



(51) International Patent Classification:

A61K 45/06 (2006.01) *A61K 31/58* (2006.01)
A61K 31/46 (2006.01) *A61P 11/06* (2006.01)
A61K 31/538 (2006.01) *A61P 11/08* (2006.01)
A61K 31/56 (2006.01) *A61P 11/00* (2006.01)
A61K 31/573 (2006.01)

(21) International Application Number:

PCT/GB2013/000328

(22) International Filing Date:

29 July 2013 (29.07.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2161/MUM/2012 27 July 2012 (27.07.2012) IN

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

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

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: PHARMACEUTICAL COMPOSITION

(57) Abstract: The present invention relates to pharmaceutical compositions for inhalation which comprise one or more bronchodilators and an inhaled corticosteroid. More particularly, the present invention relates to pharmaceutical compositions comprising olodaterol, an inhaled corticosteroid and/or an anticholinergic agent. The present invention also relates to a process for preparing the pharmaceutical composition and use thereof in the treatment and/or prevention of respiratory, inflammatory or obstructive airway disease.



PHARMACEUTICAL COMPOSITION

FIELD OF INVENTION:

The present invention relates to pharmaceutical compositions for inhalation which comprise one or more bronchodilators and an inhaled corticosteroid. More particularly, the present invention
5 relates to pharmaceutical compositions comprising olodaterol, an inhaled corticosteroid and/or an anticholinergic agent. The present invention also relates to a process for preparing the pharmaceutical composition 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 common conditions or ailments 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.

Asthma is a chronic inflammatory disorder of the airways associated with airway hyper
15 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.

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
20 global impact of disease by the year 2020.

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
25 also produces significant systemic consequences. COPD is associated with mucus hypersecretion, 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.

5 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.

10 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 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 β₂-agonists (LABAs) include salmeterol and formoterol.

Even though it is known that β₂-agonists provide a symptomatic relief in 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.

20 Inhaled corticosteroids (ICS) are the mainstay of asthma management and are used in almost 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.

25 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.

- 5 Other side effects that are associated 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
10 corticosteroids are especially more likely to occur in elderly females.

Thus, the therapeutic options in the treatment of asthma and chronic obstructive pulmonary disease (COPD) which are not adequately controlled by the use of low to moderate doses of inhaled corticosteroid (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 β_2 -
15 agonists and/or anticholinergics.

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 β_2 -agonists (LABAs) for the
20 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.

Use of anticholinergic drugs is advantageous in elderly patients since, the responsiveness to β_2 -agonists declines as age increases. Further, it is also advantageous to use in patients who have
25 developed tolerance with the continuous use of β_2 -agonist agents.

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.

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 (Symbicort[®]).

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

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.

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

US20080041370 discloses a propellant-free aerosol formulation comprising olodaterol and an active substance selected from budesonide, beclomethasone, fluticasone and ciclesonide or a metabolite thereof.

- 15 US2008041369 discloses a propellant-free aerosol formulation comprising olodaterol, an active substance selected from budesonide, beclomethasone, fluticasone and ciclesonide or a metabolite thereof and an active substance selected from tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts and trospium salts.

- 20 US20120058980 discloses a combination of olodaterol, ciclesonide, tiotropium and butylhydroxytoluene as an antioxidant.

EP1940409, US20070086957 and US20110135582 disclose a combination of olodaterol and tiotropium in the ratio 1:1 to 10:1.

EP1781298 and, US20050239778 disclose a combination of olodaterol and tiotropium.

EP1781298 discloses the combination of olodaterol and ciclesonide.

US20070088030, US20100009984 and US20110190284 disclose a combination of olodaterol and an active agent selected from tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium and tropium.

Although it is known that, 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, selection of a specific bronchodilator and inhaled corticosteroid plays a very important role in formulation of fixed dose combinations to control respiratory disorders.

- 10 Additionally, it simplifies the therapy and reduces the cost. Reducing the dose frequency to the minimum is a main step in simplifying asthma management for improving patient adherence to the therapy.

- Furthermore, selecting a combination of a long-acting β_2 -agonist (LABA) and an inhaled corticosteroid (ICS) is critical since both drugs should be capable of being administered once daily. So, a treatment method where a long-acting β_2 -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.

Thus, there is still a need to develop or formulate suitable combinations comprising a β_2 -agonist, an inhaled corticosteroid and/or an anticholinergic agent that alleviate asthma and COPD.

- 20 Also, there still exists a need to formulate pharmaceutical compositions comprising a β_2 agonist, an inhaled corticosteroid and/or an anticholinergic agent exhibiting reduced side effects and which can be administered once a day for the treatment of these respiratory disorders.

OBJECT OF THE INVENTION:

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

Another object of the present invention is to provide a pharmaceutical composition comprising β_2 -agonist and an inhaled corticosteroid (ICS) and/or anticholinergic agent for administration in the prevention or treatment of respiratory, inflammatory or obstructive airway disease.

5 Another object of the present invention is to provide a pharmaceutical composition comprising one or more β_2 -agonist and an inhaled corticosteroid (ICS) and/or an anticholinergic agent for once daily administration in 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 a pharmaceutical composition comprising one or more β_2 -agonist and an inhaled corticosteroid (ICS) and/or an
10 anticholinergic agent 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 of asthma, COPD or a related respiratory or nasal disorder which comprises administering a pharmaceutical composition comprising one or more β_2 -agonist and an inhaled corticosteroid
15 (ICS) and/or an anticholinergic agent.

