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(54) Title: STABLE PHARMACEUTICAL COMBINATIONS

(57) Abstract: Present invention relates to stable pharmaceutical combinations, methods for preparing these combinations and their medical use.



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STABLE PHARMACEUTICAL COMBINATIONS COMPRISING MONTELUKAST AND LEVOCETIRIZINE

Field of the invention

5 The present invention is related to stable pharmaceutical combinations, the preparation methods and medical uses thereof.

Background of the invention

10 The present invention provides an effective combination for the prevention and/or treatment of allergic and inflammatory diseases of skin or the upper and lower respiratory tract such as seasonal allergic rhinitis, perennial allergic rhinitis, allergic sinusitis, atopic dermatitis, urticaria, allergic asthma, aspirin mediated asthma, exercise mediated asthma and elimination of symptoms which are associated with these diseases.

The effect caused by the combination prepared according to the present invention is named as "desired effect" throughout this document.

15 The specified combination includes levocetirizine (or pharmaceutically acceptable salts, esters, solvates, derivatives, polymorphs or hydrates thereof) as a non-sedative long acting H1-antihistamine and montelukast (or pharmaceutically acceptable salts, esters, solvates, derivatives, polymorphs or hydrates thereof) as a leukotriene receptor antagonist.

Allergic reactions (hypersensitivity reactions) are extreme responses of the immune system against a substance that is normally harmless.

20 Normally, body immune system consisting of antibodies, white blood cells, mast cells, complement proteins and other substances protect the body against foreign substances called antigens. However, the immune system in people with high sensitivity may over-react to certain antigens defined as allergens, even though they are harmless. This condition is called as allergic reaction.

25 The allergens may cause allergic reactions when they are in contact with skin or eyes, when they are inhaled, eaten or injected. Allergic reactions may also occur as a result of periodic exposures to these substances as a part of seasonal allergies.

In most allergic reactions, antibodies called immunoglobulin E (IgE) are produced when the immune system is exposed to allergen for the first time. IgE binds to white blood cells called basophils in blood circulation and white blood cells called mast cells in the tissues. The first exposure may cause people to show sensitivity to allergens, but does not cause occurrence of any symptoms. When a sensitive person is re-faced with the allergen again, cells which have IgE in their surfaces secrete substances such as histamine and leukotriene that cause inflammation or tissue edema in the surrounding tissues. Substances of this kind initiate a series of reactions which harm the surrounding tissue.

Most of allergic reactions are characterized with the symptoms such as eye stream, itching, and rash (allergic conjunctivitis), nasal discharge, itching and congestion (allergic rhinitis), allergic sinusitis in sinus, skin itching, redness, and rash (urticaria), abdominal pain in the gastrointestinal system, bloating, vomiting and diarrhea, feeling of blockage in the ear, pain, hearing disorders associated with dysfunction of the eustachian tube, sneezing, coughing, bronchoconstruction, dyspnea, wheezy breathing, asthma attacks, airway narrowing related with edema.

Allergies can also trigger asthma attacks. Asthma is reversible airways narrowing characterized with dyspnea and wheeze attacks. Asthma is one of the most common chronic diseases which is seen among children and adults. Although the reasons for increasing prevalence of asthma is not known accurately, genetic factors, allergens, certain foods, certain drugs (aspirin), respiratory diseases, exercise, cigarette smoke, strong odors and sprays, chemicals, industrialization, air pollution and change of climate are considered to be effective.

Airways are flexible structures that can change the diameter in response to various warnings. In asthma, airways are hypersensitive to the non-specific stimulants. The air ways with increased sensitivity, gives exaggerated bronchoconstrictor responses even in the face of warnings which are too small to effect healthy people.

Contraction of airway is generally arised from abnormal sensitivity of cholinergic receptors caused by contraction of airway muscles which should not have been contracted.

Certain cells in the airways, particularly mast cells, is considered to initiate an excessive response. Mast cells secrete substances such as histamine and leukotriene which cause the smooth muscle to contract, increase in mucus secretion and arrival of some white blood cells

to inflammation region. It is observed that in asthma, eosinophils also contribute to the narrowing of the airways.

The typical clinical findings for patients with asthma are expectorating, coughing, wheezy breathing, shortness of breath and chest tightness feeling. These all findings may not be seen
5 at the same time. Type and intensity of findings may change from the patient to patient and in the same patient over time.

In studies, it is determined that at least 38% of patients with allergic rhinitis have asthma at the same time, at least 78% of allergic asthma patients have allergic rhinitis at the same time.

Although the patients with allergic rhinitis present no asthma symptoms, when they are
10 subjected to pulmonary function tests, it is found that the bronchial hyperreactivity is high.

It is thought that the risk of developing asthma in rhinitis patients is three times higher than the patients who have no rhinitis and rhinitis is thought to be a risk factor for asthma.

Untreated allergic rhinitis in asthma patients accompanied with rhinitis is also identified to effect asthma control adversely.

15 A large number of studies have shown that appropriate treatment of allergic rhinitis results in recovery of asthma symptoms, decrease in bronchial sensitivity, protection to bronchospasm and reduction in rescue medication.

