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— *of inventorship (Rule 4.17(iv)) for US only*

Published:
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(54) Title: TREATMENT OF ATOPIC DERMATITIS

(57) Abstract: The present invention relates to a method of treating atopic dermatitis in a patient in need thereof comprising administering to said patient a therapeutically effective amount of fexofenadine.

TREATMENT OF ATOPIC DERMATITIS

Atopic dermatitis is a chronic disease that affects the skin. In atopic dermatitis, the skin becomes extremely itchy and inflamed, causing redness, swelling, cracking, weeping, crusting, and scaling. Atopic dermatitis most often affects infants and young children, but it can continue into adulthood or first show up later in life. In most cases, there are periods of time when the disease is worse, called exacerbations or flares, followed by periods when the skin improves or clears up entirely, called remissions. Environmental factors can bring on symptoms of atopic dermatitis at any time in the lives of individuals.

Atopic dermatitis is the most common of the many types of eczema. Other types of eczema include contact eczema (a localized reaction that includes redness, itching and burning where the skin has come into contact with an allergen or with an irritant), allergic contact eczema (a red, itchy, weepy reaction where the skin has come into contact with a substance that the immune system recognizes as foreign, such as poison ivy), seborrheic eczema (yellowish, oily, scaly patches of skin on the scalp, face, and occasionally other parts of the body), nummular eczema (coin-shaped patches of irritated skin—most common on the arms, back, buttocks, and lower legs—that may be crusted, scaling, and extremely itchy), neurodermatitis (scaly patches of skin on the head, lower legs, wrists, or forearms caused by a localized itch (such as an insect bite) that become intensely irritated when scratched), stasis dermatitis (a skin irritation on the lower legs, generally related to circulatory problems), and dyshidrotic eczema (irritation on the skin on the palms of the hands and soles of the feet characterized by clear, deep blisters that itch and burn.

Atopic dermatitis is very common. It affects males and females equally and accounts for 10 to 20 percent of all referrals to dermatologists. People who live in urban areas and in climates with low humidity seem to be at an increased risk for developing atopic dermatitis. The cause of atopic dermatitis is not known, but the disease seems to result from a combination of genetic and environmental factors.

Although the symptoms of atopic dermatitis vary from person to person, the most common symptoms are dry, itchy skin, cracks behind the ears and rashes on the cheeks, arms and legs. Itching is an important factor in atopic dermatitis because scratching and rubbing in response to itching worsen the skin inflammation characteristic of this disease. People with atopic dermatitis seem to be more sensitive to itching and feel the need to scratch longer in response. They develop what is referred to as "the itch-scratch cycle". The extreme itchiness of the skin causes the person to scratch, which in turn worsens the itch and so on. Itching is particularly a problem during sleep, when conscious control of scratching decreases and the absence of other outside stimuli makes the itchiness more noticeable.

The way the skin is affected by atopic dermatitis can be changed by patterns of scratching and resulting skin infections. Some people with the disease develop red, scaling skin at locations where the immune system in the skin becomes very activated. Others develop thick and leathery skin as a result of constant scratching and rubbing. This condition is call lichenification. Still others develop papules, or small raised bumps, on their skin. When the papules are scratched, they may open (excoriations) and become crusty and infected. Other skin conditions associated with atopic dermatitis are ichthyosis (dry, rectangular scales on the skin), keratosis pilaris (small, rough bumps, generally on the face, upper arms, and thighs), hyperlinear palms (increased number of skin creases on the palms), urticaria (red, raised bumps, often after exposure to an allergen, at the beginning of flares or after exercise or a hot bath), cheilitis (inflammation of the skin on and around the lips), atopic pleat (an extra fold of skin that develops under the eye), and hyperpigmented eyelids (eyelids that have become darker in color from inflammation or hay fever).

Currently, there is no test to diagnose atopic dermatitis and no single symptom is used to identify the disease because the symptoms or symptoms described above

are also found in people without atopic dermatitis or with other types of skin disorders. Each patient experiences a unique combination of symptoms and the symptoms and severity of the disease of atopic dermatitis may vary over time. However, according to current NIH guidelines, a preliminary diagnosis of atopic dermatitis can be made if the patient has three or more symptoms from each of two categories: major symptoms and minor symptoms. Major symptoms are 1) intense itching, 2) characteristic rash in locations typical of the disease, 3) chronic or repeatedly occurring symptoms, and 4) personal or family history of atopic disorders (e.g., eczema, hay fever, asthma). Some minor symptoms are 1) early age of onset, 2) dry, rough skin, 3) high levels of immunoglobulin E (IgE), an antibody in the blood, 4) ichthyosis, 5) hyperlinear palms, 6) keratosis pilaris, 7) hand or foot dermatitis, 8) cheilitis, 9) nipple eczema, 10) susceptibility to skin infection and 11) positive allergy skin tests.

