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(54) Title: A MEDICAMENT DEVELOPED FOR THE TREATMENT OF RESPIRATORY DISEASES

(57) Abstract: The present invention relates to a medicament composition a combination of carmoterol and/or a pharmaceutically acceptable derivative thereof and mometasone and/or a pharmaceutically acceptable derivative thereof so as to be used in the treatment of respiratory diseases, especially in asthma and chronic obstructive pulmonary disease (COPD), and the delivery of this pharmaceutical composition.



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A MEDICAMENT DEVELOPED FOR THE TREATMENT OF RESPIRATORY DISEASES

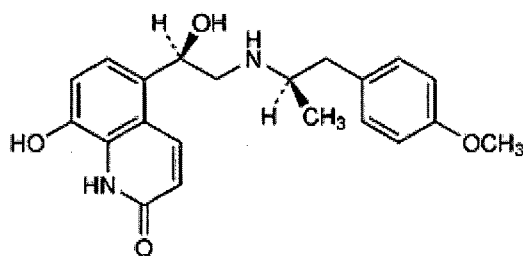
Field of the invention

The present invention relates to a pharmaceutical composition comprising the active agents
5 carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof so as to be used in the treatment of respiratory diseases, especially in asthma and chronic obstructive pulmonary disease (COPD), and the delivery of this composition.

Background of the invention

Airways, in other words bronchia, are the channels which function to distribute the inhaled air
10 into the lung tissues. In the case of respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD), stimulants such as allergen, infection, good and bad smell, smoke cause contractions in the airway muscles (bronchoconstriction) and/or excessive secretion in glands and results in contractions in the airways. Hence, one cannot breathe in as the inhaled air cannot be exhaled.

15 β_2 -agonists induce an alleviating or eliminating effect on bronchoconstriction in the treatment of respiratory diseases such as asthma and COPD. Carmoterol (Formula 1), which has the chemical name 8-hydroxy-5-[(1R)-1-hydroxy-2-[[[(2R)-1-(4-methoxyphenyl)propane-2-yl]amino]ethyl]-1H-quinolin-2-one, is a β_2 -agonist that was first disclosed in the patent numbered EP0147719.



Formula 1

Mometasone is a corticosteroid named (11 β ,16 α)-9,21-dichloro-11-hydroxy-16-methyl-3,20-dioxopregna-1,4-dien-17-yl 2-furoate. Mometasone, which is a potent anti-inflammatory drug, was first disclosed in the patent numbered US4472393.

Combined use of a β_2 agonist and a corticosteroid in the treatment of respiratory diseases such as asthma and COPD is known in the prior art. Because of the severe side effect of the beta agonists, the treatment comprising these drugs may not achieve sufficient reliability in some patients. Besides, these drugs should be taken twice or more a day because they do not have long duration of action. The adaptation of patients to the treatment decreases as a result of this frequent dose intake.

Many symptoms such as coughing, difficulty in breathing, chest tightness and wheezing may be observed, when adequate treatment for asthma is not provided. With these symptoms, very serious respiratory diseases may occur. Development of treatment methods to be applied and drugs to be used in order to prevent the occurrence and increase of these symptoms still maintain its significance today.

Consequently, there is still need for a more efficient, simpler treatment with less frequent dose delivery in order to provide the best control of respiratory diseases such as asthma and COPD.

Detailed description of the invention

The present invention provides a pharmaceutical composition comprising the active agents carmoterol or a pharmaceutically acceptable derivative thereof and mometasone and/or a pharmaceutically acceptable derivative thereof as combined in order to be used in the treatment of respiratory diseases such as asthma, COPD and allergic rhinitis. The inventor has surprisingly found that a significant unexpected therapeutic benefit, particularly a synergistic effect, in the treatment of inflammatory or obstructive airways diseases, is obtained by combination therapy using carmoterol and mometasone and/or a pharmaceutically acceptable derivative thereof.

It has been found that the pharmaceutical composition comprising carmoterol and mometasone and/or a pharmaceutically acceptable derivative thereof provides faster onset and has a more long-lasting and efficient therapeutic effect when compared with the pharmaceutical compositions containing only one of these active agents.

According to another aspect, the present invention provides a treatment method in which the medicament composition comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof is used as a symptomatolytic medicament. Carmoterol has a short onset of action when taken at particular dose amounts. Therefore, this composition can be used as a symptomatolytic medicament.