Similarity of immunopathologic processes such as allergic hypersensitivity responses and persistent allergic inflammation, which are the underlying reasons of allergic rhinitis and
20 asthma, require to treat these diseases with similar therapeutic principles. The purpose of the treatment of both diseases is to get airway inflammation under control.

In this case, according to the invention, a powerful antihistaminic and a powerful leukotriene receptor antagonist combination should be preferred as anti-inflammatory treatment to prevent inflammatory reactions initiated by substances such as histamine and leukotriene.

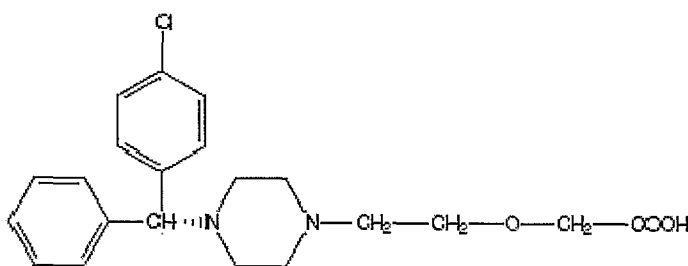
25 Chronic urticaria which is one of the allergy originated diseases in patients alone or in conjunction with asthma is difficult to treat and urticaria may not be controlled by antihistaminics. Because quinines except histamine, mediators such as prostaglandins and leukotrienes may be responsible for some symptoms of urticaria which can not be controlled by antihistaminics. Therefore, according to the invention, leukotriene antagonist should be

used along with antihistaminics for optimum effectiveness in the treatment of patients with chronic urticaria.

Antihistaminics are defined by histamine receptors which they interact with. Most commonly used ones for allergic disorders are H1 antihistaminics. Effects of H1 antihistaminics begin fast, they are long-acting (at least 24 hours) and it can be renewed. It shows very few side effects on the central nervous system and does not interact with medications.

The present invention provides a combination of H1-antihistaminic and leukotriene receptor antagonist which is effective for the treatment and/or prevention of allergic and inflammatory diseases of skin or the upper and lower respiratory tract and for elimination of symptoms which are associated with to these diseases.

Levocetirizine is a non- sedative, long-acting H1-antihistaminic which has a chemical name of 2-[2-[4-[(R)-(4-chlorophenyl)-phenyl-methyl] piperazin-1-yl]ethoxy]acetic acid.



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Cetirizine has been described for the first time in patent numbered EP0058146 A1 (patent numbered US4525358 A is included in its patent family). Patent numbered GB2225321 A for the preparation process for levocetirizine and WO9406429 A1 (EP0663828 B1 ve US5698558 A numbered patents are included within its patent family) numbered patent for using levocetirizine in the treatment of allergic diseases are available in the first patent applications of levocetirizine which is R-enantiomer of cetirizine.

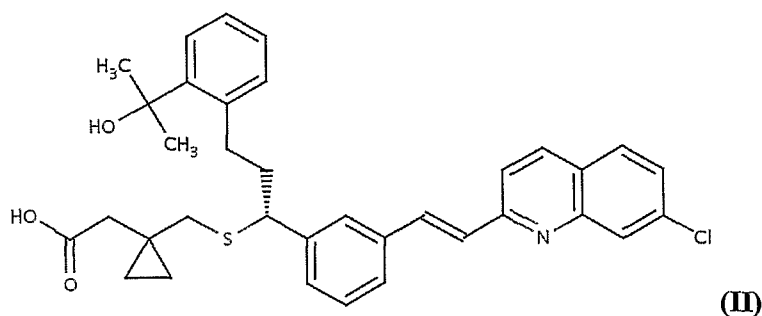
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Piperazine derivative of levocetirizin which is R-enantiomer of cetirizine is a powerful and selective H1 receptor antagonist. Levocetirizine is a new antihistaminic which bonds to H-1 receptors with high affinity, even two times higher than cetirizine. Levocetirizine prevents

histamine to bind to H1-receptors by entering in a competition with it. This antagonism blocks the effects of histamine on gastrointestinal tract, uterus, large blood vessels and bronchial smooth muscle. The blockade of H1 receptors also prevents antihistaminic activities such as edema, itching and temperature. The property of being non-sedative is partially explained by passing into central nervous system slightly and having very little affinity towards H1 receptors which are present in here.

Levocetirizine shows anti-allergic and anti-inflammatory activity. Studies revealed that levocetirizine inhibits the comprehensive and extensive sequence of events which initiates and extends the allergic inflammation.

- 10 Montelukast is a leukotriene receptor antagonist with the chemical name of 1-[[[(1R)-1-[3-[(1E)2-(7-chloro-2-quinoliny)ethenyl] phenyl]-3-[2-(1-hydroxy-1-methyl-ethyl) phenyl] propyl] thio] methyl] cyclopropane acetic acid.



- 15 Montelukast is firstly described in patent numbered EP480717 A1 (US5565473 A ve US5856322 A numbered patents present in its patent family). In the patent, processes for preparing montelukast and also its usage as leukotriene receptor antagonist are included.