SUMMARY OF THE INVENTION:

According to a first aspect of the present invention, there is provided a pharmaceutical composition comprising one or more bronchodilators and an inhaled corticosteroid (ICS).

According to another aspect of the present invention, there is provided a pharmaceutical
20 composition comprising one or more β_2 -agonist, an inhaled corticosteroid (ICS) and an anticholinergic agent.

According to yet another aspect of the present invention, there is provided a pharmaceutical composition comprising one or more β_2 -agonist and an inhaled corticosteroid (ICS) and/or an anticholinergic agent for once daily administration.

25 According to another aspect of the present invention, there is provided a process for preparing a pharmaceutical composition comprising one or more β_2 -agonist and an inhaled corticosteroid (ICS) and/or an anticholinergic agent.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising one or more β_2 -agonist and an inhaled corticosteroid (ICS) and/or an anticholinergic agent for use in treating disorders or conditions that respond to, or are prevented, ameliorated or eliminated by, the administration of one or more bronchodilators and an inhaled corticosteroid (ICS) and/or an anticholinergic agent.

According to another of the present invention there is provided a method for prevention or treatment of asthma, COPD or a related respiratory or nasal disorder which comprises administering to a subject in need thereof, a pharmaceutical composition comprising one or more β_2 -agonist and an inhaled corticosteroid (ICS) and/or an anticholinergic agent.

10 DETAILED DESCRIPTION OF THE INVENTION:

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

The present invention thus, provides pharmaceutical compositions for inhalation comprising β_2 -agonist, an inhaled corticosteroid and/or an anticholinergic agent..

15 A preferred β_2 -agonist for use in the present invention is olodaterol, which is preferably olodaterol hydrochloride.

Suitable inhaled corticosteroid (ICS) for use in the present invention includes fluticasone, mometasone, budesonide, beclomethasone and ciclesonide.

20 Suitable anticholinergics agent for use in the present invention includes tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium, trospium, aclidinium, umeclidinium and darotroprum.

In accordance with the present invention, the preferred inhaled corticosteroid is fluticasone mometasone and ciclesonide.

25 In accordance with the present invention, the preferred anticholinergic agent is tiotropium, umeclidinium and darotroprum. As used herein the terms "olodaterol", "fluticasone", "mometasone", "budesonide", "beclomethasone", "ciclesonide", "tiotropium", "oxitropium", "flutropium", "ipratropium", "glycopyrronium", "trospium", "aclidinium", "umeclidinium" and "darotroprum" are used in broad sense to include not only "olodaterol", "fluticasone",

“mometasone”, “budesonide”, “beclomethasone”, “ciclesonide”, “tiotropium”, “oxitropium”, “flutropium”, “ipratropium”, “glycopyrronium”, “trospium”, “aclidinium”, “umeclidinium” and “darotropium” *per se* but also their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable esters, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable complexes etc.

According to one aspect of the present invention there is provided a pharmaceutical composition for inhalation comprising of:

- 10 (a) olodaterol;
- (b) an inhaled corticosteroid (ICS) selected from the group consisting of: fluticasone, mometasone, budesonide, beclomethasone and ciclesonide; and/or
- (c) an anticholinergic agent selected from the group consisting of tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium, trospium, aclidinium, umeclidinium and darotropium,
- 15 preferably wherein (a), (b) and (c) are formulated for simultaneous, separate or sequential administration.

A particularly preferred pharmaceutical composition of the present invention comprises:
(a) olodaterol (b) mometasone and (c) tiotropium.

- A particularly preferred pharmaceutical composition of the present invention comprises:
20 (a) olodaterol (b) mometasone furoate and (c) tiotropium bromide.

A particularly preferred pharmaceutical composition of the present invention comprises:
(a) olodaterol (b) fluticasone and (c) tiotropium.

A particularly preferred pharmaceutical composition of the present invention comprises:
(a) olodaterol (b) fluticasone furoate and (c) tiotropium bromide.

- 25 A particularly preferred pharmaceutical composition of the present invention comprises:
(a) olodaterol (b) ciclesonide and (c) darotropium, preferably darotropium bromide.

A particularly preferred pharmaceutical composition of the present invention comprises:
(a) olodaterol (b) ciclesonide and (c) umeclidinium, preferably umeclidinium bromide.

In another preferred aspect of the invention, there is provided a pharmaceutical composition comprising olodaterol and an inhaled corticosteroid.

- 5 In a still further preferred aspect of the invention, there is provided a pharmaceutical composition comprising: (a) olodaterol and (b) an inhaled corticosteroid selected from the group consisting of fluticasone, mometasone, budesonide, beclomethasone and ciclesonide, preferably wherein (a) and (b) are formulated for simultaneous, separate or sequential administration.

- A particularly preferred pharmaceutical composition of the present invention comprises:
10 (a) olodaterol and (b) mometasone.

A further particularly preferred pharmaceutical composition of the present invention comprises:
(a) olodaterol and (b) fluticasone furoate.

- The inventors of the present invention have found that the above mentioned pharmaceutical compositions are effective for treating inflammatory and/or obstructive diseases of the
15 respiratory tract, particularly asthma or chronic obstructive pulmonary disease (COPD).