According to another aspect, the present invention provides a medicament in which carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof are reciprocally affected in a positive way. Accordingly, carmoterol enhances the anti-inflammatory effect resulting from mometasone's attaching with glucocorticoid receptors since carmoterol strengthens the translocation of these receptors. Mometasone, on the other hand, increases the transcription of β_2 – receptors with which carmoterol attaches.

According to the present invention in another aspect, carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof induce therapeutic effect at lower doses when they are used as combined compared with their use alone. Thus, side effects that the active agents may cause are minimized with the help of lower dose use.

According to another aspect, the present invention provides a simplified treatment realized by delivery of the medicament comprising carmoterol which is an ultra long-acting β_2 agonist and mometasone which is a corticosteroid inducing anti-inflammatory effect and/or pharmaceutically acceptable derivatives thereof once a day. With the help of the synergic effects obtained from the combination,, the active agents of the present invention provide a more long-lasting effect, a more effective, treatment and, as a result, a simpler treatment with less frequent dose delivery is provided and patient compatibility is increased.

According to another aspect, the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof is administered by the inhalation route. The medicament taken by the inhalation route is transmitted to the target area faster compared with the oral and the parenteral route. Thus, it provides faster and more efficient relief to the patient.

According to another aspect, the present invention enables less frequent dose intake of the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable

derivatives thereof by the inhalation route compared with the oral and the parenteral route and thus, severity of the side effects that the active agent may cause is minimized.

According to another aspect, the present invention provides the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof is provided for simultaneous, sequential or separate administration by the inhalation route in the treatment of inflammatory or obstructive airways diseases.

According to another aspect, the present invention provides a medicament composition in which carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof are preferably formulated in the same dosage form. Having the active agents in the same dosage form provides a more effective, simpler and cost-effective treatment. Additionally, it is simpler to track the progress of the patient in the treatments utilizing single dosage forms.

According to another aspect, the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof is delivered via single dose or multi dose inhalation devices. The active agents of the present invention can be inhaled from different devices while all of the active agents of the present invention can also be delivered by a single device. However, delivering the active agents as combined by a single device is preferred according to the present invention.

According to another aspect, the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof is delivered in aerosol, dry powder, solution or suspension form. The active agents in the medicament of the present invention can be delivered in the same dosage form as well as in different dosage forms. Preferably, all of the active agents of the medicament are delivered in same dosage form.

The term "aerosol" refers to dispersion or suspension of a liquid, solution or solid in the air or in a gas.

According to the present invention, the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof can be inhaled in aerosol form via a suitable device. The aerosol composition that is contained in the device can be characterized by comprising a propellant gas or not. The active agents of the present invention can be inhaled in the same aerosol composition as well as in different aerosol compositions.

According to the present invention, the active agents of the present invention are preferably inhaled in the same aerosol composition.

According to the present invention, the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof can contain propellant gas in addition to the active agents. According to the present invention, the medicament comprising propellant gas can be delivered by a pressured metered dose inhaler. These propellant gases are targeted to deliver the active agents to the lungs more easily. The propellant gases are preferably hydrocarbons and halohydrocarbons. Only one of these hydrocarbons or a mixture of them can be used. The particularly used propellant gases are HFA134a, HFA227 or mixture thereof; TG134a, TG227 or halogenated alkane derivatives selected from mixtures thereof.

According to the present invention, the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof can be transmitted to the lungs in a propellant-free aerosol composition by an appropriate inhalation device such as nebulizers.

According to the present invention, the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof can also comprise co-solvents, stabilizers, surfactants, antioxidants, lubricants and pH-adjusters in addition to the active agents.

According to the present invention, the medicament delivered in aerosol form and comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof can comprise active agent in the range of 0,001% to 8%, preferably in the range of 0,001% to 5% by weight.

According to the present invention, the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof can be delivered to the patient as a propellant-free solution or an inhalation composition in suspension form by a nebulizer. All of the active agents of the present invention can be inhaled in a single propellant-free solution or suspension together as well as in separate propellant gas-free solutions or suspensions one by one. Water or water-alcohol mixture can be used as solvent in these inhalation formulations. The rate of ethanol to water is at most 80%, preferably 60% by volume in the case that water-

alcohol mixture is used. According to the present invention, the pH value of suspensions or solutions comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof can be in the range of 2 to 7, preferably in the range of 2 to 5. In order to provide a value in these ranges, organic or inorganic acids, preferably hydrochloric acid, citric acid, ascorbic acid, formic acid, fumaric acid, tartaric acid, malic acid, sulphuric acid or a mixture of one or several of them can be used as a pH-adjuster.