Montelukast is a powerful and selective antagonist of leukotriene D4 (LTD4) which is administered by oral route and is effective on cysteinyl leukotriene receptor (CysLT1) in the respiratory tract. Cysteinyl leukotrienes (LTC4, LTD4, LTE4) are powerful inflammatory eicosanoids which are secreted by various cells including also mast cell and eosinophils. This important pro-asthmatics mediators connects to cysteinyl leukotriene receptor(CysLT1) and causes formation of a range of respiratory activity such as bronchoconstruction, intensive mucus secretion, vascular permeability and eosinophil accumulation.

Montelukast is a powerful compound which treats the parameters of asthma inflammation significantly. It bonds to CysLT₁ receptor with high affinity and selectivity and strongly inhibits the physiological effects of LTC₄, LTD₄, LTE₄ in CysLT₁ receptor without expressing any agonist activity.

- 5 Several clinical studies have demonstrated that the effect of levocetirizine and montelukast in anti-allergic and anti-inflammatory treatment increases synergistically:
- Maciej C.; Malgorzata G-C.; Lawrence M.D.; Pawel G. Montelukast with desloratadine or levocetirizine for the treatment of persistent allergic rhinitis. *Annals of allergy, asthma & immunology* 2006, 97(5), pp. 664-671
- 10
- Ciebiada M., Górski-Ciebiada M., DuBuske L., Gorski P. Combination Therapy with Montelukast and Antihistamines (desloratadine or Levocetirizine) Improves Quality of Life in Patients with Persistent Allergic Rhinitis: a Double Blind Placebo Controlled Study. *Journal of Allergy and Clinical Immunology*, 117(2), p.165
- 15
- Wilson A. M., Orr L. C., Sims E. J., Dempsey O. J., Lipworth B. J. Antiasthmatic Effects of Mediator Blockade versus Topical Corticosteroids in Allergic Rhinitis and Asthma. *Am. J. Respir. Crit. Care Med.* 2000, 162(4), 1297-1301
- KS W. Efficacy of leukotriene receptor antagonist with an anti-H1 receptor antagonist for treatment of chronic idiopathic urticaria. *J Dermatolog Treat* 2008. 11:1-4.
- 20 The present invention is directed towards obtaining a combination of levocetirizine (or a pharmaceutically acceptable salt, an ester, a solvate, a derivative, a polymorph or a hydrate thereof) and montelukast (or a pharmaceutically acceptable salt, an ester, a solvate, a derivative, a polymorph or a hydrate thereof) that provides the desired effect starting from the synergic effect of the said agents in anti-allergic and anti-inflammatory treatments
- 25 An aspect of the invention is to provide a formulation according to present invention comprising pharmaceutically acceptable, non-toxic and therapeutic amount of levocetirizine (or a pharmaceutically acceptable salt, an ester, a solvate, a derivative, a polymorph or a hydrate thereof) and montelukast (or a pharmaceutically acceptable salt, an ester, a solvate, a derivative, a polymorph or a hydrate thereof) wherein said agents are combined in a
- 30 pharmaceutical dosage form, such as tablet, to achieve desired effect.

However, as a result of studies, it is observed that the pharmaceutical composition containing montelukast and levosetirizin as the active ingredient has a stability problem arising from both of the active ingredients and therefore, this results in incompatibility between materials which form the pharmaceutical composition.

- 5 Montelukast is a highly hygroscopic substance which is sensitive to oxygen and light. Therefore, pharmaceutical compositions containing montelukast have a tendency to degrade depending on manufacturing and storage conditions. This brings about the requirement of selecting appropriate excipient composition in order to provide stability of montelukast in the pharmaceutical form prepared according to the present invention.
- 10 Mannitol is a polyol which is commonly used with highly hygroscopic active agents such as montelukast because of its non-hygroscopicity. However polyols, especially in the presence of water and/or high temperature, interact with levocetirizine and lead to the formation of unwanted byproducts. This condition bring along the requirement of selecting appropriate excipient composition and manufacturing method for preventing degradation of
- 15 levocetirizine as a result of reacting with mentioned auxiliary materials, in other words, to maintain its stability.

There is no prior art document that presents a solution to solve the stability problem of pharmaceutical compositions containing levocetirizine and montelukast combination wherein the satability problem arises from both substances. However, there are variety of

20 solutions which are developed for pharmaceutical compositions containing only levocetirizine and only montelukast.

In WO03059328 A1 numbered patent application, an oral pharmaceutical compositions which has at least two seperate formulations containing an active agent which is selected from cetirizine, salts, isomers, enantiomers, diastereomers and their mixtures thereof that a

25 first formulation which has a molar ratio of polyol-active agent is higher than 10 and does not include polyols having molecular weight lower than 300 and a second formulation which comprises at least one polyol having a molecular weight lower than 3000 and does not include any active agent was explained.

In the invention, a restricted complex formulation and a manufacturing process is tried to add

30 polyols without causing any stability problem as a result of interaction between polyols and cetirizine and derivatives thereof. Since this kind of formulation and manufacturing process

alone is very complicated even for cetirizine and derivative, it is not applicable for levocetirizine and montelukast combination.