Furthermore, the pharmaceutical compositions of the present invention advantageously provide a rapid onset of action, longer duration of action and improved control of obstructive or inflammatory airway diseases, or reduction in the exacerbations of the diseases.

- Also, the pharmaceutical compositions of the present invention advantageously reduce the risk of
20 undesirable side effects as compared to the repeated exposure of the steroid alone involved in the treatment of inflammatory or obstructive airways diseases.

Another advantage of the pharmaceutical compositions of the present invention is that the invention facilitates the treatment of an obstructive and inflammatory airway disease with use of a fixed dose combination in a single medicament.

- 25 Further the pharmaceutical compositions of the present invention provide for the administration of combination therapies by use of a single inhaler for patients who currently have to make use of multiple inhalers. By way of example, patients may administer pharmaceutical compositions

of the present invention from a single inhaler instead of administering from three different inhalers, one for corticosteroid, one for anticholinergic and one for a long acting beta₂-agonist. 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 and arthritis, and are receiving multiple other medications.

Preferably the pharmaceutical compositions of the present invention are formulated for once daily administration.

Olodaterol is chemically known as 6-hydroxy-8-[(1R)-1-hydroxy-2-[[2-(4-methoxyphenyl)-1,1-dimethylethyl]amino]ethyl]-2H-1,4-benzoxazin-3(4H)- one. A particularly preferred pharmaceutically acceptable salt of olodaterol is olodaterol hydrochloride monohydrate. According to the present invention, olodaterol may be present in an amount of from about 2mcg to about 50mcg.

In addition to olodaterol, the pharmaceutical compositions of the present invention may comprise an anticholinergic such as tiotropium preferably tiotropium bromide.

Tiotropium bromide is an anticholinergic bronchodilator that antagonises muscarinic M1, M2 and M3 receptors. Tiotropium bromide, 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.

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 terms of the effect of lung function, dyspnea, exacerbation rates and health status.

According to the present invention, tiotropium may be present in an amount of from about 2mcg to about 50mcg.

In addition to olodaterol and an anticholinergic agent, the pharmaceutical compositions of the present invention may also comprise an inhaled corticosteroid, preferably selected from the group consisting of mometasone, fluticasone, budesonide, beclomethasone and ciclesonide.

5 Particularly preferred pharmaceutically acceptable esters of fluticasone are fluticasone furoate, fluticasone propionate and fluticasone valerate, most preferably fluticasone furoate. According to the present invention, fluticasone furoate may be present in an amount of from about 25mcg to about 800mcg.

10 Fluticasone furoate is a novel corticosteroid which substantially overcomes the potential side effects that are generally produced by the use of conventional corticosteroids. Moreover, fluticasone furoate exhibits 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 hyper-responsiveness as compared to fluticasone propionate. Fluticasone furoate has a longer duration of action with an elimination half life of 15.1 hrs.

15 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 towards the glucocorticoid receptor. Further, fluticasone furoate has greater potency when compared to other clinically used corticosteroids such as mometasone furoate, budesonide, fluticasone propionate, ciclesonide, for the glucocorticoid receptor and against the pro-inflammatory transcription factors nuclear factor κ B (NF- κ B), activation protein-1, and tumor necrosis factor-
20 induced interleukin-8 cytokine production. Chronic inflammation which is commonly associated with asthma is also managed by fluticasone furoate.

A particularly preferred pharmaceutically acceptable ester of mometasone is mometasone furoate. According to the present invention, mometasone furoate may be present in an amount of from about 25mcg to about 800mcg.

25 Mometasone furoate is chemically known as (11[β], 16[α])-9, 21-dichloro-17-[(2-furanylcarbonyl) oxy]-11-hydroxy-16-methylpregna-1,4-diene-3,20-dione. Mometasone furoate is a synthetic 17-heterocyclic corticosteroid and exhibits a long duration of action

In addition to active pharmaceutical ingredients, the pharmaceutical compositions of the present invention typically may comprise one or more pharmaceutically acceptable excipients. The active ingredients may be used as separate formulations or as a single combined formulation. When combined in the same formulation, it will be appreciated that the active ingredients must
5 be stable and compatible with each other and with the other components of the formulation.

The pharmaceutical compositions of the present invention are formulated for inhalation and may therefore be administered by any suitable methods used for delivery of the drugs to the respiratory tract. For example, the composition of the present invention may be in the form of an aerosol compositions, powders, sprays, solutions, suspensions, a nasal spray, nasal drops or an
10 insufflation powder. Such aerosol compositions may be administered by any conventional means, for example using a metered dose inhaler (MDI), dry powder inhaler (DPI) or nebulizer.

The various dosage forms according to the present invention may comprise carriers/excipients suitable for formulating the same.

The pharmaceutical compositions of the present invention are preferably in a form suitable for
15 administration by a MDI, for example, in the form of an aerosol composition. Such compositions may comprise one or more pharmaceutically acceptable excipients, in particular selected from the group of HFC/HFA propellants, co-solvents, bulking agents, non-volatile components, buffers/pH adjusting agents, surface active agents, preservatives, complexing agents, or combinations thereof.

20 Suitable propellants are those which, when mixed with the cosolvent(s), form a homogeneous 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.

According to the present invention, the HFC/HFA propellants may comprise, one or more of
25 1,1,1,2-tetrafluoroethane (HFA-134(a)) and 1,1,1,2,3,3,3-heptafluoropropane (HFA-227), HFC-32 (difluoromethane), HFC-143(a) (1,1,1-trifluoroethane), HFC-134 (1,1,2,2-tetrafluoroethane), and HFC-152a (1,1-difluoroethane) or combinations thereof and such other propellants which may be known to the person having a skill in the art.