Additionally, according to the present invention, the propellant-free inhalation formulations in solution or suspension form may contain edetic acid (EDTA) or salts thereof, excipients, sodium edetate, stabilizer or complexing agents in addition to said substances. The amount of sodium edetate comprised in said solution or suspension can be in the range of 0 mg/100 ml to 120 mg/100 ml, preferably in the range of 0 mg/100 ml to 50 mg/100 ml, more preferably in the range of 0 mg/100 ml to 10 mg/100 ml.

Additionally, according to the present invention, propellant gas-free solutions or suspensions can contain co-solvents and/or other excipients and/or preservative substances in addition to the active agents. The preferred co-solvents are hydroxyl groups, alcohols, especially other polar groups comprising isopropyl alcohols and glycols. The said excipients are substances which do not hold active agent characteristics such as tocopherols, vitamins, provitamins, surfactants. The preservative agents which are used in order to prevent the contamination caused by pathogens are cetyl pyridinium chloride, benzalkonium chloride, benzoic acid or benzoates as known in the prior art.

According to the present invention, the medicament of the present invention comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof is preferably administered in dry powder form and dry powder inhalation devices are used for delivery of the medicament of the present invention.

According to another aspect, the present invention provides delivery of the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof by dry powder inhalers.

According to the present invention, said dry powder formulations comprise pharmaceutically acceptable excipients in addition to the active agents. These excipients can be selected from

monosaccharides (glucose, etc.), disaccharides (lactose, saccharose, maltose, etc.), oligosaccharides and polysaccharides (dextran, etc.), polyalcohols (sorbitol, mannitol, xylitol, etc.), salts (sodium chloride, calcium carbonate, etc.) or a combination thereof. Preferably, lactose is used as an excipient in the medicament of the present invention. According to the present invention, the amount of pharmaceutically acceptable excipient is in the range of 0 to 50 mg, for example in the range of 1 mg to 48 mg, 1 mg to 47 mg, 1 mg to 42 mg, 1 mg to 40 mg, 1 mg to 38 mg, 1 mg to 35 mg, 1 mg to 32 mg, 1 mg to 30 mg, 1 mg to 28 mg, 1 mg to 25 mg, 1 mg to 23 mg, 2 mg to 48 mg, 2 mg to 47 mg, 2 mg to 42 mg, 2 mg to 40 mg, 2 mg to 38 mg, 2 mg to 35 mg, 2 mg to 32 mg, 2 mg to 30 mg, 2 mg to 28 mg, 2 mg to 25 mg, 2 mg to 23 mg, 2 mg to 20 mg, 3 mg to 48 mg, 3 mg to 47 mg, 3 mg to 42 mg, 3 mg to 40 mg, 3 mg to 38 mg, 3 mg to 35 mg, 3 mg to 32 mg, 3 mg to 30 mg, 3 mg to 28 mg, 3 mg to 25 mg. The amount of the pharmaceutically acceptable excipient is most preferably in the range of 3 mg to 20 mg, for example 3 mg to 19 mg, 3.5 mg to 18 mg, 4 mg to 17 mg.

According to another aspect, the medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof is delivered via a dry powder inhaler in which the medicament is stored in a peelable blister pack, reservoir or capsule for the treatment of patients with respiratory diseases.

In the inhalation devices designed to provide delivery of the dry powder medicament, a specific dose of the medicament in dry powder form is prepared for inhalation in response to each actuation of the device.

In the case that the dry powder medicament is stored in a reservoir, the medicament formulation containing more than one dose is stored in the reservoir of the device and one dose of dry powder medicament is inhaled by the patient each time the device is triggered.

According to the present invention, carmoterol and/or a pharmaceutically acceptable derivative thereof, which is one of the active agents in said medicament comprising the combination of active agents, is selected from the pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, the free base, organic salts, inorganic salts, esters, polymorphs, crystalline and amorphous forms of carmoterol and/or a combination thereof. R,R diastereomer of the carmoterol is preferably used in the medicament of the present invention.