The application numbered US20080241237 A1 discloses microparticulate compositions comprising a core particle comprising a substituted benzhydrylpiperazine (e.g. levocetirizine) or a pharmaceutically acceptable salt, ester, and/or solvate thereof; and a taste-masking layer comprising a water-insoluble polymer and a gastrosoluble polymer.

In the application, in order to include polyols to the formulation without causing the stability problem that may arise from the interaction between polyols and benzhydrylpiperazine and derivatives thereof, a manufacturing process and formulation that is complex and that may effect the release profile of levocetirizine in negative way, was mentioned.

For this reason, a formulation and manufacturing method as disclosed in said application is not applicable for a pharmaceutical combination comprising levocetirizine and montelukast.

The patent application numbered WO2007144902 A1 discloses an oral chewable bilayer tablet formulation comprising: an active formulation layer comprising cetirizine or its pharmaceutically acceptable salts, combination of water-insoluble and water-soluble polymer and low molecular weight polyol, wherein said combination of water-soluble polymer and water-insoluble polymer is in ratio of about 1 :0.5 to about 1 : 5, and wherein the molar ratio of the said low molecular weight polyol to said cetirizine is more than 10, and an inactive formulation layer comprising beta-cyclodextrin and edible organic acids, wherein said beta-cyclodextrin is necessarily not in intimate contact with cetirizine.

In the application, in order to include polyols to the formulation without causing stability problems that may arise from the interaction of polyols with cetirizine, a complex and limited formulation and manufacturing method was employed.

The formulation and the processing method disclosed in said application is quite complex even for cetirizine and derivatives therefore it is not applicable for combination of levocetirizine and montelukast.

The patent application numbered US20070086974 A1 describes a complex formed by cetirizine or a salt thereof and an ion exchange resin wherein the ratio of cetirizine to resin is 1:3 – 1:5 by weight. The choice of resin is very effective on the release profile and stability of the drug. A resin that is appropriate for a pharmaceutical composition comprising

levocetirizine may not be appropriate for a pharmaceutical composition comprising combination of levocetirizine and montelukast and this might effect the release and stability of the drug in a negative way. Therefore, a formulation of this sort is not feasible for a pharmaceutical composition comprising levocetirizine and montelukast.

- 5 The patent application numbered WO2007092031 A1 describes stable pharmaceutical compositions comprising montelukast or a salt thereof and at least one excipient selected from diluent, binder, disintegrant, wetting agent, lubricant, glidant and wherein the excipient is not microcrystalline cellulose. However, the solution disclosed in this patent application is not sufficient for a pharmaceutical composition comprising combination of levocetirizine
10 and montelukast.

- These documents belonging to the state of the art are related to pharmaceutical compositions comprising only levocetirizine and comprising only montelukast. However, when levocetirizine and montelukast are combined in a single dosage form, it is necessary to solve problems originating from these active agents. Furthermore it is necessary to develop a
15 formulation that prevents incompatibility that may arise from formulating these two agents together and a production process for said formulation. Moreover the formulation and the production method should be acceptable by means of application and cost. To be more specific, in formulations comprising levocetirizine and montelukast in combined form, in order to prevent moisture absorption of highly hygroscopic montelukast and hence to
20 improve the stability of montelukast, it is necessary to use a non-hygroscopic diluent due to the fact that the diluent forms a large portion of the formulation. A diluent that is widely used for this purpose is mannitol. However, use of mannitol for increasing the stability of montelukast will result in decomposition of levocetirizine. As a result, when preparing pharmaceutical formulations comprising both levocetirizine and montelukast, there will be
25 incompatibility between the active agents forming the composition. This situation, proves the need for preparing stable pharmaceutical formulations comprising combination of levocetirizine and montelukast in a single dosage form to provide the desired effect and uncomplicated preparation methods thereof.

- The patent numbered WO9952553 A1, discloses use of cetirizine or a salt thereof and a
30 leukotriene inhibitor or a salt thereof for treatment of diseases related to leukotriene inhibition. Moreover, it was indicated that the cetirizine can be in the form of levocetirizine and the leukotriene inhibitor can be montelukast. The application states that considering the

different therapeutic activity of montelukast and levocetirizine, these two agents can be used in combined form, however, problems that may arise while formulating these two agents was not mentioned and as a result no solution for this problem was proposed.

5 The subject matter of this invention provides a composition and a manufacturing method thereof that solves stability problems of each of the active components and incompatibility problems between these agents in order to combine montelukast and levocetirizine in a way that provides the desired effect.

Summary of the Invention

10 Present invention relates to a pharmaceutical composition comprising therapeutically effective amount of levocetirizine or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof and therapeutically effective amount of montelukast or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof for the manufacture of a medicament for use in treatment of allergic and inflammatory illnesses of skin or illnesses of upper or lower respiratory tract such as seasonal
15 allergic rhinitis, perennial allergic rhinitis, allergic sinusitis, atopic dermatitis, urticaria, allergic asthma, aspirin mediated asthma, exercise mediated asthma characterized in that levocetirizine or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof and montelukast or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof are preformulated with a series of pre-treatment
20 steps.

