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(54) Title: NEBULIZATION COMPOSITION COMPRISING GLYCOPYRROLATE AND FORMOTEROL

(57) Abstract: The present invention relates to a nebulization composition comprising glycopyrrolate and formoterol for the treatment of inflammatory or obstructive airway disease and a process for preparing the composition.

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NEBULIZATION COMPOSITION COMPRISING GLYCOPYRROLATE AND FORMOTEROL

PRIORITY DOCUMENTS

5 This patent application claims priority to Indian Provisional Patent Application
number 201821040251 (filed on Oct 25, 2018) the contents of which are incorporated by
reference herein.

FIELD OF THE INVENTION

10 The present invention relates to a nebulization composition comprising
glycopyrrolate and formoterol for the treatment of inflammatory or obstructive airway
disease and a process for preparing the composition.

BACKGROUND OF THE INVENTION

Asthma and chronic obstructive pulmonary disease (COPD) are the common life
threatening respiratory disorders.

15 There has been a persistently high growth in incidences of mortality in cases of
COPD in US. It is believed to be the third leading cause of death in US and would be the
fifth largest disease burden worldwide by 2020. Emphysema and chronic bronchitis are the
two states of COPD. Emphysema is primarily characterized by irreversible enlargement of
the air spaces distal to the terminal bronchioles leading to alveolar wall destruction. Chronic
bronchitis on the other hand, is characterized by persistent productive cough in absence of
20 any other cause of excessive sputum generation. All of these effects lead to clogging of the
airways making it difficult for the patient to breathe.

Asthma is a chronic disease and is triggered by allergies, tobacco smoke and multiple
such reasons. Asthma is characterized by tightening of the airway muscles, narrowing of the
airway muscles, swollen or inflamed lining of the airways and excessive mucus production.
25 Common symptoms of asthma include coughing, wheezing, and shortness of breath.

The commonly available dosage forms for the treatment of asthma and COPD
include metered dose inhalation, dry powder inhalation and nebulization compositions. The
user has to synchronize with the patient's breathing pattern and the device characteristics in
case of metered dose inhalation and dry powder inhalation. This often requires the patient to
30 be trained with the device. The nebulization compositions on the other hand, do not require

any specialized training or synchronization. This is of ultimate convenience to pediatric and geriatric patients. Nebulized drugs are deposited directly into the respiratory tract and thus higher drug concentrations can be achieved in the bronchial tree and pulmonary bed with fewer adverse effects.

5 Currently available treatment options include corticosteroids, beta agonists, anticholinergic agents, and expectorants. There are different dosage forms available such as nebulization, dry powder inhalers, and metered dose inhalers.

Glycopyrrolate is approved in the U.S. as nebulization dosage form under the brand name Lonhala Magnair Kit®.

10 Formoterol is approved under the brand name Perforomist® as a nebulization composition. US6667344 covers a nebulization composition of formoterol.

US20160166506 relates to a method of treating chronic obstructive pulmonary disease with nebulized anticholinergics. The anticholinergic agents are administered with a high efficiency nebulizer to achieve an effect for a prolonged period.

15 A combination of Formoterol and Glycopyrrolate metered dose inhaler-Bevispi Aerosphere® is available in US as a twice-daily, fixed-dose dual bronchodilator combining glycopyrrolate and formoterol fumarate. US8808713 discloses the composition of glycopyrrolate and formoterol in a metered dose inhaler.

US20160374987 relates to inhalation solutions for administration of beta 2-agonists or combinations of muscarinic antagonists and beta 2-agonists with a high efficiency nebulizer. The patent application provides a broad disclosure about co-administration of the two drugs for the treatment of chronic obstructive pulmonary disease.

20 It is of great advantage to provide a combination of glycopyrrolate and formoterol fumarate for the treatment of chronic obstructive pulmonary disease, as this combination
25 would add the efficacy of both the drugs together, giving a synergistic effect and would possibly lead to dose reduction and eventually reducing the adverse effects.

The present invention relates to a composition comprising a fixed dose combination of the two drugs in a single ampule or keeping the two drugs in separate ampules and mixing them together in the nebulizer before administration to a patient.

The term “combination of” includes both fixed dose combination of the two drugs in a single ampule or keeping the two drugs in separate ampules and mixing them together in the nebulizer before administration to a patient.

5

SUMMARY OF THE INVENTION

The present invention provides a nebulization composition comprising a combination of glycopyrrolate or a pharmaceutically acceptable salt thereof and formoterol or a pharmaceutically acceptable salt thereof.

10 In a preferred embodiment, the nebulization composition comprises glycopyrronium bromide and formoterol fumarate.

In one more preferred embodiment, the nebulization composition comprises a fixed dose composition of glycopyrronium bromide and formoterol fumarate in a single ampule.

15 In another preferred embodiment, the nebulization composition comprises mixing of glycopyrronium bromide and formoterol fumarates are kept in separate ampules and are mixed together in a nebulizer prior to the administration to a patient.

In one embodiment, the glycopyrrolate and formoterol are present in the nebulization composition in solubilized form.

20 One embodiment relates to a nebulization composition comprising a combination of glycopyrrolate or a pharmaceutically acceptable salt thereof and formoterol or a pharmaceutically acceptable salt thereof for the treatment of an inflammatory or obstructive airway disease.

In an embodiment, the nebulization composition is a sterile, unit dose composition.

25 In a further embodiment, the nebulization composition comprises glycopyrrolate or a pharmaceutically acceptable salt thereof and formoterol or a pharmaceutically acceptable salt thereof in a weight ratio of 1: 128 to 400: 1.

In yet another embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, buffering /pH adjusting agent, and an isotonicity agent. The nebulization composition may optionally further include a chelating agent, a pharmaceutically acceptable vehicle, or any combination thereof.

In one embodiment, the nebulization composition is free, or substantially free, of a preservative (such as a benzalkonium salt, e.g., benzalkonium chloride).

In another embodiment, the nebulization composition is free, or substantially free, of a complexing agent (such as ethylene diamine tetra-acetic acid (EDTA) or a salt thereof).

5 In a further embodiment, the nebulization composition is free, or substantially free, of (a) EDTA or a salt thereof and (b) a benzalkonium salt, such as benzalkonium chloride.

In one embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, buffer, isotonicity agent, and water.

10 In another embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, citric acid, sodium chloride, and water.

In one more embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, citric acid, sodium citrate, sodium chloride, and water.

In one embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, buffer, complexing agent, isotonicity agent, and water.