According to the present invention, mometasone and/or a pharmaceutically acceptable derivative thereof, which is one of the active agents comprised in said medicament containing the combination of active agents, is selected from the pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, the free base, organic salts, inorganic salts, esters, polymorphs, crystalline and amorphous forms of mometasone and/or the combination thereof. Mometasone furoate is preferably used in the medicament of the present invention.

According to the present invention, the amount of carmoterol, which is one of the active agents comprised in the said medicament containing the combination of carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof, in the range of 0.01 µg, 0.05 µg, 0.1 µg, 0.2 µg, 0.3 µg, 0.4 µg, 0.5 µg, 0.6 µg, 0.7 µg, 0.8 µg, 0.9 µg or 1 µg to 7 µg, 8 µg, 9 µg, 10 µg, 12 µg, 15 µg, 17 µg, 20 µg, 22 µg, 25 µg or 30 µg, for example 0.01 µg to 30 µg, 0.01 µg to 27 µg, 0.01 µg to 25 µg, 0.01 µg to 23 µg, 0.01 µg to 20 µg, 0.01 µg to 18 µg, 0.01 µg to 15 µg, 0.01 µg to 12 µg, 0.01 µg to 10 µg, 0.01 µg to 8 µg, 0.01 µg to 7 µg, 0.05 µg to 30 µg, 0.05 µg to 27 µg, 0.05 µg to 25 µg, 0.05 µg to 23 µg, 0.05 µg to 20 µg, 0.05 µg to 18 µg, 0.05 µg to 15 µg, 0.05 µg to 12 µg, 0.05 µg to 10 µg, 0.05 µg to 8 µg, 0.05 µg to 7 µg, 0.1 µg to 30 µg, 0.1 µg to 27 µg, 0.1 µg to 25 µg, 0.1 µg to 23 µg, 0.1 µg to 20 µg, 0.1 µg to 18 µg, 0.1 µg to 15 µg, 0.1 µg to 12 µg, 0.1 µg to 10 µg, 0.1 µg to 8 µg, 0.1 µg to 7 µg, 0.2 µg to 30 µg, 0.2 µg to 27 µg, 0.2 µg to 25 µg, 0.2 µg to 23 µg, 0.2 µg to 20 µg, 0.2 µg to 18 µg, 0.2 µg to 15 µg, 0.2 µg to 12 µg, 0.2 µg to 10 µg, 0.2 µg to 8 µg, 0.2 µg to 7 µg, 0.3 µg to 30 µg, 0.3 µg to 27 µg, 0.3 µg to 25 µg, 0.3 µg to 23 µg, 0.3 µg to 20 µg, 0.3 µg to 18 µg, 0.3 µg to 15 µg, 0.3 µg to 12 µg, 0.3 µg to 10 µg, 0.3 µg to 8 µg, 0.3 µg to 7 µg, 0.4 µg to 30 µg, 0.4 µg to 27 µg, 0.4 µg to 25 µg, 0.4 µg to 23 µg, 0.4 µg to 20 µg, 0.4 µg to 18 µg, 0.4 µg to 15 µg, 0.4 µg to 12 µg, 0.4 µg to 10 µg, 0.4 µg to 8 µg, 0.4 µg to 7 µg, 0.5 µg to 30 µg, 0.5 µg to 27 µg, 0.5 µg to 25 µg, 0.5 µg to 23 µg, 0.5 µg to 20 µg, 0.5 µg to 18 µg, 0.5 µg to 15 µg, 0.5 µg to 12 µg, 0.5 µg to 10 µg, 0.5 µg to 8 µg, 0.5 µg to 7 µg, 0.6 µg to 30 µg, 0.6 µg to 27 µg, 0.6 µg to 25 µg, 0.6 µg to 23 µg, 0.6 µg to 20 µg, 0.6 µg to 18 µg, 0.6 µg to 15 µg, 0.6 µg to 12 µg, 0.6 µg to 10 µg, 0.6 µg to 8 µg, 0.6 µg to 7 µg, 0.7 µg to 30 µg, 0.7 µg to 27 µg, 0.7 µg to 25 µg, 0.7 µg to 23 µg, 0.7 µg to 20 µg, 0.7 µg to 18 µg, 0.7 µg to 15 µg, 0.7 µg to 12 µg, 0.7 µg to 10 µg, 0.7 µg to 8 µg, 0.7 µg to 7 µg, 0.8 µg to 30 µg, 0.8 µg to 27 µg, 0.8 µg to 25 µg, 0.8 µg to 23 µg, 0.8 µg to 20 µg, 0.8 µg to 18 µg, 0.8 µg to 15 µg, 0.8 µg to 12 µg, 0.8 µg to 10 µg, 0.8 µg to 8 µg, 0.8 µg to 7 µg, 0.9 µg to 30 µg, 0.9 µg to 27 µg, 0.9 µg to 25 µg, 0.9 µg to 23 µg, 0.9 µg to 20 µg, 0.9 µg to 18 µg, 0.9 µg to 15 µg, 0.9 µg to 12