Detailed description of the invention

The present invention relates to obtaining a combination of levocetirizine (or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof) and montelukast (or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph
25 or hydrate thereof) to prepare a combination that provides desired effect starting from the synergistic effect of levocetirizine and montelukast on anti-allergic and anti-inflammatory treatment. However, in course of the research carried out for this purpose, as mentioned before, stability problems for each of the components and incompatibility problems of the components forming the combined preparation have arisen. It is necessary to develop a
30 stable pharmaceutical composition and a method of production thereof to obtain a combination of montelukast and levocetirizine that would provide the desired effect.

According to the present invention, levocetirizine or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof and montelukast or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof that is preformulated with a series of pre-treatment steps provides optimum efficiency for treatment and/or prophylaxis of several allergic and inflammatory diseases and for eliminating symptoms related to them.

In order to prevent probable problems that may arise from formulating said active ingredients together, a simple manufacturing process wherein the active agents are formulated separately was developed. The manufacturing process according to the present invention comprises the following steps:

- In the first step montelukast or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof, mannitol and optionally at least one pharmaceutically acceptable excipient was mixed and sieved. By adding optionally at least one pharmaceutically acceptable excipient to the said mixture the first mixture is obtained. Mannitol that is used as a diluent in high amounts is non-hygroscopic and as a result presence of mannitol in high amounts prevents montelukast from absorbing moisture and hence montelukast prepared this way remained stable. Among the added pharmaceutically acceptable excipients at least one stabilizing agent can be used to contribute to maintaining stability.
- In the second step, levocetirizine or a pharmaceutically acceptable salt, derivative, polymorph or hydrate thereof and optionally at least one pharmaceutically acceptable excipient is mixed and sieved. By adding optionally at least one pharmaceutically acceptable excipient to the said mixture the second mixture is obtained. Since the polyol (mannitol) is added to the mixture that does not contain levocetirizine, it does not come in contact with levocetirizine and this eliminates the stability problem that may arise because of the incompatibility of the said agents.
- Finally, both of the mixtures obtained are combined in a preferred single pharmaceutical dosage form and preferably fed into a tablet pressing machine separately to obtain a layered tablet. The tablet forms are optionally coated with a film coating.

Another aspect of the invention is that the composition comprising; a specific amount of levocetirizine (or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof) and montelukast (or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof) and sufficient amount of mannitol and optionally
5 at least one pharmaceutically acceptable excipient selected from stabilizing agent, diluent, binder, disintegrant, lubricant, glidant and surface active agent; provides optimum efficiency for prophylaxis and/or treatment various allergic and inflammatory diseases and for eliminating symptoms related to these diseases.

The term “various allergic and inflammatory diseases” refers to; allergic and inflammatory
10 illnesses of skin or illnesses of upper or lower respiratory tract such as seasonal allergic rhinitis, perennial allergic rhinitis, allergic sinusitis, atopic dermatitis, urticaria, allergic asthma, aspirin mediated asthma, exercise mediated asthma.

The term “symptoms related to diseases” refers to; lachrymation, itching and rash in the eyes, nasal drip, itching and rhinocleisis, sneezing, coughing, itching, rash and exuviation of
15 the skin, bronchoconstriction, shortness of breath, wheezing, contraction of airways due to edema, expectoration and asthma attacks.

The terms “specific amounts”, “sufficient amounts” and “optionally” refers to; 0.1-20% by weight levocetirizine or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof, 0.1-20% by weight montelukast or pharmaceutically
20 acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof, 0.1-75% by weight mannitol and optionally at least one pharmaceutically acceptable excipient selected from stabilizing agent, diluent, binder, disintegrant, lubricant, glidant and surface active agent to obtain the desired effect.

The term “levocetirizine or pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate” refers preferentially to levocetirizine dihydrochloride salt.
25

The term “montelukast or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate” refers preferentially to montelukast sodium.

Stabilizing agent and/or agents can be chosen from a group consisting of antioxidants, chelating agents, alkalizing agents and photoprotective agents. In pharmaceutical

formulations stabilizing agent and or agents can be found in amounts 0-85 %, or preferably in amount 0.01-75% by weight.

Antioxidants can be chosen from butylated hydroxyanisole (BHA), sodium ascorbate, butylated hydroxytoluene (BHT), sodium sulphide, gallates (e.g. propyl gallete), tocopherol, 5 citric acid, malic acid, ascorbic acid, acetylcystein, fumaric acid, lecithin, ascobyl palmitate, ethylenediamine tetraacetate.

Chelating agents can be chosen from disodium EDTA, edetic acid, citric acid, sodium citrate, potassium citrate and combinations thereof. These agents prevent oxidation by masking the metal ions that can catalyze the oxidation process by surrounding them.

10 Alkalizing agents can be chosen from; alkali metal salts like sodium carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate; alkali earth metal salts like calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium acetate, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, 15 magnesium acetate, magnesium acetate, magnesium silicate, magnesium aluminate and organic compounds like primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, diethanolamine, meglumine, monosodium glutamate, polyacrylate sodium, sodium alginate.