15 In another embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, citric acid, sodium chloride, ethylene diamine tetra-acetic acid and water.

In one more embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, citric acid, sodium citrate, sodium chloride, ethylene diamine tetra-acetic acid and sterile water.

20 One more embodiment is a nebulization solution comprising glycopyrronium bromide, formoterol fumarate, sodium chloride, sodium citrate and citric acid, hydrochloric acid, sodium hydroxide, water and optionally edetate disodium. The glycopyrronium bromide and formoterol fumarate are in solubilized form in the solution. The nebulization solution is preferably free, or substantially free, of benzalkonium salts.

25 In one embodiment, the nebulization composition is administered once a day or twice a day to a subject in need thereof.

A further embodiment is a kit comprising a nebulizer and a nebulization composition of the present invention. In one preferred embodiment, the nebulization composition comprises glycopyrronium bromide and formoterol fumarate.

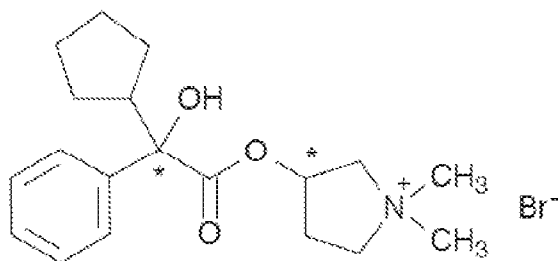
Yet another embodiment is a method of treating an inflammatory or obstructive airway disease by administering a nebulization composition of the present invention. In one preferred embodiment, the nebulization composition comprises glycopyrronium bromide and formoterol fumarate.

5 Other objects, features and advantages of the present invention will be apparent to those of ordinary skill in the art in view of the following detailed description of the invention and accompanying drawings.

10 DETAILED DESCRIPTION OF THE INVENTION

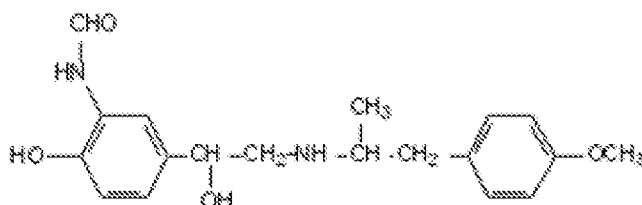
The present invention relates to a nebulization composition comprising glycopyrrolate or a pharmaceutically acceptable salt thereof and formoterol or a pharmaceutically acceptable salt thereof. The nebulization composition is useful for the treatment of an inflammatory or obstructive airway disease.

15 Glycopyrronium bromide, an anticholinergic is a quaternary ammonium salt with the following chemical name: (3RS)-3-[(2SR)-(2-cyclopentyl-2-hydroxy-2-phenylacetyl) oxy]-1,1-dimethylpyrrolidinium bromide. The quaternary ammonium compound inhibits acetyl choline binding to M3 muscarinic receptor is represented by structural formula.



20 Glycopyrrolate can be prepared using the procedures described in U.S. Pat. No.2956062. The present invention embraces using one or more of these isomeric forms, especially the 3S,2'R isomer, the 3R,2'R isomer or the 2S,3'R isomer, thus including single enantiomers, or racemates, especially the (3S,2'R/2S,3'R) racemate. As used herein, glycopyrrolate and glycopyrronium are used interchangeably.

Formoterol is a long-acting, beta 2-adrenergic receptor agonist. It is chemically described as (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide. Formoterol has a molecular formula of C₁₉H₂₄N₂O₄ and the following structure:



5

As used herein, the term “formoterol”, unless otherwise indicated, includes, but is not limited to, formoterol in any physical form such as the amorphous form and crystalline forms (e.g., anhydrous, hydrate, and other solvate forms). Salts of formoterol include, but are not limited to, acid addition salts and base salts thereof. Suitable salts of formoterol include, but are not limited to, salts of mineral acids, such as hydrochlorides and sulfates, and salts of organic acids, such as acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. One preferred salt of formoterol for the nebulization composition is formoterol fumarate, such as in the form of its dihydrate salt (formoterol fumarate dihydrate).

15 The nebulization compositions may contain glycopyrronium bromide and formoterol fumarate in solubilized form in a sterile unit dosage form.

The nebulization composition may contain glycopyrronium bromide in an amount of about 2.5 mcg/ml to about 1000 mcg/ml. Preferably, the composition contains glycopyrronium bromide in amounts of 2.5 mcg/ml, 5 mcg/ml, 10 mcg/ml, 20 mcg/ml, 40 mcg/ml, 80 mcg/ml, 160 mcg/ml, 320 mcg/ml, 500 mcg/ml, 750 mcg/ml and 1000 mcg/ml. Preferably, the nebulization composition may contain 12.5 mcg/ml, 25 mcg/ml, 50 mcg/ml of glycopyrronium bromide.

25 The nebulization composition may contain formoterol fumarate in an amount of about 2.5 mcg/ml to about 320 mcg/ml. Preferably, the composition contains formoterol fumarate in amounts of 2.5 mcg/ml, 5 mcg/ml, 10 mcg/ml, 20 mcg/ml, 40 mcg/ml, 80

mcg/ml, 160 mg/ml, and 320 mg/ml. Preferably, the nebulization composition may contain 5 mcg/ml, 10 mcg/ml, 15 mcg/ml, 20 mcg/ml of formoterol fumarate.

The ratio of glycopyrronium bromide and formoterol fumarate in the nebulization composition may range from 1:128 to 400:1.

5 The nebulization composition may additionally comprise one or more pharmaceutically acceptable excipients. Suitable pharmaceutically acceptable excipients include, but are not limited to, pH adjusting agents, buffering agents, isotonicity agents, optionally chelating agents, surfactants, anti-oxidants, and pharmaceutically acceptable vehicles. In one embodiment, the composition includes a buffering/ pH adjusting agent,
10 isotonicity agent, pharmaceutically acceptable vehicle, and optionally a chelating agent.