5 μg , 0.9 μg to 10 μg , 0.9 μg to 8 μg , 0.9 μg to 7 μg , 1 μg to 30 μg , 1 μg to 27 μg , 1 μg to 25 μg , 1 μg to 23 μg , 1 μg to 20 μg , 1 μg to 18 μg , 1 μg to 15 μg , 1 μg to 12 μg , 1 μg to 10 μg , 1 μg to 8 μg , 1 μg to 7 μg , preferably 0.01 μg to 10 μg , 0.05 μg to 10 μg , 0.1 μg to 10 μg , 0.2 μg to 10 μg , 0.3 μg to 10 μg , 0.4 μg to 10 μg , 0.5 μg to 10 μg , 0.6 μg to 10 μg , 0.7 μg to 10 μg , 0.8 μg to 10 μg , 0.9 μg to 10 μg , 1 μg to 10 μg , most preferably 0.2 μg to 6 μg , 0.5 μg to 5.5 μg , 0.5 μg to 5 μg , 0.5 μg to 4 μg , 1 μg to 4 μg .

According to the present invention, the amount of mometasone, which is one of the active agents comprised in said medicament containing the combination of carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof, is in the range of 1 μg , 5 μg , 10 μg , 15 μg , 25 μg or 30 μg to 400 μg , 450 μg , 500 μg , 550 μg , 600 μg , 650 μg , 700 μg , 750 μg , 800 μg , 850 μg , 900 μg , 950 μg or 1000 μg for example 1 μg to 1000 μg , 1 μg to 950 μg , 1 μg to 900 μg , 1 μg to 850 μg , 1 μg to 800 μg , 1 μg to 750 μg , 1 μg to 700 μg , 1 μg to 650 μg , 1 μg to 600 μg , 1 μg to 550 μg , 1 μg to 500 μg , 1 μg to 450 μg , 1 μg to 400 μg , 5 μg to 1000 μg , 5 μg to 950 μg , 5 μg to 900 μg , 5 μg to 850 μg , 5 μg to 800 μg , 5 μg to 750 μg , 5 μg to 700 μg , 5 μg to 650 μg , 5 μg to 600 μg , 5 μg to 550 μg , 5 μg to 500 μg , 5 μg to 450 μg , 5 μg to 400 μg , 10 μg to 1000 μg , 10 μg to 950 μg , 10 μg to 900 μg , 10 μg to 850 μg , 10 μg to 800 μg , 10 μg to 750 μg , 10 μg to 700 μg , 10 μg to 650 μg , 10 μg to 600 μg , 10 μg to 550 μg , 10 μg to 500 μg , 10 μg to 450 μg , 10 μg to 400 μg , 15 μg to 1000 μg , 15 μg to 950 μg , 15 μg to 900 μg , 15 μg to 850 μg , 15 μg to 800 μg , 15 μg to 750 μg , 15 μg to 700 μg , 15 μg to 650 μg , 15 μg to 600 μg , 15 μg to 550 μg , 15 μg to 500 μg , 15 μg to 450 μg , 15 μg to 400 μg , 25 μg to 1000 μg , 25 μg to 950 μg , 25 μg to 900 μg , 25 μg to 850 μg , 25 μg to 800 μg , 25 μg to 750 μg , 25 μg to 700 μg , 25 μg to 650 μg , 25 μg to 600 μg , 25 μg to 550 μg , 25 μg to 500 μg , 25 μg to 450 μg , 25 μg to 400 μg , 30 μg to 1000 μg , 30 μg to 950 μg , 30 μg to 900 μg , 30 μg to 850 μg , 30 μg to 800 μg , 30 μg to 750 μg , 30 μg to 700 μg , 30 μg to 650 μg , 30 μg to 600 μg , 30 μg to 550 μg , 30 μg to 500 μg , 30 μg to 450 μg , 30 μg to 400 μg , preferably 30 μg to 600 μg , 40 μg to 650 μg , 45 μg to 600 μg , 45 μg to 500 μg , most preferably 45 μg to 450 μg .