In the context of the present invention, the term “co-solvent” means 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 co-solvent is to increase the solubility of the medicament and the excipients in the formulation.

- 5 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;
- 10 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 and combinations thereof.

- Suitable surfactants which may be employed in an aerosol composition of the present invention include those which may serve to stabilize the solution formulation and improve the performance
- 15 of valve systems of the metered dose inhaler. Preferred surfactants include one or more ionic and/or non- ionic surfactants. Examples of suitable surfactants include, but are not limited to, oleic acid, sorbitan trioleate, lecithin, isopropylmyristate, tyloxapol, polyvinylpyrrolidone, polysorbates such as polysorbate 80, vitamin E-TPGS, and macrogol hydroxystearates such as macrogol-15-hydroxystearate and combinations thereof.

- 20 In the context of the present invention, the term “non-volatile component” refers to the suspended or dissolved constituents of the pharmaceutical composition that would remain after evaporation of the solvent(s) present.

- The non-volatile component may comprise one or more of monosaccharides such as, but not limited to, glucose, arabinose; disaccharides such as lactose, maltose; oligosaccharides and
- 25 polysaccharides such as, but not limited to, dextrans; 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 and combinations thereof.

Suitable bulking agents may be employed in the pharmaceutical compositions of the invention, in particular aerosol compositions that are intended for administration using an MDI. The
5 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 and combinations thereof.

Suitable buffers or pH adjusting agents may be employed in the pharmaceutical compositions of
10 the invention, in particular aerosol compositions that are intended for administration using an MDI. 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 and combinations thereof.

Suitable preservatives may be employed in the pharmaceutical compositions of the invention, in
15 particular aerosol compositions that are intended for administration using an MDI, to protect the formulation from contamination with pathogenic bacteria. 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 having a skill in the art and combinations thereof.

20 Suitable complexing agents may be employed in the pharmaceutical compositions of the invention, in particular aerosol compositions that are intended for administration using an MDI, capable of forming complex bonds. The complexing agent may comprise one or more of, but not limited to, sodium EDTA or disodium EDTA and combinations thereof.

The pharmaceutical compositions of the present invention are preferably in a form suitable for
25 administration by a dry powder inhaler (DPI).

The pharmaceutically acceptable excipients suitable for dry powder inhalation according to the present invention may be selected from suitable carriers which include, but are 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 example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate, etc. lactose, lactitol, dextrates, , dextrose, maltodextrin, saccharides including monosaccharides, 5 disaccharides, polysaccharides; sugar alcohols such as arabinose, ribose, mannose, sucrose, trehalose, maltose, dextran, magnesium stearate, cellobiose octaacetate and combinations thereof.

The pharmaceutical compositions of the present invention are preferably in a form suitable for administration by nebulization.

10 Nebulization therapy has an advantage over other inhalation therapies, 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. Such compositions may comprise suitable excipients such as one or more, but not limited to, tonicity agents, pH regulators, and chelating agents in a suitable vehicle.

Examples of suitable isotonicity adjusting agents include sodium chloride, potassium chloride, 15 zinc chloride, calcium chloride and mixtures thereof. Other isotonicity-adjusting agents may also include, but are not limited to, mannitol, glycerol, and dextrose and mixtures thereof.

The pH of pharmaceutical compositions of the invention may be adjusted by the addition of one or more pH regulators such as pharmacologically acceptable acids. Pharmacologically acceptable inorganic acids or organic acids may be used for this purpose. Examples of preferred inorganic 20 acids include one or more acids selected from the group consisting of hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and phosphoric acid and combinations thereof. Examples of particularly suitable organic acids include one or more acids selected from the group consisting of ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and propionic acid and combinations thereof.

25 Examples of suitable chelating agents for use in a pharmaceutical compositions of the invention include editic acid (EDTA) or a salt thereof, e.g. sodium EDTA or disodium EDTA dihydrate (sodium edetate), and mixtures of such compounds.

In addition to the excipients such as isotonicity-adjusting agents, pH regulators, chelating agents covered under nebulization therapy, the dosage form as nasal spray and nasal drops may comprise thickening agents.

5 Examples of suitable thickening agents for use in a pharmaceutical compositions of the invention include cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherized with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water
10 soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In addition to the aforementioned excipients, one or more anti-microbial preservative agents may also be added to the pharmaceutical compositions of the invention, in particular for multi-dose packages.

15 The pharmaceutical composition according to the present invention may be included in one or more suitable containers provided with means enabling the application of the contained formulation to the respiratory tract.

Where the pharmaceutical compositions of the invention are in the form of a powder for inhalation and are intended to be administered by a DPI, it may be encapsulated in capsules of
20 gelatin or HPMC, or in blisters.

The dry powder may be contained as a reservoir either in a single dose or multi-dose dry powder inhalation device

The powder for inhalation may be suspended in a suitable liquid vehicle and packed in an aerosol container along with suitable propellants or mixtures thereof.

25 The powder for inhalation may be dispersed in a suitable gas stream to form an aerosol composition.

Where the pharmaceutical compositions of the invention are in the form of an aerosol composition for administration using an MDI, it may be packed in plain aluminium cans or SS (stainless steel) cans or any such cans suitable for MDI delivery. 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. Such cans may be suitably treated to avoid any adherence of the active on the walls thereof using techniques known in the art, for example 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 anodized, plasma treated or plasma coated.

