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(54) Title: LACTOSE–FREE, NON–HYGROSCOPIC AND ANHYDROUS PHARMACEUTICAL COMPOSITIONS OF DESCARBOETHOXYLORATADINE

(57) Abstract

Stable pharmaceutical compositions of descarboethoxyloratadine (DCL), a metabolic derivative of loratadine, for the treatment of allergic rhinitis and other histamine–induced disorders are disclosed. The compositions are formulated to avoid the incompatibility between DCL and reactive excipients such as lactose and other mono– and di–saccharides. Disclosed compositions include lactose–free, non–hygroscopic and anhydrous stable pharmaceutical compositions of DCL.

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LACTOSE-FREE, NON-HYGROSCOPIC AND ANHYDROUS PHARMACEUTICAL COMPOSITIONS OF DESCARBOETHOXYLORATADINE

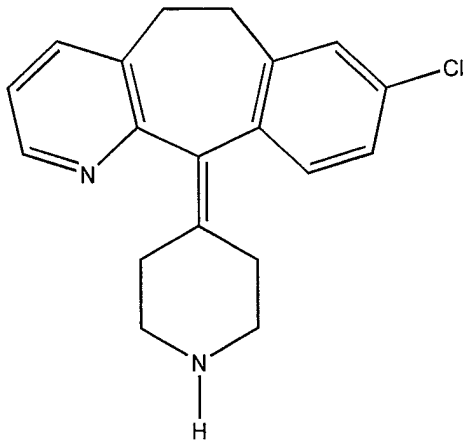
CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority of United States provisional patent applications, 60/053,050 filed July 21, 1997, 60/045,184 filed April 30, 1997, and 60/037,325 filed February 7, 1997.

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions of 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, known as descarboethoxyloratadine (DCL).

DESCARBOETHOXYLORATADINE



DCL is a metabolic derivative of loratadine, an H-1 histamine receptor antagonist. The H-1 histamine receptors mediate the response antagonized by conventional antihistamines. Loratadine has been shown to be comparable in antihistaminic activity to terfenadine and astemizole, and to be, on a milligram by milligram basis, four times more potent than terfenadine in the inhibition of allergic bronchospasm.

Loratadine has also been shown to be effective in treating numerous disorders, including colds, chronic urticaria, seasonal allergic rhinitis and seasonal and perennial rhinitis. Due to its antihistaminic activity, loratadine may also be useful for the treatment of allergic asthma, diabetic retinopathy and other small vessel disorders associated with diabetes mellitus.

The administration of antihistamines is frequently associated with adverse side-effects, which include, for example, sedation, headache, dry mouth, constipation or diarrhea, weight gain and gastrointestinal distress. Loratadine belongs to a class of antihistamines referred to as non-sedating antihistamines. This class also includes two other well known antihistamines, terfenadine and astemizole. In comparison to terfenadine, it has been shown that loratadine causes significantly less sedation than terfenadine and that the incidence of fatigue, headache and nausea associated with loratadine is comparable to that seen with terfenadine.

As a disadvantage to the non-sedating antihistamines, compounds in this class have been reported to cause other severe electrophysicologic side-effects. These adverse side-effects include, but are not limited to, ventricular fibrillation and cardiac arrhythmias, such as ventricular tachyarrhythmias or torsades de pointes. Several of these serious cardiovascular side-effects have been reported in "healthy" patients who received terfenadine concurrently with either ketoconazole or erythromycin. Arrhythmias have also been observed with the concomitant administration of astemizole and erythromycin, and astemizole with erythromycin and ketoconazole. Additionally, it is known that each of ketoconazole, itraconazole and erythromycin interfere with cytochrome P450 and thereby inhibit the metabolism of non-sedating antihistamines such as terfenadine and astemizole. Thus, a strong potential also exists for an adverse interaction between these inhibitors of cytochrome P450 and loratadine. Therefore, due to the similarity in pharmacological activity of loratadine, terfenadine and astemizole, it is also cautioned to avoid the concurrent administration of loratadine with either ketoconazole, itraconazole or a macrolide antibiotic, such as erythromycin.

A further drawback to both astemizole and loratadine is that the administration of each drug has been associated with the growth of both melanoma and fibrosarcoma tumors. The dosage of loratadine being maintained during this observation was 10 mg/day.

Although loratadine is well absorbed, it is extensively metabolized, yielding pharmacologically active descarboethoxyloratadine (DCL) as its main metabolite. Significantly, U.S. Patent 5,595,997, issued January 21, 1997, discloses that DCL, while providing effective, non-sedating antihistaminic therapy, also avoids the many, often severe, adverse side-effects commonly associated with the administration of both

antihistamines in general and with other non-sedating antihistamines, such as loratadine, terfenadine and astemizole, in particular.

