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(54) Title: A METHOD FOR PREVENTING URTICARIA

(57) Abstract: The present invention relates to the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, an urticaria attack in a patient.

A Method for Preventing Urticaria

The present invention relates to a method for preventing, or delaying the onset of urticaria attack with a compound selected from efletirizine, cetirizine, or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these.

The present invention relates to a method for preventing, or delaying the onset of primary urticaria with a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these.

Urticaria is an inflammatory disease characterized by erythematous, itchy edematous and whealing lesions of the skin or mucous membranes. Individual wheals may be as small as 1-2 mm in diameter, but they can reach several centimeters. Acute urticaria has been defined as episodes lasting for less than 12 weeks particularly 6-12 weeks, chronic urticaria has been defined as episodes lasting beyond 12 weeks.

Different types of urticaria are described such as, but not limited to, acute idiopathic, chronic idiopathic, IgE-mediated , pseudo-allergic, serum-sickness, contact, hereditary angioedema, acquired C1 inhibitor deficiency and physical as well as urticaria vasculitis.

The onset of urticaria attack can be defined as a new flare up of urticaria in a patient, who had already experienced urticaria. Rash or flare up means that an urticaria lesion is already present. The onset of primary urticaria can be defined as the first urticaria attack during a patient's life or an attack at a time when the patient did not otherwise show any presence of urticaria; in this latter case, no urticaria lesions are present at the time of onset.

The term "cetirizine" as used herein refers to 2-[2-[4-(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid.

The term "individual optical isomer of cetirizine" as used herein refers to the levorotatory and the dextrorotatary enantiomers of cetirizine. More precisely, it refers to the active substance comprising 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. The dextrorotatory enantiomer of cetirizine is also known as levocetirizine and in the form of its dihydrochloride salt is levorotatory. Each individual optical isomer may be obtained by conventional means, i.e., resolution from the corresponding racemic mixture or by asymmetric synthesis.

Processes for preparing cetirizine, an individual optical isomer thereof or a pharmaceutically acceptable salt thereof have been described in European Patent No. EP 0 058 146 B1, Great Britain Patents Nos. 2.225.320 and 2.225.321, United States

Patent No. 5,478,941, published European Patent Application Nos. EP 0 601 028 A1 and EP 0 801 064 A1 and published International Patent Application No. WO 97/37982.

The term "efletirizine" as used herein refers to 2-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid.

Two pseudopolymorphic crystalline forms of efletirizine dihydrochloride, namely anhydrous efletirizine dihydrochloride and efletirizine dihydrochloride monohydrate are described in the European patent No. 1 034 171.

Processes for preparing efletirizine or a pharmaceutically acceptable salt thereof have been described in European Patent 1 034 171, and in the international patent application WO 97/37982.

Unless otherwise mentioned, the invention concerns all forms of efletirizine and cetirizine and pharmaceutically acceptable salts thereof.

Antihistamines are also known for the symptomatic treatment of urticaria and other skin disorders in which histamine plays a role (J. Allergy Clin. Immunol., 1995, 95,759-64).

However, there remains a need for therapeutic methods and pharmaceutical compositions which prevent, or delay the onset of, urticaria attack and/or primary urticaria particularly in infants and/or young children, one of the major groups at risk of developing the disease, because of the relative immaturity of their immune systems and their physiological barriers to allergens.

A first purpose of the invention therefore concerns the primary prevention of primary urticaria.

A second purpose of the invention is the prevention of urticaria attacks in high risk patients, such as patients who have already suffered from urticaria attacks.

A third purpose of the invention is the prevention of primary urticaria in children and particularly in atopic children or children with a direct relative family history of atopy.

A fourth purpose of the invention is the prevention of urticaria attacks in children suffering from atopic dermatitis and/or with a direct relative family history of atopy.

A fifth purpose of the invention is the prevention of acute urticaria attacks.

The present invention is based on the unexpected finding that administration of efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these prevents urticaria attacks especially in infants.

The present invention therefore concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically

acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, an urticaria attack in a patient.

The present invention further concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, primary urticaria in a patient, the said medicament being administered to the patient prophylactically prior to the onset of the urticaria .

The present invention further concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, acute urticaria in a patient.

The present invention further concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the occurrence or re-occurrence of urticaria in a patient.

In addition the present invention concerns a method for preventing or delaying the onset of urticaria attack which comprises administering to a patient a therapeutically effective amount of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these.

The present invention also concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, urticaria.

In accordance with the invention the selected compound is administered to the patient prior to the onset of the urticaria attack or the primary urticaria (e.g. before any biological or clinical symptoms of urticaria disease occur (primary prevention) or after biological signs of sensitization to an allergen but before the onset of symptoms of an urticaria attack (secondary prevention)).

The present invention also concerns the use of the selected compound for the preparation of a medicament intended for preventing the onset of primary urticaria in a patient, the said medicament being administered to the patient prophylactically after a resolved urticaria attack in order to prevent the re-occurrence of the disease .

It has been shown that the effect of cetirizine in urticaria is two-fold: firstly cetirizine prevents the occurrence of acute urticaria and secondly when acute urticaria occurs the patients, especially children, treated with cetirizine have fewer episodes of acute urticaria than non-treated patients.

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 to metal salts (for example sodium or potassium salts) or ammonium salts, the amine salts and the amino acid salts. Accordingly efletirizine and cetirizine may each be employed as the free acid or in the form of a pharmaceutically acceptable salt. The best results have been obtained with the dihydrochloride salt.

By patient, is to be understood adults, infants and children, in particular young children. Generally, the patients most benefiting from treatment in accordance with the invention are infants or children aged 1 week to 10 years, preferably aged 6 months to 5 years, and more preferably 10 months to 5 years. The best results have been obtained with patients aged 1 to 3.5 years.

Preferably patients treated in accordance with the invention are those not currently affected by urticaria disease and most preferably, those who have never been affected thereby.

A therapeutically effective amount of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these is used to prevent, or delay onset of, an urticaria attack and/or primary urticaria. The dosage employed will depend essentially on the specific method of administration and on the purpose of the prophylaxis. 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 for use in accordance with the invention is from about 0,0005 mg to about 2 mg of the selected compound, per kg of body weight per patient. A particularly preferred daily dosage is from about 0,005 to about 2 mg per kg of body weight per patient. The best results are obtained with a daily dosage from about 0,05 to 1 mg per kg of body weight per patient, preferably 0,5 mg. 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 administered over about a 24 hours time period to reach a total given dosage. Best results are obtained with administration twice a day in two equal doses per day or once a day in retarded release form. The exact dosages in which the compositions are administrated 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 practitioner, in view of the severity of the condition, the specific formulation used, and other drugs which may be involved.

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