The doctor has three main goals in treating atopic dermatitis: healing the skin and keeping it healthy, preventing flares and treating symptoms when they do occur. Currently, atopic dermatitis is most frequently treated with corticosteroid creams and ointments. Sedating antihistamines are sometimes used to reduce nighttime scratching and allow more restful sleep when taken at bedtime.

The following are references that discuss utilizing non-sedating antihistamines for treating assorted dermatological conditions, Klein and Clark, Arch Dermatology (1999); 135, 1522-5; Rubin, WO 99/52554, published October 21, 1999; Jensen et al., WO 99/32125, published July 1, 1999; Pierard et al., Rev Med Liege (2000); 55(8), 763-766; Chae and Tharp, Dermatologic Therapy (2000); 13, 374-383; Sidbury and Hanifin, Dermatologic Clinics (2000); 18(1), 1-11; Demoly et al., J Allergy Clin Immunol (1999); 104, 504-5; Tharp, Current Problems in Dermatology (1998); 10(5), 181-210; Marshall, J Allergy and Clin Immunol (2000); (5 Suppl.), S303-9; Kawashima and Harada, Int Arch Allergy Immunol (2001); 124, 343-345; Purohit et al., Ann Allergy, Asthma & Immunol (2001); 86, 387-392; Umesh et al., Indian Vet J (1998); 75(5), 345-346; Umesh et al., Indian Vet J (1995); 72(4), 418-419; Umesh et al., Indian Vet J (1995); 72(1), 56-60; Advenier, Drugs (1989); 38(4), 634-644; Phillips and Koening, J Family Practice (2000); 49(3), 267; Leung et al., J Royal Soc for the Promotion of Health (1998); 118(5), 280-286; Menz, Medicine Today (2001); 2(5), 67-

73; McFeely et al., Eur J Clin Pharmacol (2001); 57(4), 313-320; Fowler and Edge, Contact Dermatitis (2001), 45(1), 38; Rodriquez-Galvan et al., Boletin Medico del Hospital Infantil de Mexico (1995); 52(5), 316-328; Akova et al., Ocular Immunol and Inflamm (1994); 2(3), 125-44; Giminez Camarasa, Monografias de Dermatologia (1992); 5(6), 449-454; Pincus, Dermatologic Clinics (1992); 10(2), 297-308; Kobza Black, Skin Pharmacology (1992); 5(1), 21-24; Bevier, Vet Clinics of N America—Small Animal Practice (1990); 20(6), 1487-1507;Watanabe and Matsuda, Prog Med (1999); 19(5), 1201-1205; Hanuki et al., Rinsho Iyaku (1993); 9(3), 719-731; Koichi et al., Rinsho Iyaku (1993); 9(3), 705-718; Yoichi, Prog Med (1991); 11(6), 1495-1500; and Atsushi et al., Rinsho Iyaku (1986); 2(5), 723-734.

The present invention relates to the use of fexofenadine in the treatment of and relief of symptoms associated with atopic dermatitis. Fexofenadine is a non-sedating, H_1-receptor-selective antihistamine indicated for the treatment of allergic rhinitis and chronic idiopathic urticaria. [See US Pat Nos. 4,254,129, 5,932,247, 5,855,912, 7,738,872, 6,039,974, 6,113,942, 6,037,353 and 6,187,791, which are hereby incorporated by reference in their entirety].

SUMMARY OF THE INVENTION

The present invention relates to a method of treating atopic dermatitis in a patient in need thereof comprising administering to said patient a therapeutically effective amount of fexofenadine.

DETAILED DESCRIPTION OF THE INVENTION

Fexofenadine may be prepared as described in US Patent Nos. 4,254,129, 5,589,487, 5,581,011, 5,750,703, 6,147,216, 6,242,606, 5,618,940, 5,631,375, 5,644,061, 5,650,516, 5,652,370, 6,654,433 and 5,675,009, all of which are hereby incorporated by reference in their entirety.

The present invention relates to a method of treating atopic dermatitis in a patient in need thereof comprising administering to said patient a therapeutically effective amount of fexofenadine. As used in the present invention, fexofenadine may either be used alone or in conjunction with other treatments for atopic dermatitis, including, but not limited to the use of corticosteroid creams and ointments, such as hydrocortisone.

As used herein, "treating or treatment of atopic dermatitis" refers to the 1) alleviation of, 2) reduction of and/or 3) providing relief to-- any one or more symptoms associated with atopic dermatitis in a patient suffering from atopic dermatitis as determined by an attending diagnostician.

As used herein, "symptoms associated with atopic dermatitis" are 1) itching; 2) red, scaling skin; 3) lichenification; 4) papules, or small raised bumps, on the skin; 5) ichthyosis (dry, rectangular scales on the skin); 6) keratosis pilaris (small, rough bumps, generally on the face, upper arms, and thighs), 7) hyperlinear palms (increased number of skin creases on the palms), 8) urticaria (red, raised bumps, often after exposure to an allergen, at the beginning of flares or after exercise or a hot bath); 9) cheilitis (inflammation of the skin on and around the lips); 10) atopic pleat (an extra fold of skin that develops under the eye), and 11) hyperpigmented eyelids (eyelids that have become darker in color from inflammation or hay fever).