 The nebulization composition is substantially free of preservative (such as benzalkonium and salts thereof), preferably substantially benzalkonium chloride free. A composition is “substantially benzalkonium chloride free” or “substantially free of benzalkonium chloride” when the amount of benzalkonium chloride is not an amount
15 sufficient to materially act as a preservative for the nebulization composition i.e less than 0.1%w/w. In one embodiment, benzalkonium chloride may be present in a concentration less than 0.008% w/w based on total weight of the composition. The term “substantially free of preservative” denotes that preservative is not an amount sufficient to materially act as a preservative for the nebulization composition. In one embodiment, the preservative may be
20 present in a concentration less than 0.008% w/w based on total weight of the composition. Generally, nebulization compositions contain a preservative such as benzalkonium chloride. A common problem with benzalkonium chloride is that it may cause paradoxical bronchoconstriction if the solution is administered repeatedly over short intervals, and frequent exposure to benzalkonium chloride may lead to occupational asthma. Another
25 problem is that, when inhaled by patients, the benzalkonium chloride can cause dose-dependent bronchoconstriction. The nebulization compositions of the present invention may be provided without benzalkonium chloride, thereby making them suitable for repeated administration over a short period of time. Also, administering a substantially benzalkonium chloride-free nebulization composition to a patient reduces the concomitant liability of
30 adverse effects associated with benzalkonium chloride alone or in combination with other

excipients and/or the active agents. It also negates the toxicity and other side effects associated with benzalkonium chloride.

The nebulization composition may be free, or substantially free, of complexing agents such as ethylene diamine tetra-acetic acid (EDTA) and salts thereof. The nebulization composition or solution may contain less than about 0.1% by weight of complexing agent such as EDTA. The absence of or reduction in the concentration of the additive EDTA and its salts helps to reduce the paradoxical effect associated with cough.

The nebulization composition may be formulated as a single composition comprising glycopyrrolate and formoterol. Such a nebulization composition can be contained in a single chamber container. Such a single composition comprising both glycopyrronium and formoterol (such as the combination glycopyrronium bromide and formoterol fumarate) is stable under during long term storage. The pharmaceutical composition or solution may contain greater than about 80%, such as greater than about 85%, greater than about 90%, greater than about 95% or greater than about 98% of the initial amount of glycopyrronium /formoterol or salts thereof in the nebulization composition after being stored for 3 or 6 months or 1, 2 or 3 years at 2-8° C and 25° C when stored in a suitable container.

The two active agents can also be separately formulated and contained in separate containers, which are then mixed prior to administration to a patient. In this instance, a composition comprising glycopyrronium bromide and one or more pharmaceutically acceptable excipients is contained in one chamber and another composition comprising formoterol fumarate and one or more pharmaceutically acceptable excipients is contained in a separate chamber. This combination comprising separate compositions of glycopyrronium bromide and formoterol fumarate can be contained in a dual chamber container. The two chambers of the dual chamber container may be separate or may be connected by a common septum. The dual chamber container with a common septum may contain a common top which when broken would provide simultaneous access to both compositions. The composition comprising glycopyrronium bromide may be mixed with the composition comprising formoterol fumarate before being added to the reservoir of the nebulizer. In one instance, the composition comprising glycopyrronium bromide may be added to the reservoir of the nebulizer followed by addition of the composition comprising formoterol

fumarate and vice versa. In this instance, the two compositions would be mixed in the reservoir of the nebulizer device and then administered to the patient.

The pH of the nebulization composition may vary from about 1 to about 7. The pH of the glycopyrrolate nebulization composition is preferably between about 3 to about 6, preferably about 4.5. The pH of the formoterol nebulization composition is between about 3 to about 6, preferably about 5.5. The pH of the nebulization composition containing both glycopyrrolate and formoterol is about 3 to about 6, preferably about 5.5.

The pH may be adjusted by the addition of one or more pharmaceutically acceptable acids. Non-limiting examples of suitable pharmaceutically acceptable acids include inorganic acids, such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, and phosphoric acid, and any combination of any of the foregoing. Non-limiting examples of other suitable pharmacologically acceptable acids include organic acids, such as ascorbic acid, citric acid, malic acid, maleic acid, tartaric acid, succinic acid, fumaric acid, acetic acid, formic acid, propionic acid, and any combination of any of the foregoing. The pH adjusting agents may be selected from one or more organic acids selected from ascorbic acid, fumaric acid and citric acid. A preferred organic acid is citric acid. Mixtures of the abovementioned acids may also be used, particularly in the case of acids which have other properties in addition to their acidifying properties, e.g., those which act as flavorings or antioxidants, such as citric acid or ascorbic acid.

The nebulization composition may contain sodium citrate, for example, at a concentration of about 0.0001% w/v to about 2.20% w/v, and citric acid, for example, at a concentration of about 0.0001% w/v to about 0.53% w/v, to control pH.

The pharmaceutically acceptable vehicle in the nebulization composition includes water and optionally a cosolvent. Any cosolvent that is suitable for inhalation and capable of dissolving or solubilizing the glycopyrronium in the mixture of cosolvent and water can be used. Examples of suitable cosolvents include, for example, alcohols, ethers, hydrocarbons, and perfluorocarbons. Preferably, the cosolvent is a short chain polar alcohol. More preferably, the cosolvent is an aliphatic alcohol having from one to six carbon atoms, such as ethanol or isopropanol. A preferred cosolvent is ethanol. Non-limiting examples of suitable hydrocarbons include n-butane, isobutane, pentane, neopentane and isopentanes.

Non-limiting examples of suitable ethers include dimethyl ether and diethyl ether. Non-limiting examples of suitable perfluorocarbons include perfluoropropane, perfluorobutane, perfluorocyclobutane, and perfluoropentane.

Suitable surfactants include, but are not limited to, C₅₋₂₀-fatty alcohols, C₅₋₂₀-fatty acids, C₅₋₂₀-fatty acid esters, lecithin, glycerides, propylene glycol esters, polyoxyethylenes, polysorbates, sorbitan esters, carbohydrates, and any combination of any of the foregoing. C₅₋₂₀-fatty acids, propylene glycol diesters of the C₅₋₂₀-fatty acids, triglycerides of the C₅₋₂₀-fatty acids, and sorbitans of the C₅₋₂₀-fatty acids are preferred. In one preferred embodiment, the surfactant is selected from oleic acid, sorbitan mono-, di- or trioleates, and any combination of any of the foregoing.

The nebulization composition may optionally include a buffer. Buffers in the pH range of about 2.0 to about 8.0 include, but are not limited to, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES, BIS-TRIS, ADA, ACES, PIPES, MOPSO, BIS-TRIS PROPANE, BES, MOPS, TES, HEPES, DIPSO, MOBS, TAPSO, TRIZMA, HEPPSO, POPSO, TEA, EPPS, TRICINE, GLY-GLY, BICINE, HEPBS, TAPS, and AMPD buffers.

