selected from fluticasone, ciclesonide and mometasone, and, optionally, one or
5 more pharmaceutically acceptable excipients.
2. A pharmaceutical composition according to claim 1, wherein the corticosteroid is ciclesonide.
- 10 3. A pharmaceutical composition according to claim 1 or 2, wherein ciclesonide is an amount ranging from 20–800mcg.
4. A pharmaceutical composition according to claim 1, wherein the corticosteroid is mometasone.
- 15 5. A pharmaceutical composition according to claim 4, wherein the mometasone is in the form of an ester of mometasone
6. A pharmaceutical composition according to claim 4, or 5, wherein the mometasone is
20 present in an amount ranging from 20–800mcg.
7. A pharmaceutical composition according to claim 1, wherein the corticosteroid is fluticasone.
- 25 8. A pharmaceutical composition according to claim 7, wherein the fluticasone is in the form of an ester of fluticasone.
9. A pharmaceutical composition according to claim 7 or 8, wherein the fluticasone is present in an amount ranging from 0.5 –800mcg.
- 30 10. A pharmaceutical composition according to claim 7, 8 or 9, wherein the fluticasone is in the form of fluticasone furoate.

11. A pharmaceutical composition according to any one of the preceding claims, wherein the carmoterol is present in an amount ranging from 0.5–10mcg.

5 12. A pharmaceutical composition according to any one of the preceding claims, wherein the carmoterol is in the form of carmoterol hydrochloride.

13. A pharmaceutical composition according to any of the preceding claims, comprising carmoterol and fluticasone furoate.

10

14. A pharmaceutical composition according to any of the preceding claims comprising carmoterol and ciclesonide.

15. A pharmaceutical composition according to any of the preceding claims, comprising
15 carmoterol and mometasone.

16. A pharmaceutical composition comprising carmoterol in combination with a corticosteroid, and one or more anticholinergics, optionally with one or more pharmaceutically acceptable excipients.

20

17. A pharmaceutical composition according to claim 16, wherein the corticosteroid is selected from fluticasone, ciclesonide, mometasone.

18. A pharmaceutical composition according to claim 16 or 17, wherein the
25 anticholinergic is tiotropium.

19. A pharmaceutical composition according to claim 18, wherein the tiotropium is present in an amount ranging from 2.25–30mcg.

30 20. A pharmaceutical composition according to claim 18 or 19, wherein the tiotropium is tiotropium bromide.

21. A pharmaceutical composition according to any of the preceding claims, comprising carmoterol, fluticasone furoate and tiotropium.

22. A pharmaceutical composition according to any one of the preceding claims wherein
5 pharmaceutical composition along with any excipients are formulated in a single pharmaceutical composition

23. A pharmaceutical composition according to any one of the preceding claims, formulated as a composition for inhalation.

10

24. A pharmaceutical composition according to any one of claims 1 to 22, formulated for use in a metered dose inhaler.

25. A pharmaceutical composition according to claim 23 or 24, further comprising a
15 propellant.

26. A pharmaceutical composition according to claim 23, 24 or 25, further comprising an excipient selected from a cosolvent, an antioxidant, a surfactant, a bulking agent and a lubricant.

20

27. A pharmaceutical composition according to any one of claims 1 to 22, formulated for use as a dry powder inhalation formulation.

28. A pharmaceutical composition according to claim 27, further comprising at least one
25 finely divided pharmaceutically acceptable carrier suitable for use in dry powder inhalation formulations.

29. A combination composition according to claim 28, wherein said carrier includes a saccharide and/or a sugar alcohol.

30

30. A combination composition according to any one of claims 1 to 22, formulated for use as an inhalation solution/suspension.

31. A combination composition according to claim 30, further comprising an excipient selected from a wetting agent, osmotic agent, a pH regulator, a buffering agent and a complexing agent, provided in a pharmaceutically acceptable vehicle.

5 32. A pharmaceutical composition according to any one of the preceding claims for once daily administration.

33. A pharmaceutical composition according to any one of the preceding claims, for twice daily administration

10

34. A process for manufacturing a pharmaceutical composition according to any one of the preceding claims, comprising combining carmoterol with a corticosteroid selected from fluticasone, ciclesonide or mometasone, and, optionally, one or more pharmaceutically acceptable excipients.

15

35. A process for manufacturing a pharmaceutical composition according to any one of claims 1 to 33 comprising combining carmoterol with a corticosteroid selected from fluticasone, ciclesonide or mometasone, and anticholinergic tiotropium, optionally, one or more pharmaceutically acceptable excipients.