Photoprotective agents can be chosen from metal oxides such as titanium oxide, iron oxide 20 or zinc oxide.

Pharmaceutically acceptable diluents can be chosen from compounds like lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, calcium phosphate (dibasic and/or tribasic), calcium sulphate trihydrate, calcium sulphate dihydrate, calcium carbonate, kaolin, powdered cellulose, dextrose, dextrates, dextrin, sucrose, maltose, 25 fructose, mannitol, sorbitol and xylitol. Diluent is present in the pharmaceutical formulations preferably in an amount 0-85 % and more preferably in an amount 0.1-75 % by weight.

Pharmaceutically acceptable binders can be chosen from a group of compounds like sugars such as starch (potato starch, corn starch, wheat starch), sucrose, glucose, dextrose, lactose, maltodextrin, natural and synthetic gums (e.g. acacia), gelatin, cellulose derivatives (e.g. 30 microcrystalline cellulose, HPC, HEC, HPMC, carboxymethyl cellulose, methyl cellulose,

ethyl cellulose), polyvinylpyrrolidone, polyethyleneglycols, waxes, calcium carbonate, calcium phosphate, alcohols (e.g. sorbitol, xylitol, mannitol) and water. Binder is present in the pharmaceutical formulation preferably in an amount 0-10 % or more preferably in an amount 0.1-5 % by weight.

- 5 Pharmaceutically acceptable disintegrants can be chosen from starch (e.g. corn starch, potato starch), sodium starch glycolate, pregelatinized starch, cellulose derivatives (e.g. croscarmellose sodium or microcrystalline sodium), polyvinylpyrrolidone (PVP), crospovidone, alginic acid, sodium alginate, clays (e.g. xanthan gum or vee gum), ion
10 Exchange resins and effervescent systems (alkali or earth alkali metal carbonates [e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, potassium hydrogen carbonate, calcium carbonate etc.]; polybasic organic acids or their salts such as sodium hydrogen sulphate, potassium hydrogen sulphate, sodium dihydrogen phosphate, succinic acid, tartaric acid, adipic acid, citric acid etc.). Disintegrant can be present in the pharmaceutical formulation preferably in an amount 0-85 % or more preferably in an amount
15 0.1-75 % by weight.

- Pharmaceutically acceptable lubricants can be chosen from metallic stearates (e.g. magnesium stearate, calcium stearate, aluminium stearate), fatty acid esters (e.g. sodium stearyl fumarate), fatty acids (e.g. stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethyleneglycols, metallic lauryl
20 sulphates (e.g. sodium lauryl sulphate, magnesium lauryl sulphate), sodium chloride, sodium benzoate, sodium acetate and talc. Lubricant can be present in the pharmaceutical formulation preferably in an amount 0-10 % or more preferably in an amount 0.1-5%.

- Pharmaceutically acceptable glidants can be chosen from a group of compounds such as silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, tribasic calcium
25 phosphate, metallic stearates, calcium silicate and metallic lauryl sulphates. Glidant can be present in the pharmaceutical formulation in an amount less than 1% by weight.

- Pharmaceutically acceptable surface active agents can be chosen from a group of compounds such as polyoxyethylene sorbitan fatty acid esters (polysorbates), sodium lauryl sulphate, sodium stearyl fumarate, polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyethylene
30 glycols (PEG), polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, aminoacids like L-leucine, sugar esters of fatty acids and glycerides

of fatty acids. Surface active agent is present in the pharmaceutical formulation preferably in an amount 0-10% or more preferably in an amount 0.1-5% by weight.

In addition to these, other pharmaceutically acceptable excipients such as; solubility modulators, electrolytes, coloring agents and coating agents can be used in the formulation.

- 5 Pharmaceutical dosage forms according to the present invention are conventional tablet film coated tablet, chewable tablet, rapidly dissolving tablet, effervescent tablet, micro tablet, pellet tablet, caplet, capsule, effervescent granule, rapidly dissolving granule, rapidly dissolving powder mixture or dry powder mixture for syrups.

- 10 Formulation examples according to the present invention are given below. The examples are given for the sake of explaining the invention and hence the invention is not limited with these examples.

Examples

Example 1.

Content	Amount (mg)
Montelukast sodium *	10.4
Mannitol	127.75
Red iron oxide	0.05
Croscarmellose Sodium	6
HPC	8
Sodium hydrogen carbonate	35
Colloidal silicon dioxide	0.2
L-leucine	10
Levocetirizine dihydrochloride	5
Lactose	60
Microcrystalline cellulose	35
Colloidal silicon dioxide	0.6
Magnesium stearate	2
Total weight	300
Coating agent	5

* Equivalent to 10 mg montelukast

Example 2.