The medicament composition in accordance with the present invention is preferably in the form of micronized dry powder particles. The active agents present in said medicament composition have average particle size of 1 μm to 20 μm , preferably from 1 μm to 10 μm , most preferably 1 μm to 6 μm . Lactose particles present in said medicament composition as

an excipient has average particle size of not more than 300 μm , preferably not more than 250 μm . The lactose particles in the medicament composition can be found in more than one fraction with different average particle size.

According to the present invention, the pharmaceutical composition comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof may additionally comprise one or more substances selected from the group comprising mast cell stabilizer, anticholinergic, adrenergic agonist, glucocorticosteroid, xanthine, anti-leukotriene, PDE IV inhibitor, EGFR inhibitor, anti-allergic, anti-inflammatory, antihistaminic and anti-muscarinic agents.

According to the present invention, the pharmaceutical composition comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof can additionally comprise one or more substances selected from the group consisting of mast cell stabilizers such as cromoglycate, nedocromil; anticholinergics such as tiotropium, ipratropium, glicopirronium, cromoglycate, oxytropium; β_2 - agonists such as formoterol, arformoterol, bambuterol, salmeterol, clenbuterol, salbutamol, fenoterol, terbutaline, carbuterol, pirbuterol; corticosteroids such as beclomethasone, budesonide, fluticasone, ciclesonide; xanthines such as doxophylline, theobromine, theophylline, aminophylline; anti-leukotrienes such as montelukast, pranlukast, zafirlukast, ritolukast, sulukast, tomelukast, verlukast, iralukast, ablukast ve cinalukast; antihistamines such as cetirizine, levocetirizine, loratadine, desloratadine, clemastine, chlorphenamine, diphenhydramine and pheniramine; PDE IV inhibitors such as roflumilast, piclamilast, cilomilast; preferably cromoglycate, tiotropium, montelukast, levocetirizine, desloratadine, roflumilast.

According to the present invention, the pharmaceutical composition comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof can additionally comprise cromoglycate and/or a pharmaceutically acceptable derivative thereof. Cromoglycate derivatives mentioned in the invention comprise the pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, the free base, organic salts, inorganic salts, esters, polymorphs, crystalline and amorphous forms of cromoglycate and/or a combination thereof. Sodium cromoglycate is preferably used in the preparation of the medicament of the present invention.

The medicament comprising carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof according to the present invention can be used in the treatment of many respiratory diseases, particularly in asthma, chronic obstructive pulmonary disease (COPD) and allergic rhinitis. Accordingly, these respiratory diseases can be, but not limited to, asthma
5 at any phase, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), exacerbation of airway hyperactivity, bronchiectasis, chronic obstructive pulmonary including emphysema and chronic bronchitis, respiratory diseases or lung diseases (COPD, COAD or COLD), pneumoconiosis, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis. This treatment can be prophylactic or symptomatic. In
10 addition, the composition of the present invention is especially used for symptomatic treatment of asthma and COPD.

The pharmaceutical composition pertaining to the present invention can be explained with, but not limited to, the examples given below.

The active agent carmoterol given in the following examples comprises all pharmaceutically
15 acceptable racemates, enantiomers or diastereomers, salts, solvates, esters, hydrates and/or the free base, polymorphs, amorphous and crystalline forms thereof. The active agent mometasone given in the following examples comprises all pharmaceutically acceptable salts, solvates, esters, hydrates and/or enantiomers, polymorphs, amorphous and crystalline forms thereof. Carmoterol or a pharmaceutically acceptable derivative thereof is preferably in the
20 form of R,R-carmoterol. The pharmaceutically acceptable excipient given in the following examples can optionally be added in a higher or a lower amount.

The capsule described in the following examples is made of gelatin; however, it can optionally be made of chitosan, starch and/or starch derivatives, cellulose and/or cellulose derivatives or synthetic polymers.