Where the pharmaceutical compositions of the invention are in the form of nasal sprays and nasal drops for administration into the nasal passages it may be done by means of a dropper (or pipette) that includes a glass, plastic or metal dispensing tube. Fine droplets and sprays can be provided by an intranasal pump dispenser or squeeze bottle as well known in the art.

The pharmaceutical compositions of the present invention may further comprise, in addition to those pharmaceutically active ingredients detailed above, one or more active(s) selected from the group comprising of, antihistamines, antiallergics or leukotriene antagonists, or their pharmaceutically acceptable salts, solvates, tautomers, derivatives, enantiomers, isomers, hydrates, prodrugs or polymorphs thereof.

The pharmaceutical compositions of the present invention comprise olodaterol, an inhaled corticosteroid and/or an anticholinergic agent. These active ingredients are formulated for simultaneous, separate or sequential administration. When the active ingredients are administered sequentially, either olodaterol, the inhaled corticosteroid, or where present, the anticholinergic agent may be administered first. When administration is simultaneous, the active ingredients may be administered either in the same or different pharmaceutical compositions. Adjunctive therapy, i.e. where one active ingredient is used as the primary treatment and the other active ingredient(s) is/are used to assist that primary treatment is also an embodiment of the present invention.

According to a further aspect of the invention, there is provided a product comprising: (a) olodaterol and (b) an inhaled corticosteroid selected from the group comprising mometasone or fluticasone; as a combined preparation for simultaneous, separate or sequential use for treatment and /or prevention of respiratory, inflammatory or obstructive airway disease.

- 5 According to another aspect of the invention, there is provided a product comprising (a) olodaterol; (b) an inhaled corticosteroid selected from the group comprising mometasone or fluticasone; (c) an anticholinergic agent, which is preferably tiotropium as a combined preparation for simultaneous, separate or sequential use for treatment and /or prevention of respiratory, inflammatory or obstructive airway disease.
- 10 Compositions for use according to the present invention may be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. These may for example, comprise metal or plastic foil, such as a blister pack. Where compositions are intended for administration as two separate compositions these may be presented in the form of a twin pack.
- 15 Pharmaceutical compositions may also be prescribed in "patient packs" containing the whole course of treatment in a single package. The inclusion of a package insert has been shown to improve patient compliance with the prescribing physician's instructions. According to a further aspect of the present invention, there is provided a patient pack comprising at least one active ingredient of the combination according to the invention and an information insert containing
- 20 directions to use the combination of the invention. In one aspect, the present invention provides a fixed dose combination.

- The pharmaceutical compositions of the present invention may be conveniently presented in a unit dosage form and may be prepared by any of the methods well known in the art. Suitable methods include the step of bringing into association the active ingredients with a carrier which
- 25 constitutes one or more pharmaceutically acceptable excipients. In general, compositions may be prepared by uniformly and intimately bringing into association the active ingredients with one or more liquid carriers or finely divided solid carriers, or both. It will be appreciated that when the active ingredients are administered independently, each may be administered by a different means.

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

In one aspect, the present invention provides a process of preparing pharmaceutical compositions for administration by a metered dose inhaler, which process comprises admixing a pharmaceutically acceptable carrier or excipient with one or more active pharmaceutical ingredients of the invention and a propellant, and thereafter transferring the composition to a suitable container, preferably a pre-crimped can.

In another aspect, the invention provides a process of preparing a pharmaceutical compositions for administration by dry powder inhalation, which process comprises admixing of a pharmaceutically acceptable carrier or excipient with one or more active pharmaceutical ingredients of the invention and providing the composition as a dry powder.

In a further aspect, the invention provides a process of preparing pharmaceutical compositions for administration by nebulisation, which process comprises dissolving the drugs, optionally chelating agents, osmotic/isotonicity adjusting agents and any other suitable ingredients in the vehicle and adjusting the pH using a suitable pH adjusting agent.

In a further aspect, the invention also provides a method for the prevention and/or treatment of a respiratory, inflammatory or obstructive airway disease, in particular chronic obstructive pulmonary disease, in a mammal, such as a human, which method comprises administration of a therapeutically effective amount of pharmaceutical compositions according to the present invention.

The present invention also provides pharmaceutical compositions according to the present invention for use in preventing and/or treating disorders or conditions that respond to, or are prevented, ameliorated or eliminated by, the administration one or more bronchodilators and an inhaled corticosteroid (ICS), such as a respiratory, inflammatory or obstructive airway disease, in particular chronic obstructive pulmonary disease.

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.

MDI Compositions**Example 1**

Sr. No.	Ingredients	Qty /Spray
1.	Fluticasone Furoate	50 mcg
2.	Olodaterol	5 mcg
3.	HFA134A OR HFA227	q.s

Process:

- 5 1) Fluticasone furoate and Olodaterol 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.
- 3) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

10 Example 2

Sr. No.	Ingredients	Qty /Spray
1.	Fluticasone Furoate	50 mcg
2.	Olodaterol	5 mcg
4.	Lactose	100% of the active ingredient
5.	HFA134A OR HFA227	q.s.

Process:

- 1) Fluticasone furoate and Olodaterol were homogenized with lactose and 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.

