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(54) Title: USE OF LEVOCETIRIZINE FOR THE TREATMENT OF PERSISTENT ALLERGIC RHINITIS

(57) Abstract: The present invention relates to a pharmaceutical use of levocetirizine for the treatment of persistent allergic rhinitis.

The present invention relates to the use of levocetirizine for the preparation of drugs effective for the treatment of the persistent allergic rhinitis.

5 International patent application 94/06429 describes a method utilising levocetirizine for the treatment of seasonal and perennial allergic rhinitis.

It has now surprisingly been found that levocetirizine possesses therapeutic properties which render it particularly useful in the treatment of persistent allergic rhinitis. These activities are not observed in the dextrocetirizine.

10 The purpose of the invention concerns the treatment of persistent allergic rhinitis.

The present invention is based on the unexpected recognition that administration of pharmaceutical compositions comprising levocetirizine, or a pharmaceutically acceptable salt thereof to a patient treats the persistent allergic
15 rhinitis.

The present invention encompasses a method for treating persistent allergic rhinitis which comprises administering to a patient a therapeutically effective amount of levocetirizine or a pharmaceutically acceptable salt thereof.

20 The present invention also encompasses the use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for the treatment of persistent allergic rhinitis.

The present invention relates to the use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for decreasing the symptoms of persistent allergic rhinitis and improving the quality of life.

25 In another aspect, the present invention relates to a method of treating in a patient persistent allergic rhinitis by administering an effective dose of levocetirizine or a pharmaceutically acceptable salt thereof.

The term "cetirizine" refers to the racemate of [2-[4-[(4
chlorophenyl)phenylmethyl] -1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride
30 salt which is well known as cetirizine dihydrochloride; its levorotatory and dextrorotatory enantiomers are known as levocetirizine and dextrocetirizine. Processes for preparing cetirizine, an individual optical isomer thereof or a pharmaceutically acceptable salt thereof have been described in European Patent 0 058 146, Great Britain Patent 2.225.320, Great Britain Patent 2.225.321, United States Patent
35 5,478,941, European Patent application 0 601 028, European Patent Application 0 801 064 and International Patent Application WO 97/37982.

The term "levocetirizine" as used herein means the levorotatory enantiomer of cetirizine. More precisely, it means that the active substance comprises at least 90%

by weight, preferably at least 95% by weight, of one individual optical isomer of cetirizine and at most 10% by weight, preferably at most 5% by weight, of the other individual optical isomer of cetirizine. Each individual optical isomer may be obtained by conventional means, i.e., resolution from the corresponding racemic mixture or by asymmetric synthesis. Each individual optical isomer may be obtained from its racemic mixture by using conventional means such as disclosed in British patent application No. 2,225,321. Additionally, each individual optical isomer can be prepared from the racemic mixture by enzymatic biocatalytic resolution, such as disclosed in U.S. Patents No. 4,800,162 and 5,057,427.

The term "pharmaceutically acceptable salts" as used herein refers not only to addition salts with pharmaceutically acceptable non-toxic organic and inorganic acids, such as acetic, citric, maleic, succinic, ascorbic, hydrochloric, hydrobromic, sulfuric, and phosphoric acids and the like, but also its metal salts (for example sodium or potassium salts) or ammonium salts, the amine salts and the aminoacid salts. The best results have been obtained with levocetirizine dihydrochloride.

By patient, we understand children, adolescents and adults.

By the term "allergic rhinitis", we understand a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membrane of the nose. Symptoms of allergic rhinitis include rhinorrhea, nasal obstruction, nasal itching, sneezing, ocular pruritis. The term "persistent allergic rhinitis", as used herein, refers to a disease when symptoms last more than 4 days per week and for more than 4 weeks. It is subdivided into mild and moderate-severe rhinitis. It is said "mild" when there are normal sleep, or no impairment of normal daily activities, sport, leisure, normal work and school, or no troublesome symptoms. It is said "moderate-severe" when there are abnormal sleep, or impairment of daily activities, sport, leisure, or problems caused at work or school, or troublesome symptoms.

A therapeutically effective amount of levocetirizine or a pharmaceutically acceptable salt thereof is used to treat or alleviate the effects of persistent allergic rhinitis. The dosage depends essentially on the specific method of administration and on the purpose of the treatment. The size of the individual doses and the administration program can best be determined based on an individual assessment of the relevant case. The methods required to determine the relevant factors are familiar to the expert.