The osmolality of the nebulization composition may be from about 200-500 mOsm/kg. The nebulization composition may comprise a tonicity adjusting agent, such as an ionic salt (e.g., about 0.0001% w/v to about 264% w/v ionic salt). Suitable tonicity adjusting agents include, but are not limited to, ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethyl sulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium

citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine, zinc sulfate, and any combination of any of the foregoing. Suitable osmotic
5 adjusting agents include, but are not limited to, sodium chloride, potassium chloride, zinc chloride, calcium chloride and any combination of any of the foregoing. Other osmotic adjusting agents include, but are not limited to, mannitol, glycerol, dextrose and any combination of any of the foregoing.

The nebulization compositions may contain osmolality adjusting agents such as
10 sodium chloride in amount of about 0.375% to about 1.125%, preferably about 0.9%.

Suitable antioxidants include, but are not limited to, ascorbic acid, vitamin A, vitamin E, tocopherols, and any combination of any of the foregoing.

A nebulization composition of the present invention may have a fill volume of from about 0.5 ml to about 5 ml. Preferably, the nebulization composition has a fill volume of 2
15 ml.

The nebulization composition may be contained in a prefilled, unit-dose, low-density polyethylene (LDPE) container. Each unit-dose container may be disposed in a foil pouch, and each foil pouch may contain one or more unit-dose containers. Each foil pouch containing the unit dose container may be disposed in a shelf carton. The container may have
20 a TWIST-FLEX™ top, such top comprising an easy-to-grip tab-like handle such that the container may be opened, for example, by twisting off the tab by hand. The TWIST-FLEX™ top is advantageous in that it allows for easy dispensing of the solution, prevents spillage and eliminates the need to open the container by cutting or tearing off the top, thereby reducing cross-contamination. One or more of the single unit dose containers may be
25 prepackaged in an aluminum foil pouch, such that the foil provides a protective barrier against environmental contaminants and light as it helps to improve the shelf-life and stability of the nebulization composition. Dispensing vials may include, but are not limited to, any container comprising glass, low density polyethylene, or any other material capable of preventing the solution from leaking out of the container. The vial may be enclosed by

any conventional means including, but not limited to, screw cap, heat seal, snap-on top, flip-top, twist-off stopper, and peel away top.

The nebulization composition may comprise of one or more prefilled containers containing a nebulization composition of the present invention. Each container comprises a
5 single unit dose of a nebulization composition of the present invention.

One embodiment is a prefilled container containing about 2 ml of the nebulization composition comprising about 25 mcg of glycopyrronium bromide and 10 mcg formoterol fumarate. The nebulization composition may additionally contain a buffer, an isotonicity agent and optionally a complexing agent. In one embodiment, the nebulization composition
10 further comprises citric acid, sodium chloride, and water. In another embodiment, the nebulization composition further comprises citric acid, sodium citrate, sodium chloride, and water. In one more embodiment, the nebulization composition comprises citric acid, sodium chloride, ethylene diamine tetra-acetic acid and water. In a further embodiment, the nebulization composition comprises citric acid, sodium citrate, sodium chloride, ethylene
15 diamine tetra-acetic acid and water.

Another embodiment is a prefilled container containing about 2 ml of the nebulization composition comprising about 25 mcg of glycopyrronium bromide and 15 mcg formoterol fumarate. The nebulization composition may additionally contain a buffer, an isotonicity agent and optionally a complexing agent. In one embodiment, the nebulization
20 composition further comprises citric acid, sodium chloride, and water. In another embodiment, the nebulization composition further comprises citric acid, sodium citrate, sodium chloride, and water. In one more embodiment, the nebulization composition comprises citric acid, sodium chloride, ethylene diamine tetra-acetic acid and water. In a further embodiment, the nebulization composition comprises citric acid, sodium citrate,
25 sodium chloride, ethylene diamine tetra-acetic acid and water.

Yet another embodiment is a prefilled container containing about 2 ml of the nebulization composition comprising about 25 mcg of glycopyrronium bromide and 20 mcg formoterol fumarate. The nebulization composition may additionally contain a buffer, an isotonicity agent and optionally a complexing agent. In one embodiment, the nebulization
30 composition further comprises citric acid, sodium chloride, and water. In another

embodiment, the nebulization composition further comprises citric acid, sodium citrate, sodium chloride, and water. In one more embodiment, the nebulization composition comprises citric acid, sodium chloride, ethylene diamine tetra-acetic acid and water. In a further embodiment, the nebulization composition comprises citric acid, sodium citrate,
5 sodium chloride, ethylene diamine tetra-acetic acid and water.

An embodiment is a prefilled container containing about 2 ml of the nebulization composition comprising about 50 mcg of glycopyrronium bromide and 10 mcg formoterol fumarate. The nebulization composition may additionally contain a buffer, an isotonicity agent and optionally a complexing agent. In one embodiment, the nebulization composition
10 further comprises citric acid, sodium chloride, and water. In another embodiment, the nebulization composition further comprises citric acid, sodium citrate, sodium chloride, and water. In one more embodiment, the nebulization composition comprises citric acid, sodium chloride, ethylene diamine tetra-acetic acid and water. In a further embodiment, the nebulization composition comprises citric acid, sodium citrate, sodium chloride, ethylene
15 diamine tetra-acetic acid and water.

One more embodiment is a prefilled container containing about 2 ml of the nebulization composition comprising about 50 mcg of glycopyrronium bromide and 15 mcg formoterol fumarate. The nebulization composition may additionally contain a buffer, an isotonicity agent and optionally a complexing agent. In one embodiment, the nebulization
20 composition further comprises citric acid, sodium chloride, and water. In another embodiment, the nebulization composition further comprises citric acid, sodium citrate, sodium chloride, and water. In one more embodiment, the nebulization composition comprises citric acid, sodium chloride, ethylene diamine tetra-acetic acid and water. In a further embodiment, the nebulization composition comprises citric acid, sodium citrate,
25 sodium chloride, ethylene diamine tetra-acetic acid and water.

Another embodiment is a prefilled container containing about 2 ml of the nebulization composition comprising about 50 mcg of glycopyrronium bromide and 20 mcg formoterol fumarate. The nebulization composition may additionally contain a buffer, an isotonicity agent and optionally a complexing agent. In one embodiment, the nebulization
30 composition further comprises citric acid, sodium chloride, and water. In another

embodiment, the nebulization composition further comprises citric acid, sodium citrate, sodium chloride, and water. In one more embodiment, the nebulization composition comprises citric acid, sodium chloride, ethylene diamine tetra-acetic acid and water. In a further embodiment, the nebulization composition comprises citric acid, sodium citrate,
5 sodium chloride, ethylene diamine tetra-acetic acid and water.