Example 3

Sr. No.	Ingredients	Qty /Spray
1.	Mometasone	200 mcg
2.	Olodaterol	5 mcg
3.	HFA134A OR HFA227	q.s

Process:

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

Example 4

Sr. No.	Ingredients	Qty /Spray
1.	Mometasone	200 mcg
2.	Olodaterol	5 mcg

4.	Lactose	100% of the active ingredient
5.	HFA134A OR HFA227	q.s.

Process:

- 1) Mometasone and Olodaterol were homogenized with lactose and 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.

Example 5

Sr. No.	Ingredients	Qty /Spray
1.	Mometasone	200 mcg
2.	Olodaterol	5 mcg
3.	Tiotropium	9 mcg
4.	HFA134A OR HFA227	q.s

10 Process:

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

Example 6

Sr. No.	Ingredients	Qty /Spray
1.	Mometasone	200 mcg
2.	Olodaterol	5 mcg
3.	Tiotropium	9 mcg
4.	Lactose	100% of the active ingredient
5.	HFA134A OR HFA227	q.s.

Process:

- 1) Mometasone, Olodaterol 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 quantity of HFA was added.
- 3) The resulting suspension was mixed, recirculated and filled in into pre-crimped aluminum cans.

Example 7

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200 mcg
2.	Darotropium Bromide	20 mcg
3.	Olodaterol	5 mcg
4.	HFA134A OR HFA227	q.s.

Process:

- 1) Ciclesonide, Darotropium Bromide and Olodaterol were homogenized and 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.

Example 8

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200 mcg
2.	Darotropium Bromide	20 mcg
3.	Olodaterol	5 mcg
4.	Lactose	100% of the active ingredient
4.	HFA134A OR HFA227	q.s.

10 Process:

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

Example 9

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200 mcg
2.	Darotropium Bromide	20 mcg
3.	Olodaterol	5 mcg
4.	PEG 400/1000	0.3% of total formulation
5.	PVP K 25	0.001% of total formulation
6.	HFA134A OR HFA227	q.s.

Process:

1) PVP and PEG were dissolved in part quantity of HFA.

5 2) Ciclesonide, Darotropium Bromide and Olodaterol were homogenized and part quantity of HFA.

2) The suspension obtained in step 1 and 2 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 10

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200 mcg

2.	Darotropium Bromide	20 mcg
3.	Olodaterol	5 mcg
4.	Ethanol	15-20% of total formulation
5.	Glycerol	1% of total formulation
6.	HCL (0.08N)	pH2.5 - 3.5
7.	HFA134A	q.s.

Process:

- 1) Glycerol was dissolved in ethanol and required quantity of HCl was added.
- 2) Ciclesonide, Darotropium Bromide and Olodaterol 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.

Example 11

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200mcg
2.	Darotropium Bromide	20mcg
3.	Olodaterol	5 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) Ciclesonide, Olodaterol and Darotropium Bromide 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.

Example 12

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200mcg
2.	Darotropium Bromide	20mcg
3.	Olodaterol	5 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.
- 2) Ciclesonide, Olodaterol and Darotropium Bromide 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.

Example 13

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200mcg
2.	Darotropium Bromide	20mcg
3.	Olodaterol	5 mcg
4.	Ethanol	1-2% of total formulation
5.	Lecithin	0.02 of the API
6.	HFA134a or HFA227	q.s.

10 Process:

- 1) Lecithin was dissolved in ethanol.
- 2) Ciclesonide, Olodaterol and Darotropium Bromide were homogenized with part quantity of HFA and transferred to the mixing vessel.
- 3) The solution of lecithin and ethanol homogenized with part quantity of HFA.

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 cans.

5 Example 14

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200mcg
2.	Darotropium Bromide	20mcg
3.	Olodaterol	5 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) Ciclesonide, Olodaterol and Darotropium Bromide were homogenized with part quantity of HFA and transferred to the mixing vessel.

10 3) The solution of oleic acid and ethanol homogenized with part quantity of HFA.

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 cans.

Example 15

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200mcg
2.	Umeclidinium Bromide	62.5mcg
3.	Olodaterol	5 mcg
4.	HFA134A OR HFA227	q.s.

Process:

- 1) Ciclesonide, Umeclidinium Bromide and Olodaterol were homogenized and 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.

Example 16

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200 mcg
2.	Umeclidinium Bromide	62.5 mcg
3.	Olodaterol	5 mcg
4.	Lactose	100% of the active ingredient
4.	HFA134A OR HFA227	q.s.

Process:

- 1) Ciclesonide, Umeclidinium Bromide and Olodaterol were homogenized with lactose and 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 in into pre-crimped aluminum cans.

Example 17

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200 mcg
2.	Umeclidinium Bromide	62.5 mcg
3.	Olodaterol	5 mcg
4.	PEG 400/1000	0.3% of total formulation
5.	PVP K 25	0.001% of total formulation
6.	HFA134A OR HFA227	q.s.

10 Process:

- 1) PVP and PEG were dissolved in part quantity of HFA.
- 2) Ciclesonide, Umeclidinium Bromide and Olodaterol were homogenized and part quantity of HFA.

2) The suspension obtained in step 1 and 2 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.

5 Example 18

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200 mcg
2.	Umeclidinium Bromide	62.5 mcg
3.	Olodaterol	5 mcg
4.	Ethanol	15-20% of total formulation
5.	Glycerol	1% of total formulation
6.	HCL (0.08N)	pH2.5 - 3.5
7.	HFA134A	q.s.