Importantly, it has been shown that DCL is five to seven times less active in tumor promotion than loratadine and that DCL is at least about twenty times more potent at the histamine receptor when compared to loratadine. Thus, pharmaceutical compositions containing DCL, or a pharmaceutically acceptable salt thereof, as the active ingredient are particularly desirable.

SUMMARY OF THE INVENTION

Recognizing the desirability of DCL-containing pharmaceutical compositions, we have concluded that under typical manufacturing and storage conditions, DCL is not stable and degrades in the presence of lactose, a compound commonly used as a filler in various pharmaceutical dosage forms, such as tablets, capsules or powders. Over time, the lactose and DCL compound form a brown-colored product, and there is a high degree of DCL degradation. The intensity of the brown color is typically dependent on the amount of DCL present, the conditions of storage, such as humidity and temperature, as well as the length of storage time.

Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container, to remain within its physical, chemical, microbiological, therapeutic and toxicological specification, although there are exceptions, and to maintain at least about 90% of the product's labeled potency level. Thus, for example, expiration dating is defined as the time in which the pharmaceutical product will remain stable when stored under recommended conditions.

The stability of a pharmaceutical product may be affected by several factors, including the stability of the therapeutic ingredient(s), the potential interaction between therapeutic and inactive ingredient(s) and the like. In addition, as previously indicated, physical factors such as heat, light and moisture may accelerate or initiate chemical interactions and the degradation of the product.

While not wishing to be restricted to any particular theory, it is believed that in the present case, lactose may react with DCL, degrading it to form an enamine. Such a reaction may also occur with other similar reactive excipients, such as other mono- or di-saccharides. Stable pharmaceutical compositions of DCL, or a pharmaceutically

acceptable salt thereof, in blended, granulated or compressed form, which are substantially free of reactive excipients are therefore especially desirable.

The present invention relates to stable pharmaceutical compositions of DCL wherein DCL is in intimate admixture with one or more excipient(s), including, but not limited to, blended, granulated or compressed dosage forms, that avoid the incompatibility between DCL and reactive excipients, such as lactose and other mono- or di-saccharides.

Accordingly, a preferred embodiment of the present invention provides stable pharmaceutical compositions, substantially free of reactive excipients, such as lactose or other mono- or di-saccharides, in blended or granulated form, comprising descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable inert excipients. In another embodiment, the present invention relates to chemically stable pharmaceutical compositions, in blended or granulated dosage forms, that are substantially free of reactive excipients, and that comprise about 1% to about 50% by weight of DCL, or a pharmaceutically acceptable salt thereof, and about 99% to about 50% by weight of at least one pharmaceutically acceptable inert excipient. The compositions provide effective, non-sedating antihistaminic activity, while avoiding the often severe adverse side-effects associated with the use of other antihistamines. Thus, the disclosed compositions are beneficial in the treatment of numerous histamine-induced disorders including, but not limited to, allergic rhinitis, allergic asthma, urticaria, symptomatic dermographism, diabetic retinopathy and other small vessel disorders associated with diabetes mellitus.

Moreover, because the disclosed compositions avoid the effects associated with other non-sedating antihistamines, an interaction between the compositions and agents that inhibit cytochrome P450 is also avoided. Such agents include, but are not limited to, ketoconazole, itraconazole and macrolides, such as erythromycin.

In addition to the active DCL ingredient, the disclosed compositions may also include a therapeutically effective amount of a non-steroidal antiinflammatory agent or other non-narcotic analgesic, such as acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen or naproxen. Such combination compositions are beneficial for the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, headache, fever and general malaise associated therewith.

Other combination compositions beneficial in the treatment of these symptoms may include, in addition to an analgesic, a therapeutically effective amount of one or more other active components, such as a decongestant, *e.g.*, pseudoephedrine, a cough suppressant/antitussive, *e.g.*, dextromethorphan, or an expectorant, *e.g.*, guaifenesin.

Interestingly, our studies have also shown that in the absence of unbound water very little to no degradation occurs in DCL compositions that include lactose. While under typical packaging and storage conditions, DCL pharmaceutical composition dosage forms would be exposed to unbound water, *e.g.*, in the form of humidity, there are known manufacturing and storage procedures by which exposure to unbound water and humidity is reduced or eliminated.

Moreover, although excipients other than lactose may be readily used to manufacture the disclosed pharmaceutical compositions of DCL without impacting the manufacturability and therapeutic performance of the composition, spray-dried lactose continues to be an excipient of choice. In the spray-dried form, lactose is among the best of all direct compression fillers in fluidity and is very effective for low dose formulations (<50 mg per dosage) where the compactability of the active dose does not play a major role. *See, e.g.*, R. Shangraw, *Selection of Manufacturing Process and Excipients with an Emphasis on Direct Compression*, Course material from Granulation, Tableting and Capsule Technology, Center for Professional Advancement, East Brunswick, N.J. (1996). Therefore, when possible, it is desirable to include lactose among the available potential excipients for the development of solid dosage forms.