In one embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, buffer, isotonicity agent, and water.

In another embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, citric acid, sodium chloride, and water.

10 In one more embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, citric acid, sodium citrate, sodium chloride, and water.

In one embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, buffer, complexing agent, isotonicity agent, and water.

In another embodiment, the nebulization composition comprises glycopyrronium
15 bromide, formoterol fumarate, citric acid, sodium chloride, ethylene diamine tetra-acetic acid and water.

In one more embodiment, the nebulization composition comprises glycopyrronium bromide, formoterol fumarate, citric acid, sodium citrate, sodium chloride, ethylene diamine tetra-acetic acid and water.

20 The nebulization composition may contain 25 mcg/15 mcg or 25mcg/20 mcg or 50 mcg/ 10 mcg or 50 mg/15 mcg or 50 mcg/20 mcg of glycopyrronium bromide/formoterol fumarate. The nebulization composition may additionally contain a buffer, isotonicity agent and optionally, a complexing agent. In one embodiment, the nebulization composition further comprises citric acid, sodium chloride, and water. In another embodiment, the
25 nebulization composition further comprises citric acid, sodium citrate, sodium chloride, and water. In one more embodiment, the nebulization composition comprises citric acid, sodium chloride, ethylene diamine tetra-acetic acid and water. In a further embodiment, the nebulization composition comprises citric acid, sodium citrate, sodium chloride, ethylene diamine tetra-acetic acid and water.

30 The nebulization composition can be prepared as follows.

A. Composition comprising Glycopyrronium and Formoterol together

1. Add approximately 75-90% quantity of purified water to an appropriately sized stainless steel mixing vessel.
- 5 2. Add sodium chloride to mixing vessel and mix until dissolved (e.g., no visible solid particles observed).
3. Add citric acid to mixing vessel and mix until dissolved (e.g., no visible solid particles observed).
4. Add sodium citrate to mixing vessel and mix until dissolved (e.g., no visible solid particles observed).
- 10 5. Add EDTA to mixing vessel and mix until dissolved (e.g., no visible solid particles observed).
6. Add glycopyrrolate to mixing vessel and mix until dissolved (e.g., no visible solid particles observed).
- 15 7. Add formoterol to mixing vessel and mix until dissolved (e.g., no visible solid particles observed).
8. Make up volume with remainder of purified water and continue mixing for a minimum of 15 minutes.
9. Measure pH and adjust with HCL/NaOH if required to achieve target pH.
10. Sterilize solution by filtration.
- 20 11. Fill 2 mL of solution into appropriately sized vial for nebulization.

B. Composition comprising Glycopyrronium and Formoterol in separate containers**B.1. Composition of Glycopyrronium**

- 25 A nebulization composition of glycopyrronium can be prepared in a similar manner as illustrated above.

B.2. Composition of Formoterol

A nebulization composition of formoterol can be prepared in a similar manner as illustrated above.

- 30 B.3 Mixing of the compositions B.1 and B.2

- (i) Mix the nebulization compositions B.1 and B.2 to obtain a nebulization composition B.3
- (ii) Add the B.3 nebulization composition to the reservoir of the nebulizer device.
- (iii) Nebulization compositions B.1 and B.2 can be separately added to the reservoir of the nebulizer device and mixed to form a nebulization composition B.3

The nebulization composition provided herein has a long shelf life, i.e., it is stable during long term storage. The composition may contain greater than about 80%, such as greater than about 85%, greater than about 90%, greater than about 95% or greater than about 98% of the initial amount of glycopyrronium (or its salt) and formoterol (or its salt) in the composition after being stored for 3 or 6 months or 1, 2 or 3 years at 2-8° C and 25° C when stored in a suitable container (such as a LDPE container in an aluminium pouch). The stability may be determined using Arrhenius kinetics.

The nebulization composition may be administered by nebulizer. Suitable nebulizers include, but are not limited to, a jet nebulizer, an ultrasonic nebulizer, vibrating mesh nebulizer and a breath actuated nebulizer. The nebulization composition may be administered by nebulizers manufactured, designed or sold by Omron, such as the Omron MICRO AIR™ Ultrasonic Nebulizer or those manufactured, designed, or sold by Aerogen, or with the Nebu-Tec device, M-Neb® or with the Zephair® device from Aerosonix, or with the Fox inhaler® from Vectura, or with the Alphazer® device from Omega or with the e-flow device from Pari. Additionally, the nebulization compositions described herein can also be nebulized using inhalers other than those described above.

The nebulization compositions also may be provided as a kit wherein the kit comprises a nebulizer and the nebulization composition comprising glycopyrronium bromide and formoterol fumarate.

The nebulization compositions of the present invention may be administered once a day or twice a day to a subject in need thereof.

The present invention includes methods of treating an inflammatory or obstructive airway disease such as asthma and COPD by administering to a patient a nebulization

composition comprising glycopyrronium (or its salt) and formoterol (or its salt) via a nebulizer.

The nebulization compositions of the present invention comprising the combination of glycopyrrolate and formoterol may be useful in cases where monotherapy i.e. glycopyrrolate or formoterol alone have been ineffective in the treatment of inflammatory or obstructive airway disease such as asthma or COPD.

The nebulization composition of the present invention comprising glycopyrrolate and formoterol provide a synergistic effect. Accordingly, it may be possible to reduce the effective daily dose of these agents, thus, reducing the adverse effects posed by these agents.

The nebulization composition provides a rapid onset of action and the effect may be extended for a long duration. A significant improvement in lung function leading to effective control of inflammatory or obstructive disease may be observed. The methods of treating inflammatory or obstructive airway disease such as asthma or COPD by the nebulization compositions as per the present invention may eliminate the need for other concurrent treatment modalities.

Throughout this specification it is to be understood that the words "comprise" and "include" and variations such as "comprises", "comprising", "includes", "including" are to be interpreted inclusively, unless the context requires otherwise. That is, the use of these words may imply the inclusion of an element or elements not specifically recited.

The following examples further illustrate the invention, but are not limiting.