Process:

1) Glycerol was dissolved in ethanol and required quantity of HCl was added.

2) Ciclesonide, Umeclidinium Bromide and Olodaterol were dissolved in the solution obtained in
10 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.

Example 19

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200mcg
2.	Umeclidinium Bromide	62.5 mcg
3.	Olodaterol	5 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.

5 2) Ciclesonide, Olodaterol and Umeclidinium Bromide 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 20

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200 mcg

2.	Umeclidinium Bromide	62.5 mcg
3.	Olodaterol	5 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.
- 2) Ciclesonide, Olodaterol and Umeclidinium Bromide 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-cripped aluminum cans.

Example 21

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200 mcg
2.	Umeclidinium Bromide	62.5 mcg
3.	Olodaterol	5 mcg
4.	Ethanol	1-2% of total formulation
5.	Lecithin	0.02 of the API
6.	HFA134a or HFA227	q.s.

Process:

- 1) Lecithin was dissolved in ethanol.
- 2) Ciclesonide, Olodaterol and Umeclidinium Bromide were homogenized with part quantity of HFA and transferred to the mixing vessel.
- 3) The solution of lecithin and ethanol homogenized with part quantity of HFA.
- 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 cans.

Example 22

Sr. No.	Ingredients	Qty /Spray
1.	Ciclesonide	200mcg
2.	Umeclidinium Bromide	62.5 mcg
3.	Olodaterol	5 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) Ciclesonide, Olodaterol and Umeclidinium Bromide were homogenized with part quantity of HFA and transferred to the mixing vessel.
- 5 3) The solution of oleic acid and ethanol homogenized with part quantity of HFA.
- 4) The suspension obtained in step (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 cans.

10 **DPI Compositions****Example 23**

Sr. No.	Ingredients	Qty / unit (mg)
1.	Tiotropium bromide	0.0225
2.	Mometasone Furoate	0.4000
3.	Olodaterol	0.0100
4.	Lactose monohydrate	24.5675
	Total	25.0000

Process:

- 1) Mometasone furoate, Olodaterol and Tiotropium bromide were sifted with a part quantity of
15 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 24

Sr. No.	Ingredients	Qty / unit (mg)
1.	Tiotropium bromide	0.0225
2.	Mometasone Furoate	0.2000
3.	Olodaterol	0.0050
4.	Lactose monohydrate	24.7725
	Total	25.0000

Process:

- 1) Mometasone furoate, Olodaterol and Tiotropium bromide were sifted with a part quantity of
5 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 25

Sr. No.	Ingredients	Qty / unit (mg)
1.	Fluticasone Furoate	0.4000
2.	Olodaterol	0.0050
3.	Lactose monohydrate	24.5950
4.	Total	25.0000

Process:

- 1) Fluticasone furoate and Olodaterol 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.

5

Example 26

Sr. No.	Ingredients	Qty / unit (mg)
1.	Fluticasone Furoate	0.6000
2.	Olodaterol	0.0100
3.	Lactose monohydrate	24.3900
4.	Total	25.0000

Process:

- 1) Fluticasone furoate and Olodaterol 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.

15

Example 27

Sr. No.	Ingredients	Qty / unit (mg)
1.	Mometasone Furoate	0.2000
2.	Olodaterol	0.0050
3.	Lactose monohydrate	24.7950
4.	Total	25.0000

Process:

- 1) Mometasone furoate and Olodaterol were sifted with a part quantity of lactose.
- 5 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

Sr. No.	Ingredients	Qty / unit (mg)
1.	Mometasone Furoate	0.4000
2.	Olodaterol	0.0100
3.	Lactose monohydrate	24.5900
4.	Total	25.0000

Process:

- 1) Mometasone furoate and Olodaterol 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.

- 5 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 and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and
- 10 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 "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

- 15 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 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: (i) olodaterol, (ii) an inhaled corticosteroid and/or an anticholinergic agent.
2. A pharmaceutical composition according to claim 1, wherein the olodaterol is in the form of a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, pharmaceutically acceptable hydrate, pharmaceutically acceptable ester, pharmaceutically acceptable enantiomer, pharmaceutically acceptable derivative, pharmaceutically acceptable polymorph, pharmaceutically acceptable complex or pharmaceutically acceptable prodrug.
3. A pharmaceutical composition according to claim 2 wherein the pharmaceutically acceptable salt of olodaterol is olodaterol hydrochloride.
4. A pharmaceutical composition according to any one of claims 1 to 3, wherein the inhaled corticosteroid is one or more compounds selected from beclomethasone, budesonide, fluticasone, mometasone, and ciclesonide.
5. A pharmaceutical composition according to claim 4, wherein fluticasone, beclomethasone, budesonide, mometasone and ciclesonide are in the form of a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, pharmaceutically acceptable hydrate, pharmaceutically acceptable ester, pharmaceutically acceptable enantiomer, pharmaceutically acceptable derivative, pharmaceutically acceptable polymorph, pharmaceutically acceptable complex or pharmaceutically acceptable prodrug.
6. A pharmaceutical composition according to claim 5, wherein the pharmaceutically acceptable ester of fluticasone is furoate, valerate, or propionate.
7. A pharmaceutical composition according to claim 5, wherein the pharmaceutically acceptable ester of mometasone is mometasone furoate.
8. A pharmaceutical composition according to any one of the preceding claims, wherein the anticholinergic agent is one or more compounds selected from tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium, tropium, aclidinium, umeclidinium and darotropium.