Accordingly, another embodiment of the present invention encompasses non-hygroscopic pharmaceutical compositions comprising DCL, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. Non-hygroscopic pharmaceutical compositions according to the present invention may contain excipients that are substantially free of unbound water, *i.e.*, water which is available to participate in DCL/reactive excipient interactions, such as, but not limited to, interactions between lactose and DCL, such excipients include lactose and other reactive excipients, for example, other mono- or di-saccharides.

It should be noted that non-hygroscopic pharmaceutical compositions of the present invention may nevertheless include some hygroscopic ingredients; however, the overall composition must be substantially non-hygroscopic. Further, suitable excipients

for use in such non-hygroscopic pharmaceutical compositions include hydrated excipients, such as α-lactose monohydrate and the like.

Traditionally, when pharmaceutical compositions or formulations are prepared, the active ingredient or therapeutic agent (*e.g.*, DCL) is milled and/or screened to decrease the particle size and/or narrow the particle size distribution. Most often, this is done in order to optimize various physicochemical characteristics of the formulation, such as dissolution, content uniformity, bioavailability of the active ingredient, and the like. However, the interaction between DCL and reactive excipients, such as lactose, may be affected by the surface area of the DCL particles in the pharmaceutical composition or formulation.

Thus, another embodiment of the present invention encompasses pharmaceutical compositions for the treatment of histamine-induced disorders, comprising DCL, or a pharmaceutically acceptable salt thereof, consisting of large particles, and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers suitable for use in these compositions may comprise one or more excipients selected from the group consisting of inert excipients and reactive excipients, such as lactose or other mono- or di-saccharides. These "large particle" pharmaceutical compositions of DCL have suitable physicochemical characteristics (in terms of dissolution, content uniformity, bioavailability, and the like), but do not exhibit incompatibility with reactive excipients, such as lactose.

In a preferred embodiment, the DCL, or a pharmaceutically acceptable salt thereof, present in the composition has a particle size distribution in which greater than about 40% by weight of DCL, or a pharmaceutically acceptable salt thereof, comprises particles having a size of 250 μm or larger.

Another means for inhibiting or preventing the interaction between DCL and reactive excipients, such as lactose, in a pharmaceutical composition is to prevent DCL from coming into contact with any reactive excipients in the composition. One manner in which this may be achieved is to coat the DCL particles with an inert or non-reactive coating prior to formulation with reactive excipients. Preferably, the inert coating should not significantly influence the pharmacodynamic characteristics (*e.g.*, time to onset of efficacy, and adsorption *in vivo*) of the composition.

Accordingly, yet another embodiment of the present invention relates to solid pharmaceutical compositions for the treatment of histamine-induced disorders comprising a therapeutically effective amount of coated DCL, or a pharmaceutically acceptable salt thereof, which comprises DCL, or a pharmaceutically acceptable salt thereof, coated with an inert coating agent, and a pharmaceutically acceptable carrier. In a preferred embodiment, the DCL or a pharmaceutically acceptable salt thereof, is first granulated with an inert excipient, such as starch, and then the resulting granules are coated with an inert or non-reactive coating agent. Thereafter, the resulting coated DCL may be blended with other excipients, including reactive excipients.

Suitable inert coating agents, and methods for coating particles or granules, are well known in the art. Inert coating agents typically comprise an inert film-forming agent dispersed in a suitable solvent, and may further comprise other pharmaceutically acceptable adjuvants, such as colorants and plasticizers. Preferably, the particles or granules of DCL are coated using aqueous or non-aqueous film coating techniques or microencapsulation. Suitable inert film-forming agents include, but are not limited to, cellulosics, such as methylcellulose, hydroxymethyl cellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, methylhydroxyethylcellulose and sodium carboxymethyl cellulose; vinyls, such as polyvinyl pyrrolidone; glycols, such as polyethylene glycols; acrylics, such as dimethylaminoethyl methacrylate-methacrylate acid ester copolymer, and ethylacrylate-methylacrylate copolymer; and other carbohydrate polymers, such as maltodextrins, and polydextrose. Preferably, the inert coating agent contains a hydrophilic film-forming agent, such as hydroxypropyl methylcellulose, so that absorption *in vivo* is not significantly delayed.

Once the particles or granulated formulations of DCL are coated with the inert coating agent, the coated DCL may be formulated using standard techniques, including, but not limited to, blending, granulation, compression and combinations thereof, with other inert and reactive excipients, such as lactose, to make various dosage forms, for example, tablets, caplets, capsules, troches, and the like.