A. Examples of Nebulization composition comprising Glycopyrronium bromide and Formoterol fumarate in a single composition

#	Amount in %w/v								
	1	2	3	4	5	6	7	8	9
Glycopyrrolate	0.00125								
Formoterol	0.0005								

NaCl	0.9	0.9	0.9	0.9	0.9	0.9	0.078 5	0.079	0.079
Citric acid	0.135	0.135	0.135	0.135	0.045	0.045	0.135	0.135	0.135
Sodium citrate	0.4	-	0.4	-	0.133	0.133	0.4	0.4	-
EDTA	-	-	0.01	0.01	-	0.01	-	0.01	0.01
Water for injection	qs	qs	Qs	qs	qs	qs	qs	qs	qs

#	Amount in %w/v								
	10	11	12	13	14	15	16	17	18
Glycopyrrolate	0.00125								
Formoterol	0.001								
NaCl	0.9	0.9	0.9	0.9	0.9	0.9	0.078 5	0.079	0.079
Citric acid	0.135	0.135	0.135	0.135	0.045	0.045	0.135	0.135	0.135
Sodium citrate	0.4	-	0.4	-	0.133	0.133	0.4	0.4	-
EDTA	-	-	0.01	0.01	-	0.01	-	0.01	0.01
Water for injection	qs	qs	Qs	qs	qs	qs	qs	qs	qs

#	Amount in %w/v								
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	19	20	21	22	23	24	25	26	27
Glycop-yrrolate	0.0025								
Formot-erol	0.001								
NaCl	0.9	0.9	0.9	0.9	0.9	0.9	0.0785	0.079	0.079
Citric acid	0.135	0.135	0.135	0.135	0.045	0.045	0.135	0.135	0.135
Sodium citrate	0.4	-	0.4	-	0.133	0.133	0.4	0.4	-
EDTA	-	-	0.01	0.01	-	0.01	-	0.01	0.01
Water for injection	qs	qs	Qs	qs	qs	qs	qs	qs	qs

Manufacturing process:

1. Dissolve batch quantity of sodium chloride, Citric acid, Sodium Citrate & edetate disodium, in water for injection under stirring. Check clarity of the solution. Check the pH of solution.
2. Weigh accurately batch quantity of Glycopyrrolate & Formoterol Fumarate. Add it to the bulk of step 1 under stirring. Continue the stirring till the clear solution is obtained.
3. Make up volume with water for injection. Filter the solution through 0.22micron PES/PVDF filter.
4. Fill the filtered bulk in LDPE ampules.

B. Examples of Nebulization composition comprising Glycopyrronium bromide and Formoterol fumarate prepared separately and to be mixed prior to administration

The following examples illustrate the compositions of glycopyrronium and formoterol which are formulated separately and are mixed prior to administration to a patient.

5 **B.1 Nebulization compositions comprising Glycopyrronium bromide**

#	Amount in % w/v
Glycopyrronium bromide	0.025
Sodium chloride	0.9
Citric Acid	q.s. to pH
Water for injection	q.s. to 100%

Manufacturing process

1. Dissolve batch quantity of sodium chloride in water for injection under stirring.
- 10 Check clarity of the solution. Adjust the pH of solution using dilute hydrochloric acid.
2. Weigh accurately batch quantity of Glycopyrronium bromide. Add it to the bulk of step 1 under stirring. Continue the stirring till the clear solution is obtained.
3. Make up volume with water for injection. Filter the solution through 0.22micron PES/PVDF filter.
- 15 4. Fill the filtered bulk in LDPE ampules.

B.2 Nebulization compositions comprising formoterol fumarate

#	Amount in % w/v
Formoterol Fumarate	0.002
Sodium chloride	0.9
Citric Acid	0.135
Sodium citrate	0.4
Water for injection	q.s to 100%

Manufacturing process

1. Dissolve batch quantity of sodium chloride, Citric acid, Sodium Citrate & edetate disodium, in water for injection under stirring. Check clarity of the solution. Check the pH of solution.

2. Weigh accurately batch quantity of Formoterol Fumarate. Add it to the bulk of step 1 under stirring. Continue the stirring till the clear solution is obtained.

3. Make up volume with water for injection. Filter the solution through 0.22micron PES/PVDF filter.

4. Fill the filtered bulk in LDPE ampules.

The stability data for the above compositions is provided in the below table:

A. For Nebulization composition comprising Glycopyrronium bromide and Formoterol fumarate in a single composition:

Glycopyrronium 50 mcg + Formoterol Fumarate 20 mcg/ 2 ml Inhalation Solution							
Condition	% Assay		pH	% Related Substances			
	Glyco	Formo		Impurity C/ A		Total impurities	
				Glyco (C)	Formo (A)	Glyco	Formo
Initial	101.1	98.2	4.8	ND	0.17	0.12	0.22
1 M 2 ± 8°C	103.2	100.8	4.79	0.03	0.34	0.10	0.42
2 M 2 ± 8°C	101.6	100.0	4.77	0.04	0.33	0.16	0.51
3 M 2 ± 8°C	101.9	103.5	4.78	0.03	0.35	0.07	0.54
6 M 2 ± 8°C	101.0	92.4	4.75	NP	0.58	NP	0.83
9 M 2 ± 8°C	101.3	103.7	4.71	0.09	0.55	0.24	0.97
12 M 2 ± 8°C	99.8	98.6	4.78	0.17	0.58	0.33	1.38
18 M 2 ± 8°C	100.7	93.3	4.69	0.15	0.38	0.36	1.17
1 M 25/60	103.4	99.3	4.80	0.07	0.61	0.15	0.78
2 M 25/60	101.9	97.1	4.78	0.15	0.64	0.24	0.92
3 M 25/60	101.4	97.5	4.79	0.20	1.54	0.35	2.45
6 M 25/60	101.5	81.3	4.85	NP	4.30	NP	7.34
9 M 25/60	101.2	86.5	4.68	0.80	5.88	0.92	7.70

12 M 25/60	98.7	74.8	4.65	1.20	4.77	1.72	10.74
1 M 30/75	102.7	97.8	4.80	0.18	1.09	0.26	1.39
2 M 30/75	101.7	94.1	4.79	0.30	1.15	0.48	1.91
3 M 30/75	99.8	93.5	4.76	0.40	4.30	0.52	6.27