Content	Amount (mg)
Montelukast sodium *	10.4
Mannitol	131.74
Red iron oxide	0.06
Croscarmellose sodium	7
HPC	10
Sodium hydrogen carbonate	24
Magnesium stearate	10
Levocetirizine dihydrochloride	5
Lactose	62
Microcrystalline cellulose	38
Colloidal silicon dioxide	0.8
Magnesium Stearate	1
Total Weight	300
Coating agent	5

* Equivalent to 10 mg montelukast

Claims

1. Use of a pharmaceutical composition comprising therapeutically effective amount of levocetirizine and therapeutically effective amount of montelukast for the manufacture of a medicament for use in treatment of allergic and inflammatory illnesses of skin or illnesses of upper or lower respiratory tract such as seasonal allergic rhinitis, perennial allergic rhinitis, allergic sinusitis, atopic dermatitis, urticaria, allergic asthma, aspirin mediated asthma, exercise mediated asthma characterized in that the manufacturing process for the pharmaceutical composition comprising levocetirizine and montelukast consists of preformulating said active ingredients with a series of pre-treatment steps.
2. A manufacturing process of a pharmaceutical composition according to claim 1 characterized in that the pre-treatment step for montelukast comprises the steps of;
 - mixing and sieving of montelukast or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof, mannitol and optionally at least one pharmaceutically acceptable excipient, and
 - obtaining the first mixture by optionally adding at least one pharmaceutically acceptable excipient to said mixture.
3. A manufacturing process of a pharmaceutical composition according to claim 1 characterized in that the pre-treatment step for levocetirizine comprises the steps of;
 - mixing and sieving of levocetirizine or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof, and
 - optionally a pharmaceutically acceptable excipient and obtaining the second mixture by optionally adding at least one pharmaceutically acceptable excipient to said mixture.
4. A manufacturing process of a pharmaceutical composition according to claim 1, characterized in that the last step of the process comprises combining two mixtures in a single formulation with regard to preferred pharmaceutical dosage form.
5. A manufacturing process of a pharmaceutical composition according to claim 4, characterized in that the last step of the process comprises optionally feeding two mixtures separately to tablet pressing machine to obtain a layered tablet.
6. A pharmaceutical composition, prepared by the manufacturing process according to claim 1, comprises;
 - Levocetirizine or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof in a range of 0.1-20 % by weight,

- Montelukast or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof in a range of 0.1-20 % by weight,
 - Mannitol in a range of 0.1-75 % by weight.
 - Optionally at least one pharmaceutically acceptable excipient selected from stabilizing agent, diluent, binder, disintegrant, lubricant, glidant and surface active agent.
- 5
7. A pharmaceutical composition, prepared by the manufacturing process according to claim 1, characterized in that the composition is used for the treatment of symptoms related to allergic and inflammatory diseases of skin or the upper and lower
- 10 respiratory tract such as seasonal allergic rhinitis, perennial allergic rhinitis, allergic sinusitis, atopic dermatitis, urticaria, allergic asthma, aspirin mediated asthma, exercise mediated asthma are symptoms such as eye stream, itching, and rash, nasal discharge, itching and congestion, sneezing, coughing, skin itching, redness, and rash, bronchoconstruction, dyspnea, wheezy breathing, airways narrowing related with
- 15 edema, expectorating and asthma attacks.
8. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises levocetirizine dihydrochloride salt as pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate of levocetirizine.
9. A pharmaceutical composition, prepared by the manufacturing process according to
- 20 claim 1 comprises montelukast sodium as pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate of montelukast.
10. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises an antioxidant selected from butylated hydroxyanisole (BHA), sodium ascorbate, butylated hydroxytoluene (BHT), sodium sulphide, gallates (e.g.
- 25 propyl gallate), tocopherol, citric acid, malic acid, ascorbic acid, acetylcystein, fumaric acid, lecithin, ascorbyl palmitate, ethylenediamine tetraacetate as stabilizing agent.
11. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises a chelating agent selected from disodium EDTA, edetic acid, citric
- 30 acid, sodium citrate, potassium citrate or combinations thereof as stabilizing agent.

12. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises a alkalazing agent selected from alkali metal salts such as sodium carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate; alkali earth metal salts such as calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium acetate, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, magnesium acetate, magnesium silicate, magnesium aluminate; or organic compounds such as primary, secondary, tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, diethanolamine, ethylenediamine, meglumine, monosodium glutamate, polacrylene sodium, sodium alginate as stabilizing agent.
13. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises a photoprotective agent selected from metal oxides such as titanium dioxide, iron ozide or zinc oxide as stabilizing agent.
14. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 characterized in that the stabilizing agent is present in the composition in an amount 0-85% or preferably in an amount 0.01-75 % by weight.
15. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises a diluent selected from lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, calcium phosphate (dibasic and/or tribasic), calcium sulphate trihydrate, calcium sulphate dihydrate, calcium carbonate, kaolin, lactitol, powdered cellulose, dextrose, dextrans, dextrin, sucrose, maltose, fructose, mannitol, sorbitol and xylitol.
16. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 characterized in that the diluent is present in the composition in an amount 0-85% or preferably 0.1-75% by weight.
17. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises a binder selected from starch (e.g. potato starch, corn starch, wheat starch), sugars like sucrose, glucose, dextrose, lactose, maltodextrin, natural and synthetic gums (e.g. acacia), gelatine, cellulose derivatives (e.g. microcrystalline cellulose, HPC, HEC, HPMC, carboxymethylcellulose, methylcellulose,

ethylcellulose), polyvinylpyrrolidone, polyethyleneglycol, wax, calcium carbonate, calcium phosphate, alcohols (e.g. sorbitol, xylitol, mannitol) and water.