9. A pharmaceutical composition according to claim 8, wherein the tiotropium, oxitropium, flutropium, ipratropium, glycopyronium, trospium, aclidinium, umeclidinium and darotroprum is in the form of a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, pharmaceutically acceptable hydrate, pharmaceutically acceptable ester, pharmaceutically acceptable enantiomer, pharmaceutically acceptable derivative, pharmaceutically acceptable polymorph, pharmaceutically acceptable complex or pharmaceutically acceptable prodrug.
10. A pharmaceutical composition according to claim 9 wherein the pharmaceutically acceptable salt of tiotropium is tiotropium bromide.
11. A pharmaceutical composition according to claim 9 wherein the pharmaceutically acceptable salt of darotroprum is darotroprum bromide.
12. A pharmaceutical composition according to claim 9 wherein the pharmaceutically acceptable salt of umeclidinium is umeclidinium bromide.
13. A pharmaceutical composition according to any of the preceding claims, comprising olodaterol and fluticasone furoate.
14. A pharmaceutical composition according to any of the preceding claims, comprising olodaterol, fluticasone furoate and tiotropium.
15. A pharmaceutical composition according to any of the preceding claims, comprising olodaterol and mometasone.
16. A pharmaceutical composition according to any of the preceding claims, comprising olodaterol, mometasone and tiotropium.
17. A pharmaceutical composition according to any of the preceding claims, comprising olodaterol, ciclesonide and darotroprum.
18. A pharmaceutical composition according to any of the preceding claims, comprising olodaterol, ciclesonide and umeclidinium.
19. A pharmaceutical composition according to any one of the preceding claims, wherein the olodaterol is present in an amount of from about 2 mcg to about 50 mcg.

20. A pharmaceutical composition according to any one of the preceding claims, wherein tiotropium is present in an amount of from about 2 mcg to about 50 mcg.
21. A pharmaceutical composition according to any one of the preceding claims, wherein fluticasone furoate is present in an amount of from about 25 mcg to about 800 mcg.
- 5 22. A pharmaceutical composition according to any one of the preceding claims, wherein mometasone is present in an amount of from about 25 mcg to about 800 mcg.
23. A pharmaceutical composition according to any one of the preceding claims, further comprises one or more pharmaceutically acceptable excipients.
24. A pharmaceutical composition according to any one of the preceding claims, is in the
10 form of aerosol compositions, powders, sprays, solutions, suspensions, nebulizers, nasal sprays, nasal drops or insufflation powders.
25. A pharmaceutical composition according to any one of claims 1 to 24, is in a form for use in a metered dose inhaler, preferably comprising a propellant.
26. A pharmaceutical composition according to any one of claims 1 to 24, is in a form for
15 use as a dry powder inhaler, preferably comprising at least one finely divided pharmaceutically acceptable carrier suitable for use in dry powder inhaler.
27. A pharmaceutical composition according to claim 24, further comprising a pharmaceutically acceptable excipients selected from co-solvent, an antioxidant, a surfactant, a bulking agent and a lubricant, wetting agent, osmotic agent, a pH regulator, a buffering agent
20 and a complexing agent, provided in a pharmaceutically acceptable vehicle.
28. A pharmaceutical composition according to any one of the preceding claims for once daily administration.
29. A process for manufacturing a pharmaceutical composition according to according to any one of claims 1 to 28, comprising combining olodaterol with an inhaled corticosteroid and
25 optionally, one or more pharmaceutically acceptable excipients.

30. A process for manufacturing a pharmaceutical composition according to any one of claims 1 to 28 comprising combining olodaterol with an inhaled corticosteroid and anticholinergic and optionally, one or more pharmaceutically acceptable excipients.

31. A pharmaceutical composition comprising olodaterol and an inhaled corticosteroid,
5 wherein the inhaled corticosteroid is one or more compounds selected from beclomethasone, budesonide, fluticasone furoate, mometasone and ciclesonide, for use in the treatment of a respiratory, inflammatory or obstructive airway disease.

32. A pharmaceutical composition comprising olodaterol, an inhaled corticosteroid, wherein the inhaled corticosteroid is one or more compounds selected from beclomethasone, budesonide,
10 fluticasone furoate, mometasone and ciclesonide, and an anticholinergic, wherein the anticholinergic is one or more compounds selected from tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium, tropium, aclidinium, umeclidinium and darotroprum, for use in the treatment of a respiratory, inflammatory or obstructive airway disease.

33. A pharmaceutical composition according to claim 31 or 32 wherein the disease is
15 COPD or asthma.

34. A pharmaceutical composition according to claim 31, 32 or 33, wherein the treatment includes once daily administration.

35. A method of prophylaxis or treatment of a respiratory, inflammatory or obstructive airway disease, comprising administering a therapeutically effective amount of a pharmaceutical
20 composition according to any one of claims 1 to 28 to a patient in need thereof.

36. A method according to claim 31, wherein the disease is COPD or asthma.

37. A method according to claim 31 or 32, wherein said pharmaceutical composition is administered once daily.

38. A pharmaceutical composition as substantially described herein, with reference to any
25 one of the examples.

39. A process for preparing a pharmaceutical composition as substantially described herein, with reference to any one of the examples.