Glycopyrronium 25 mcg + Formoterol Fumarate 20 mcg/ 2 ml Inhalation Solution							
Condition	% Assay		pH	% Related Substances			
	Glyco	Formo		Impurity C/ A		Total impurities	
				Glyco (C)	Formo (A)	Glyco	Formo
Initial	101.6	102.9	5.0	ND	0.13	0.05	0.16
1 M 2 ± 8°C	99.1	100.5	5.01	0.15	0.66	0.18	0.76
2 M 2 ± 8°C	101.7	104.1	4.99	0.08	0.74	0.21	0.84
3 M 2 ± 8°C	98.3	106.6	4.98	0.08	0.68	0.19	0.85
6 M 2 ± 8°C	96.2	97.6	4.95	0.19	1.00	0.25	1.33
9 M 2 ± 8°C	98.5	96.0	4.97	0.12	0.83	0.19	1.10
12 M 2 ± 8°C	98.7	99.8	4.94	0.29	1.00	0.42	1.33
1 M 25/60	100.0	100.0	5.01	0.10	0.73	0.15	0.91
2 M 25/60	101.2	102.3	5.02	0.24	1.13	0.36	1.62
3 M 25/60	98.3	104.1	4.99	0.39	1.65	0.49	2.58
6 M 25/60	96.9	90.2	4.92	0.84	2.09	0.91	4.34
9 M 25/60	98.1	89.0	4.88	1.05	3.99	1.33	6.21
12 M 25/60	98.3	91.8	4.91	1.81	3.08	1.86	7.34
1 M 40/75	96.8	94.5	4.98	0.87	2.13	1.08	3.43
2 M 40/75	99.2	94.1	4.97	1.64	2.55	1.82	5.85
3 M 40/75	98.1	92.0	4.96	2.59	3.97	2.59	8.55
6 M 40/75	86.6	65.9	ND	5.58	3.89	5.52	11.91

<u>Glycopyrronium 50 mcg + Formoterol Fumarate 20 mcg/ 2 ml Inhalation Solution</u>				
Condition	% Assay	pH	% Related Substances	
			Impurity C/ A	Total impurities

	Glyco	Formo		Glyco (C)	Formo (A)	Glyco	Formo
Initial	102.5	104.3	5.0	0.02	0.05	0.10	0.12
1 M 2 ± 8°C	102.0	103.1	5.01	0.04	0.10	0.13	0.19
2 M 2 ± 8°C	101.4	101.9	5.02	0.04	0.24	0.09	0.32
3 M 2 ± 8°C	101.8	99.1	4.98	0.12	0.26	0.15	0.36
6 M 2 ± 8°C	100.9	98.7	4.94	0.06	0.70	0.19	0.82
9 M 2 ± 8°C	99.7	101.0	4.93	ND	0.61	ND	0.91
12 M 2 ± 8°C	100.1	97.8	4.94	ND	ND	ND	ND
1 M 25/60	101.6	101.9	4.99	0.29	0.51	0.49	0.82
2 M 25/60	101.6	96.9	4.98	0.29	1.49	0.39	1.66
3 M 25/60	101.4	95.5	4.99	0.56	1.92	0.60	2.03
6 M 25/60	99.10	91.1	4.92	0.92	3.33	1.39	3.59
9 M 25/60	98.8	91.4	4.91	ND	5.14	ND	6.12
12 M 25/60	99.1	85.6	4.88	1.79	ND	1.94	ND
1 M 40/75	100.7	97.9	5.01	0.97	1.88	1.25	3.05
2 M 40/75	99.8	92.0	5.02	1.80	4.50	2.08	7.43
3 M 40/75	98.0	84.1	4.99	3.26	5.65	3.31	7.93
6M 40/75	94.9	67.9	5.01	5.57	4.47	6.07	9.71

Glycopyrronium 50 mcg + Formoterol Fumarate 20 mcg/ 2 ml Inhalation Solution

Condition	% Assay		pH	% Related Substances			
				Impurity C/ A		Total impurities	
	Glyco	Formo		Glyco (C)	Formo (A)	Glyco	Formo
Initial	102.5	104.7	5.5	0.06	0.05	0.63	0.10
1 M 2 ± 8°C	102.2	103.1	5.51	0.46	0.09	0.05	0.15
2 M 2 ± 8°C	101.5	98.9	5.52	0.09	0.19	0.14	0.24
3 M 2 ± 8°C	102.3	99.6	5.49	0.26	0.21	0.32	0.31
6 M 2 ± 8°C	102.1	100.1	5.45	0.16	0.62	0.19	0.71
9 M 2 ± 8°C	100.3	102.0	5.44	ND	0.54	ND	0.78
12 M 2 ± 8°C	102.4	99.3	5.41	0.54	ND	0.74	ND
1 M 25/60	102.2	102.6	5.48	0.81	0.35	0.90	0.96
2 M 25/60	99.2	95.2	5.49	0.87	0.89	1.05	0.65
3 M 25/60	100.2	96.4	5.51	1.74	1.25	1.78	1.38

6 M 25/60	100.9	96.7	5.41	2.58	2.31	2.70	2.54
9 M 25/60	95.3	94.2	5.39	ND	3.29	ND	4.15
1 M 40/75	98.6	97.9	5.51	3.00	1.84	3.05	2.03
2 M 40/75	91.6	85.9	5.52	5.41	4.47	5.69	5.32
3 M 40/75	90.3	84.2	5.49	9.73	4.80	10.04	6.77
6M 40/75	80.6	88.2	5.43	15.61	5.02	15.89	1.93

B. For nebulization composition comprising Glycopyrronium bromide and Formoterol fumarate prepared separately and to be mixed prior to administration

5

<u>Formoterol Fumarate 20 mcg/ 1 ml Inhalation Solution</u>				
Condition	% Assay	pH	Impurity A	Total impurities
Initial	101.1	5.0	0.08	0.27
1 M 2 ± 8°C	101.9	5.01	0.06	0.41
2 M 2 ± 8°C	100.1	4.98	0.17	0.43
3 M 2 ± 8°C	98.3	4.99	0.23	0.59
6 M 2 ± 8°C	99.3	4.96	0.09	1.29
9 M 2 ± 8°C	98.8	4.95	0.37	0.52
12 M 2 ± 8°C	98.8	5.02	0.08	0.36
18 M 2 ± 8°C	96.0	5.10	0.11	0.45
1 M 25/60	101.4	4.94	0.14	0.46
2 M 25/60	98.2	4.95	0.30	0.55
3 M 25/60	96.4	4.96	0.28	0.61
6 M 25/60	92.4	4.90	0.85	2.41
9 M 25/60	88.8	4.87	1.17	1.85
12 M 25/60	84.4	4.89	1.79	7.52
1 M 40/75	99.7	4.95	0.24	0.59
2 M 40/75	93.0	4.97	1.54	1.94
3 M 40/75	92.8	4.98	2.22	2.80
6M 40/75	78.7	4.88	5.42	9.34