20

36. The use of carmoterol and a corticosteroid selected from fluticasone, ciclesonide or mometasone, in the manufacture of a medicament for the prophylaxis or treatment of a respiratory, inflammatory or obstructive airway disease.

25 37. The use of carmoterol and a corticosteroid selected from fluticasone, ciclesonide or mometasone, and tiotropium, in the manufacture of a medicament for the prophylaxis or treatment of a respiratory, inflammatory or obstructive airway disease.

38. The use according to claim 36 or 37 wherein the fluticasone is provided in the form of
30 fluticasone furoate

39. The use according to claim 36, 37 or 38, wherein said medicament is for once daily administration.

40. The use according to claim 36, 37, 38 or 39, wherein the disease is COPD or asthma.

41. A method of prophylaxis or treatment of a respiratory, inflammatory or obstructive
5 airway disease, comprising administering a therapeutically effective amount of a
pharmaceutical composition according to any one of claims 1 to 33 to a patient in need
thereof.

42. A method according to claim 41, wherein said pharmaceutical composition is
10 administered once daily.

43. A method according to claim 41, wherein said pharmaceutical composition is
administered twice daily

15 44. A method according to claim 41, 42, or 43, wherein the disease is COPD or asthma.

45. A pharmaceutical composition substantially as herein described with reference to the
examples.

20 46. A process for making a pharmaceutical composition substantially as herein described
with reference to the examples.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/001114

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/46 A61K31/4704 A61K31/56 A61K31/573 A61K45/06 A61K9/00 A61P11/06 A61P11/00 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 A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, 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 2008/102128 A2 (CIPLA LTD [IN]; CURTIS PHILIP ANTHONY [GB]; LULLA AMAR [IN]; MALHOTRA) 28 August 2008 (2008-08-28) abstract; claims 1-6, 9,12,15-20,22-36; example 17 -----	1-6,11,12,14-37,39-46		
X	EP 1 944 018 A1 (CHIESI FARMA SPA [IT]) 16 July 2008 (2008-07-16) paragraph [0059]; claims 1-2, 20-23 -----	1-15,22-34,36,38-46		
X	WO 2006/105401 A2 (SCHERING CORP [US]; SEQUEIRA JOEL A [US]; YANG TSONG-TOH [US]) 5 October 2006 (2006-10-05) abstract; claims 1-3, 11-23, 25 ----- -/--	1,4-9,11,15-20,22-46		
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.				
* Special categories of cited documents : <table border="0"> <tr> <td style="vertical-align: top;"> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="vertical-align: top;"> "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 </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family			
Date of the actual completion of the international search 27 September 2011		Date of mailing of the international search report 07/10/2011		
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 Ansaldo, M		

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2011/001114

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2011/048412 A1 (PROSONIX LTD; RUECROFT GRAHAM [GB]; PARIKH DIPESH [GB]) 28 April 2011 (2011-04-28) page 29, paragraph 1; claims 21,23,24,36 page 22, paragraph 1 page 26, paragraph 5 - page 27, paragraph 1 -----	1-15, 22-34, 36,39-46
X,P	WO 2010/097188 A1 (CHIESI FARMA SPA [IT]; COCCONI DANIELA [IT]; MUSA ROSSELLA [IT]; BRAMB) 2 September 2010 (2010-09-02) abstract; claims 1-4,11-14,16-18 -----	1-15, 22-34, 36,39-46

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2011/001114

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008102128 A2	28-08-2008	AU 2008217586 A1	28-08-2008
		CA 2677573 A1	28-08-2008
		CL 5002008 A1	05-09-2008
		EP 2124915 A2	02-12-2009
		EP 2327403 A2	01-06-2011
		JP 2010519195 A	03-06-2010
		KR 20090121338 A	25-11-2009
		PE 17882008 A1	18-12-2008
		US 2010063016 A1	11-03-2010
EP 1944018 A1	16-07-2008	EP 2104490 A2	30-09-2009
		WO 2008084312 A2	17-07-2008
		US 2010055192 A1	04-03-2010
WO 2006105401 A2	05-10-2006	CA 2603433 A1	05-10-2006
		EP 1879620 A2	23-01-2008
		JP 2008534611 A	28-08-2008
		US 2009298802 A1	03-12-2009
WO 2011048412 A1	28-04-2011	NONE	
WO 2010097188 A1	02-09-2010	US 2010269825 A1	28-10-2010