- 5 18. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 characterized in that the binder is present in the composition in an amount 0-10% or preferably in an amount 0.1-5% by weight.
- 10 19. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises a disintegrant selected from starch (corn starch, potato starch), sodium starch glycolate, pregelatinized starch, cellulose derivatives (e.g. croscarmellose sodium or microcrystalline cellulose), polyvinylpyrrolidone (PVP), crospovidone, alginic acid, sodium alginate, clays (e.g. xanthan gum or vee gum), ion exchange resins and effervescent systems (alkali or earth alkali metal carbonates [e.g. sodium carbonates, sodium hydrogen carbonate, potassium carbonate, potassium hydrogen carbonate, calcium carbonate]; water soluble polybasic organic acids or their salts like sodium hydrogen sulfate, potassium hydrogen sulphate, sodium
- 15 dihydrogen phosphate, succinic acid, tartaric acid, adipic acid, citric acid, etc.)
- 20 20. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 characterized in that the disintegrant is present in the composition in an amount 0-85% or preferably in an amount 0.1-75% by weight.
- 20 21. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises a lubricant selected from metallic stearates (e.g. magnesium stearate, calcium stearate, aluminum stearate), esters of fatty acids (e.g. sodium stearyl fumarate), fatty acids (e.g. stearic acid), fatty acid alcohols, glyceryl beheanate, mineral oils, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulphates (e.g. sodium lauryl sulphate, magnesium lauryl
- 25 sulphate), sodium chloride, sodium benzoate, sodium acetate and talc.
22. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 characterized in that the lubricant is present in the composition in an amount 0-10% or preferably in an amount 0.1-5% by weight.
- 30 23. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises a glidant selected from silicon dioxide, magnesium trisilicate,

powdered cellulose, starch, talc, tribasic calcium phosphate, metallic stearates, calcium silicate and metallic lauryl sulphates.

24. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 characterized in that the glidant is present in the composition in an amount less than 1% by weight.
25. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 comprises a surface active agent selected from polyoxyethylene sorbitan fatty acid esters (polysorbates), sodium lauryl sulphate, sodium stearyl fumarate, polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyethylene glycols (PEG), polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, aminoacids like L-leucine, sugar esters of fatty acids and glycerides of fatty acids.
26. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 characterized in that surface active agent is present in the composition in an amount 0-10% or preferably in an amount 0.1-5% by weight.
27. A pharmaceutical composition, prepared by the manufacturing process according to claim 1 characterized in that, the pharmaceutical composition is in the form of conventional tablet, film coated tablet, chewable tablet, rapidly dissolving tablet, effervescent tablet, micro tablet, pellet tablet, caplet, capsule, effervescent granule, rapidly dissolving granule, rapidly dissolving powder mixture or dry powder for preparing syrup.

INTERNATIONAL SEARCH REPORT

International application No

PCT/TR2010/000051

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/47 A61K31/495 A61K45/06 A61P37/08

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, WPI Data, PAJ, BIOSIS, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IN 891D EL2 007 A (RANBAXY LAB LTD) 26 December 2008 (2008-12-26) the whole document	1-27
X	WO 03/101434 A2 (BHATTACHARYA SAMPAD [IN]; LAGU KIRAN [IN]; CHHABADA SANGEETA [IN]) 11 December 2003 (2003-12-11) claims 1-19	1-27
X	WO 2008/079312 A2 (SCHERING CORP [US]; DANZIG MELVYN RICHARD [US]; DOWN GERALD ROBERT BRI) 3 July 2008 (2008-07-03) the whole document	1-27
	----- -/-	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No

PCT/TR2010/000051

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CIEBIADA MACIEJ ET AL: "Montelukast with desloratadine or levocetirizine for the treatment of persistent allergic rhinitis." ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY : OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF ALLERGY, ASTHMA, & IMMUNOLOGY NOV 2006 LNKD- PUBMED:17165277, vol. 97, no. 5, November 2006 (2006-11), pages 664-671, XP002581077 ISSN: 1081-1206 the whole document	1-27
X	CIEBIADA M ET AL: "Quality of life in patients with persistent allergic rhinitis treated with montelukast alone or in combination with levocetirizine or desloratadine." JOURNAL OF INVESTIGATIONAL ALLERGOLOGY & CLINICAL IMMUNOLOGY : OFFICIAL ORGAN OF THE INTERNATIONAL ASSOCIATION OF ASTHMOLOGY (INTERASMA) AND SOCIEDAD LATINOAMERICANA DE ALERGIA E INMUNOLOGÍA 2008 LNKD- PUBMED:18973097, vol. 18, no. 5, 2008, pages 343-349, XP009133205 ISSN: 1018-9068 the whole document	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/TR2010/000051

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
IN 891DEL2007	A	NONE	
WO 03101434	A2	11-12-2003 AU 2003264859 A1	19-12-2003
WO 2008079312	A2	03-07-2008 EP 2121022 A2	25-11-2009