<u>Glycopyrronium 50 mcg / 1 ml Inhalation Solution</u>				
Condition	% Assay	pH	Impurity C	Total impurities
Initial	101.1	4.8	ND	ND
1 M 2 ± 8°C	103.2	4.79	0.03	0.03
2 M 2 ± 8°C	101.6	4.77	0.04	0.04

3 M 2 ± 8°C	101.9	4.78	0.03	0.03
6 M 2 ± 8°C	101.0	4.75	NP	NP
9 M 2 ± 8°C	101.3	4.71	0.09	0.09
12 M 2 ± 8°C	99.8	4.78	0.17	0.17
18 M 2 ± 8°C	100.7	4.69	0.15	0.15
1 M 25/60	103.4	4.80	0.07	0.07
2 M 25/60	101.9	4.78	0.15	0.15
3 M 25/60	101.4	4.79	0.20	0.20
6 M 25/60	101.5	4.85	NP	NP
9 M 25/60	101.2	4.68	0.80	0.80
12 M 25/60	98.7	4.65	1.20	1.20
1 M 40/75	102.7	4.80	0.18	0.18
2 M 40/75	101.7	4.79	0.30	0.30
3 M 40/75	99.8	4.76	0.40	0.40

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and application of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments.

All publications, patents, and patent applications cited in this application are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated herein by reference.

WE CLAIM:

1. A nebulization composition comprising:
 - (a) glycopyrronium or a pharmaceutically acceptable salt thereof
 - (b) formoterol or a pharmaceutically acceptable salt thereof
 - 5 (c) isotonicity agent
 - (d) buffer, and
 - (e) optionally, a complexing agent.
2. The nebulization composition according to claim 1, wherein the composition contains glycopyrronium bromide and formoterol fumarate.
- 10 3. The nebulization composition according to claim 1, wherein the isotonicity agent is sodium chloride.
4. The nebulization composition according to claim 1, wherein the buffer is citric acid, sodium citrate or a combination thereof.
5. The nebulization composition according to claim 1, wherein the complexing agent is
15 ethylene diamine tetra-acetic acid or salts thereof.
6. The nebulization composition according to claim 1, wherein the composition is contained in a pre-filled container.
7. The nebulization composition according to claim 1, wherein the composition comprises glycopyrronium or a pharmaceutically acceptable salt thereof and formoterol or a
20 pharmaceutically acceptable salt thereof in a weight ratio of 1: 128 to 400: 1.
8. The nebulization composition according to claim 1, wherein the composition has a pH of about 3 to about 6.
9. The nebulization composition according to claim 1, wherein the composition contains 25 mcg glycopyrronium bromide and 15 mcg formoterol fumarate.
- 25 10. The nebulization composition according to claim 1, wherein the composition contains 25 mcg glycopyrronium bromide and 20 mcg formoterol fumarate.
11. The nebulization composition according to claim 1, wherein the composition contains 50 mcg glycopyrronium bromide and 10 mcg formoterol fumarate.
12. The nebulization composition according to claim 1, wherein the composition contains
30 50 mcg glycopyrronium bromide and 15 mcg formoterol fumarate.

13. The nebulization composition according to claim 1, wherein the composition contains 50 mcg glycopyrronium bromide and 20 mcg formoterol fumarate.
14. The nebulization composition according to claim 1, wherein the volume of the composition is 0.5 ml to 5 ml.
- 5 15. The nebulization composition according to claim 1, wherein the volume of the composition is 2 ml.
16. A nebulization composition comprising:
- (a) glycopyrronium or a pharmaceutically acceptable salt thereof
 - (b) formoterol or a pharmaceutically acceptable salt thereof
 - 10 (c) sodium chloride
 - (d) citric acid.
17. A nebulization composition comprising:
- (a) glycopyrronium or a pharmaceutically acceptable salt thereof
 - (b) formoterol or a pharmaceutically acceptable salt thereof
 - 15 (c) sodium chloride
 - (d) citric acid
 - (e) ethylene diamine tetra-acetic acid or salts thereof.
18. A nebulization composition comprising:
- (a) glycopyrronium or a pharmaceutically acceptable salt thereof
 - 20 (b) formoterol or a pharmaceutically acceptable salt thereof
 - (c) sodium chloride
 - (d) citric acid
 - (e) sodium citrate.
19. A nebulization composition comprising:
- 25 (a) glycopyrronium or a pharmaceutically acceptable salt thereof
 - (b) formoterol or a pharmaceutically acceptable salt thereof
 - (c) sodium chloride
 - (d) citric acid
 - (e) sodium citrate
 - 30 (f) ethylene diamine tetra-acetic acid or salts thereof.

20. The nebulization composition according to any one of the preceding claims, wherein the composition is substantially free of preservative.
21. The nebulization composition according to any one of the preceding claims, wherein the composition is a solution.
- 5 22. The nebulization composition according to any one of the preceding claims, wherein the composition is a suspension.
23. The nebulization composition according to any one of the preceding claims for the treatment of an inflammatory or obstructive airway disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/059106

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/40, A61P11/10 Version=2020.01

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 practicable, search terms used)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X;Y	EP 2749280 A2 (CIPLA LTD) 02 JULY 2014 Abstract; Paragraphs [0053, 0059], [0071], [0079], [0107-0110], [0292]; examples; Abstract	1-6, 8, 11-13, 16-19, 21-23; 7, 9-10, 14-15, 20
Y	WO 2011076842 A2 (CHIESI FARMACEUTICI S.P.A.) 30 JUNE 2011 Abstract; claims; page 6, line 21	1-23
Y	WO 2015101576 A1 (CHIESI FARMA SPA [IT]) 09 JULY 2015 Abstract; all claims; all examples	1-23
Y	WO 2017077488 A1 (GLENMARK PHARMACEUTICALS LTD [IN]) 11 MAY 2017 (FAMILY NONE) Abstract; page 2, line 15-24; example 1 and 2	1-23
Y	WO 2017089404 A1 (JAGOTEC AG [CH]) 01 JUNE 2017 (FAMILY NONE) page 2, line 14-41; page 3, line 20-36; page 5, line 15-40; example 1	1-23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

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"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

24-01-2020

Date of mailing of the international search report

24-01-2020

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2019/059106

Citation	Pub.Date	Family	Pub.Date
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