25 The active agent cromoglycate given in the following examples comprises all pharmaceutically acceptable racemates, enantiomers or diastereomers, solvates, esters, hydrates and/or the free base, polymorphs, amorphous and crystalline forms of cromoglycate.

Example 1

A dry powder formulation which is suitable to be stored in blisters so as to be used via a multi dose inhalator comprises 1 part of carmoterol and 400 parts of mometasone having a particle diameter in the range of 1 to 5 μm , and 10000 parts of lactose having a particle diameter below 300 μm as an excipient all of which were micronized in an air jet mill.

The example can be repeated by replacing the amounts used in example 1 with the amounts given in the table below.

Example	Amount of Carmoterol (parts)	Amount of Mometasone (parts)	Amount of Lactose (parts)
2	1	200	13850
3	2	200	15960
4	1	400	16500
5	2	400	14500
6	2	200	16600
7	2	400	13120
8	1	400	15900
9	1	400	13000
10	2	200	15900
11	2	400	16600
12	2	400	13820
13	2	200	14250
14	1	400	17000
15	1	400	16900
16	1	400	14690
17	2	200	14780
18	2	200	15960
19	2	200	16360

Example 20

A dry powder formulation which is suitable to be stored in a gelatin capsule so as to be used via an inhaler comprises 1 part of carmoterol and 200 parts of mometasone having a particle diameter in the range of 1 to 5 μm , and 5500 parts of lactose having a particle diameter below 300 μm as an excipient all of which were micronized in an air jet mill.

The example can be repeated by replacing the amounts used in example 20 with the amounts given in the table below.

Example	Amount of Carmoterol (parts)	Amount of Mometasone (parts)	Amount of Lactose (parts)
21	1	200	5020
22	2	200	4820
23	2	400	6070
24	2	400	7820
25	2	200	8580
26	2	200	7560
27	1	400	9830
28	1	400	10800
29	1	400	11050
30	2	400	12350
31	2	200	11920
32	2	300	10980
33	1	400	13000
34	1	400	9660
35	2	200	8600
36	2	200	4900
37	1	400	6230
38	1	400	5360

Example 39

5 A dry powder formulation which is suitable to be stored in blisters so as to be used via a multiple dose inhaler comprises 2 parts of carmoterol, 200 parts of mometasone, 10000 parts of cromoglycate having a particle diameter in the range of 1 to 5 μm , and 10000 parts of lactose having a particle diameter below 300 μm as an excipient all of which were micronized in an air jet mill.

Example 40

10 A dry powder formulation which is suitable to be stored in a gelatin capsule so as to be used via an inhaler comprises 2 parts of carmoterol, 200 parts of mometasone, 10000 parts of sodium cromoglycate having a particle diameter in the range of 1 to 5 μm , and 10000 parts of lactose having a particle diameter below 300 μm as an excipient all of which were micronized in an air jet mill.

Example 41

15 An aerosol formulation prepared to be used via a metered dose inhalator comprises 2 parts of carmoterol and 200 parts of mometasone and 97% of excipients by weight of the total formulation.

Claims

1. A medicament comprising a combination of carmoterol and/or a pharmaceutically acceptable derivative thereof and mometasone and/or a pharmaceutically acceptable derivative thereof for simultaneous, sequential or separate administration in the treatment of respiratory diseases.
2. The medicament composition according to claim 1 characterized in that said composition is delivered once a day.
3. The medicament composition according to claim 1 characterized in that said formulation comprises carmoterol and mometasone and/or pharmaceutically acceptable derivatives thereof together.
4. The medicament composition according to claims 1 to 3, wherein the amount of carmoterol and/or the pharmaceutically acceptable derivative thereof is in the range of 0.01 to 30 µg.
5. The medicament composition according to claim 4, wherein the amount of carmoterol and/or the pharmaceutically acceptable derivative thereof is in the range of 0.01 to 10 µg.
6. The medicament composition according to claim 5, wherein the amount of carmoterol and/or the pharmaceutically acceptable derivative thereof is in the range of 0.02 to 6 µg.
7. The medicament composition according to claims 1 to 3, wherein the amount of mometasone and/or the pharmaceutically acceptable derivative thereof is in the range of 1 to 1000 µg.
8. The medicament composition according to claim 7, wherein the amount of mometasone and/or the pharmaceutically acceptable derivative thereof is in the range of 30 to 600 µg.
9. The medicament composition according to claims 1 to 3 characterized in that carmoterol and/or a pharmaceutically acceptable derivative comprise the pharmaceutically acceptable solvates, the free base, hydrates, diastereomers, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline and amorphous forms of carmoterol and/or the combination thereof.
10. The medicament composition according to claim 9 characterized in that the pharmaceutically acceptable derivative of carmoterol is in the form of R,R carmoterol.
11. The medicament composition according to claims 1 to 3 characterized in that mometasone and/or a pharmaceutically acceptable derivative thereof comprise the pharmaceutically acceptable solvates, the free base, hydrates, enantiomers, racemates, organic