As used herein, a "patient" refers to a warm-blooded animal, such as a mammal, including, but not limited to dogs, cats, rats, mice and humans.

As used herein, "therapeutically effect amount" can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective amount or dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the size, age, and general health of the patient, the response of the individual patient, the mode of administration, the bioavailability characteristics of the preparation administered, the dose regimen selected, the use of concomitant medication, and other relevant circumstances.

A therapeutically effective amount of fexofenadine is that amount which produces the desired therapeutic response (e.g. alleviation or reduction of one or more symptoms associated with atopic dermatitis) upon oral administration according to a single or multiple dosage regimen. A therapeutically effective amount of fexofenadine may vary over a wide range from about 0.01 milligrams per kilogram (mg/kg) to about 20 milligrams per kilogram (mg/kg) of body weight per dose. A pharmaceutical composition which provides from about 5 mg to about 360 mg of fexofenadine per unit dose is preferred and those which provide from about 30 mg to about 240 mg per unit dose are most preferred.

In effecting treatment of a patient, fexofenadine can be administered in any form or mode which makes the fexofenadine bioavailable in effective amounts, including oral and parenteral routes. For example, fexofenadine can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

Fexofenadine can be administered in the form of pharmaceutical compositions or medicaments which are made by combining fexofenadine with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

Example

The efficacy and safety of fexofenadine was investigated in patients with atopic dermatitis in a randomized, multicenter, double-blind, placebo-controlled, parallel-group study. Patients aged ≥16 years underwent a 3-day subject-selection period. Those with an itching score ≥4 points and <8 points (self-assessed using a 5-point scale, 0=virtually no itching; 4=severe itching) were randomized to receive fexofenadine HCl 60mg (n=201) or placebo (n=199) bid for 1 week. 0.1% hydrocortisone butyrate was used concomitantly throughout the placebo lead-in and treatment periods. During the treatment period, patients reflectively recorded itching scores twice daily (day and night) using the 5-point scale. The primary efficacy endpoint was mean change in itching score from baseline.

No significant difference was seen in terms of patient demographics or baseline characteristics. Fexofenadine HCl 60mg bid significantly decreased the severity of itching compared with placebo (mean change in score: –0.75 versus –0.5, respectively; p=0.0005). A significant improvement in itching score was seen with fexofenadine after just 1 day of treatment compared with placebo (p=0.0390). The clinical benefit was maintained throughout the treatment period. Compared with placebo, fexofenadine was found to significantly improve both diurnal and nocturnal itching (p=0.0001 and p=0.0127, respectively) when assessed separately, and significantly reduced the ratio of itching area to body surface area (p=0.0073). There was no significant difference (p=0.8143) between fexofenadine (23.2%) and placebo (22.1%) in the incidence of adverse events (frequency of subjects with 1 or more subjective/objective symptom, abnormal change in laboratory test values, or ECG abnormality). None of the subjects showed a deviation from the standard value for QTc.

In contrast to the apparent lack of unequivocal data on antihistamines in atopic dermatitis to date, fexofenadine HCl 60mg bid demonstrated a rapid, significant improvement in itching associated with this condition, with a safety profile equivalent to that of placebo.

The preceding example is illustrative only and is not intended to limit the scope of the present invention in any way.

CLAIMS

1. A method of treating atopic dermatitis in a patient in need thereof comprising administering to said patient a therapeutically effective amount of fexofenadine.

2. The method of claim 1 wherein the therapeutically effective amount of fexofenadine is between about 5 mg to about 360 mg.

3. The method of claim 2 wherein the therapeutically effective amount of fexofenadine is between about 20 mg to about 280 mg.

4. The method of claim 3 wherein the therapeutically effective amount of fexofenadine is between about 30 mg to about 240 mg

5. The method of claim 4 wherein the therapeutically effective amount of fexofenadine is about 30 mg.

6. The method of claim 4 wherein the therapeutically effective amount of fexofenadine is about 60 mg.

7. The method of claim 4 wherein the therapeutically effective amount of fexofenadine is about 120 mg.

8. The method of claim 4 wherein the therapeutically effective amount of fexofenadine is about 180 mg.

9. The method of claim 4 wherein the therapeutically effective amount of fexofenadine is about 240 mg.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/27754

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61P17/00

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)
IPC 7 A61K

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, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 1 214 937 A (SEPRACOR INC) 19 June 2002 (2002-06-19) claims 1-23	1-9
E	WO 02 067938 A (HARRIS ALAN G ;SCHERING CORP (US); MEDEIROS PAUL T (US)) 6 September 2002 (2002-09-06) claims 1-51	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2002	23/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stienon, P

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/27754

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/27754

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