A preferred daily dosage provides from about 0,0005 mg to about 2 mg of levocetirizine or a pharmaceutically acceptable salt thereof, per kg of body weight per patient. A particularly preferred daily dosage is from about 0,001 to about 2 mg per kg of body weight per patient. The best results have been obtained with a daily dosage

from about 0,005 to 1 mg per kg of body weight per patient. The dosage may be administered once per day of treatment, or divided into smaller dosages, for examples 1 to 4 times a day, and preferably 1 to 3 times a day, and administrated over about a 24 hours time period to reach a total given dosage. Bests results have been obtained with an administration of a compositions of the invention are twice a day for children; and 5 mg once a day for adults. The exact dosages in which the compositions are administered can vary according to the type of use, the mode of use, the requirements of the patient, as determined by a skilled practitioner. The exact dosage for a patient may be specifically adapted by a skilled person in view of the severity of the condition, the specific formulation used, and other drugs which may be involved.

Pharmaceutical compositions used according to the present invention may be administered by any conventional means. The routes of administration include intradermal, transdermal, slow release administration, intramuscular, oral and intranasal routes. Any other convenient route of administration can be used, for example absorption through epithelial or mucocutaneous linings.

The pharmaceutical forms according to the present invention may be prepared according to conventional methods used by pharmacists. The forms can be administered together with other components or biologically active agents, pharmaceutically acceptable surfactants, excipients, carriers, diluents and vehicles.

The pharmaceutical compositions of the invention include any conventional therapeutical inert carrier. The pharmaceutical compositions can contain inert as well as pharmacodynamically active additives. Liquid compositions can for example take the form of a sterile solution which is miscible with water. Furthermore, substances conventionally used as preserving, stabilizing, moisture-retaining, and emulsifying agents as well as substances such as salts for varying the osmotic pressure, substances for varying pH such as buffers, and other additives can also be present. If desired an antioxidant can be included in the pharmaceutical compositions.

Pharmaceutical acceptable excipients or carriers for compositions include saline, buffered saline, dextrose or water. Compositions may also comprise specific stabilizing agents such as sugars, including mannose and mannitol. Carrier substances and diluents can be organic or inorganic substances, for example water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycol and the like. A prerequisite is that all adjuvants and substances used in the manufacture of the pharmaceutical compositions are nontoxic.

Pharmaceutical compositions can be administered by spray inhalation. Any conventional pharmaceutical composition for spray inhalation administration may be used. Another preferred mode of administration is by aerosol.

The pharmaceutical composition of the invention can also be formulated for topical application. The composition for topical application can be in the form of an aqueous solution, lotion or jelly, an oily solution or suspension or a fatty or emulsion ointment.

5 The pharmaceutical composition of the invention can also be used for slow prolonged release with a transdermal therapeutic system in polymer matrix or with an appropriate formulation for oral slow release.

The pharmaceutical compositions according to the present invention may also be administered orally or rectally. They may also be administered by nasal instillation,
10 aerosols or in the form of unguents or creams. The pharmaceutical compositions which can be used for oral administration may be solid or liquid, for example, in the form of uncoated or coated tablets, pills, dragees, gelatine capsules, solutions, syrups and the like. For administration by the rectal route, the compositions containing the compounds of the present invention are generally used in the form of suppositories.

15 The pharmaceutical forms, such as tablets, drops, suppositories and the like, are prepared by conventional pharmaceutical methods. The compounds of the present invention are mixed with a solid or liquid, non-toxic and pharmaceutically acceptable carrier and possibly also mixed with a dispersing agent, a disintegration agent, a stabilizing agent and the like. If appropriate, it is also possible to add preservatives,
20 sweeteners, coloring agents and the like.

Preferably, the pharmaceutical compositions of the invention is administered in traditional form for oral administration, as film coated tablets, lozenges, dragees, and oral liquid preparation such as syrup.

Best results have been obtained with an oral dosage form, in particular liquid
25 formulations such as syrup for children, and film-coated tablet for adults. For example, patients can receive 2 doses of 0,25 mg/kg (total daily dose : 0,50 mg/kg/day) of an oral solution of levocetirizine dihydrochloride 10 mg/ml per day; one ml of the solution contains 20 drops and one drop of levocetirizine dihydrochloride solution contains 0,5 mg.

30 As an Example of a composition according to the present invention, the following formulation of a film coated tablet is preferred: levocetirizine dihydrochloride, magnesium stearate, cellulose, lactose and silicon dioxide.

As an Example of a composition according to the present invention, the following formulation of a syrup is preferred: levocetirizine dihydrochloride, methyl-
35 and propylparaben, saccharinum, and purified water.

Pharmaceutical compositions of the invention are useful to treat the persistent allergic rhinitis. These compositions can alleviate the effects of the persistent allergic rhinitis.

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