salts, inorganic salts, esters, polymorphs, crystalline and amorphous forms of mometasone and/or the combination thereof.

12. The medicament composition according to claim 11, wherein the pharmaceutically acceptable derivative of mometasone is mometasone furoate.

5 **13.** The medicament composition according to claim 1 characterized in that said composition is delivered by the inhalation route.

14. The medicament composition according to claim 13 characterized in that said medicament is delivered to the lungs via an inhaler.

10 **15.** The medicament composition according to claim 14 characterized in that said medicament is delivered via single or multiple dose inhalers.

16. The medicament composition according to claims 13 to 15 characterized in that said composition is in aerosol, dry powder, solution or suspension forms.

17. The medicament composition according to claim 16 characterized in that said composition is in aerosol form.

15 **18.** The medicament composition according to claim 17, wherein said composition is in propellant-free aerosol form.

19. The medicament composition according to claim 17 characterized in that said composition is in aerosol form with propellant.

20 **20.** The medicament composition according to claim 19 characterized in that the propellants that said composition comprises are selected from a group comprising hydrocarbons and halohydrocarbons.

21. The medicament composition according to claim 20 characterized in that said composition is in dry powder form.

25 **22.** The medicament composition according to claim 21 characterized in that said composition comprises a pharmaceutically acceptable excipient.

23. The medicament composition according to claim 22 characterized in that said pharmaceutically acceptable excipient is selected from a group comprising monosaccharides, disaccharides, polysaccharides and oligosaccharides.

30 **24.** The medicament composition according to claim 23 characterized in that said pharmaceutically acceptable excipient is lactose.

25. The medicament composition according to claim 16 characterized in that said composition is in solution or suspension form.

26. The medicament composition according to any one of the preceding claims characterized in that said composition additionally comprises one or more substances selected from a group comprising anticholinergic, adrenergic agonist, glucocorticosteroid, xanthine, anti-leukotriene, PDE IV inhibitor, EGFR inhibitor, anti-allergic, anti-inflammatory, antihistaminic and anti-muscarinic agents.

27. The medicament composition according to claim 26 characterized in that said composition additionally comprises one or more substances selected from a group consisting of mast cell stabilizers such as cromoglycate, nedocromil; anticholinergics such as tiotropium, ipratropium, glicopyrronium and, oxytropium; β_2 - agonists such as formoterol, arformoterol, bambuterol, salmeterol, clenbuterol, salbutamol, fenoterol, terbutaline, carbuterol and pirbuterol; corticosteroids such as beclomethasone, budesonide, fluticasone and ciclesonide; xanthines such as doxophylline, theobromine, theophylline and aminophylline; anti-leukotrienes such as montelukast, pranlukast, zafirlukast, ritolukast, sulukast, tomelukast, verlukast, iralukast, ablukast ve cinalukast; antihistamines such as cetirizine, levocetirizine, loratadine, desloratadine, clemastine, chlorphenamine, diphenhydramine and pheniramine; and PDE IV inhibitors such as roflumilast, piclamilast and cilomilast.

28. The medicament composition according to claim 27 characterized in that said composition additionally comprises one or more active agents selected from the group comprising cromoglycate, tiotropium, montelukast, levocetirizine, desloratadine and roflumilast.

29. The medicament composition according to claim 28 characterized in that said composition comprises a cromoglycate.

30. The medicament composition according to claim 29 characterized in that cromoglycate is preferably in the form of sodium salt.

31. The medicament according to any one of the preceding claims characterized in that said medicament is used in the treatment of many respiratory diseases, particularly in asthma, chronic obstructive pulmonary disease (COPD) and allergic rhinitis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2011/000115

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K31/47 A61K31/575
ADD. A61P11/00 A61P11/06 A61P11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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International application No

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