DCL may also be formulated in instant release dosage forms, such as those taught in United States Patent 4,371,516 to Gregory *et al.* Instant release dosage forms of DCL may be particularly advantageous for certain uses as these dosage forms allow the DCL to

be rapidly absorbed by the patient. The term "instant release" as used herein means that the dosage form or pharmaceutical composition disintegrates rapidly, *e.g.*, within 10 seconds, in water. The disintegration time may be measured using procedures well known in the art, such as the procedures set forth in United States Patent 4,371,516. DCL may also be formulated in effervescent dosage forms, which may be prepared using techniques well known in the art. Effervescent dosage forms typically contain sodium bicarbonate and either citric acid, tartaric acid or sodium biphosphate in addition to the active ingredient (*e.g.*, DCL). When mixed with water, carbon dioxide is released as a result of the acid-base reaction. It should be noted that instant release or effervescent dosage forms of DCL should not be formulated with reactive excipients, such as lactose or other mono- or di-saccharides.

Accordingly, yet another embodiment of the present invention encompasses instant release solid pharmaceutical dosage forms for treating histamine-induced disorders comprising an open matrix network carrying a therapeutically effective amount of DCL, or a pharmaceutically acceptable salt thereof, wherein the open matrix network comprises a pharmaceutically acceptable water-soluble or water-dispersible carrier that does not interact with DCL, or a pharmaceutically acceptable salt thereof.

Suitable carriers or fast dissolving inert carriers for use in the instant release pharmaceutical dosage forms of the present invention include, but are not limited to, polypeptides, such as gelatin, and in particular, hydrolyzed gelatin; polysaccharides, such as hydrolyzed dextran or dextrin; alginates, such as sodium alginate; and mixtures thereof. The carrier may also include other inert excipients, such as polyvinyl alcohol, polyvinylpyrrolidone, acacia, mannitol, sorbitol, glycine, and mixtures thereof. *See*, United States Patent 4,371,516. In addition, the carrier may further include pharmaceutically acceptable adjuvants, such as, for example, coloring agents, flavoring agents, preservatives, and the like.

Still another embodiment of the present invention provides anhydrous pharmaceutical compositions of descarboethoxyloratadine for the treatment of histamine-induced disorders, comprising a therapeutically effective amount of DCL, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. Carriers or excipients that may be used in the anhydrous compositions of the present invention include the inert excipients useful in the stable pharmaceutical

compositions substantially free of reactive excipients according to the present invention, as well as lactose or other reactive excipients such as mono- or di-saccharide excipients.

Anhydrous pharmaceutical compositions should be prepared and stored in a manner that maintains an overall substantially anhydrous composition. For example, such compositions may be prepared using anhydrous or low moisture ingredients, using low moisture or humidity conditions, and the like, such that the resulting pharmaceutical compositions are substantially anhydrous, *i.e.*, substantially free of unbound water.

In addition, as with the disclosed pharmaceutical compositions, in blended, granulated or compressed form, that are substantially free of reactive excipients, the non-hygroscopic and anhydrous pharmaceutical compositions of DCL may include a therapeutically effective amount of a non-steroidal antiinflammatory agent or other non-narcotic analgesic, as well as a therapeutically effective amount of one or more other active components, such as a decongestant, an antitussive, or an expectorant. Examples of such therapeutic agents include all of those available for the DCL compositions substantially free of reactive excipients, such as lactose.

Anhydrous DCL pharmaceutical compositions prepared in accordance with the present invention should be prepared and stored such that the anhydrous nature is maintained. Accordingly, these compositions will be packaged using materials known in the art for preventing exposure of the composition to water, allowing them to be included in suitable formulary kits. Such packaging will include, but not be restricted to, hermetically sealed foil, plastic or the like, and unit dose containers, *e.g.,* blister packs or strip packs. These forms of packaging may also be used with any of the other dosage forms disclosed herein.

Numerous other advantages and features of the present invention will become readily apparent from the following detailed description of the preferred embodiments and the appended claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Although this invention is susceptible to embodiment in many different forms, preferred embodiments of the invention are shown. It should be understood, however, that the present disclosure is to be considered as an exemplification of the principles of this invention and is not intended to limit the invention to the embodiments illustrated.

As mentioned above, pharmaceutical compositions or formulations of DCL containing lactose, or other reactive excipients, that are exposed to unbound water, *e.g.*, moisture or humidity, degrade more rapidly. The addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.,* Jens T. Cartensen, *Drug Stability: Principles & Practice,* 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and temperature accelerate the study.

Further, the effect of water on a formulation is of great significance since conditions favorable for hygroscopicity, *e.g.*, moisture and/or humidity, are commonly encountered during manufacture, handling, packaging, storage, shipment and use of the formulation. Thus, it is clear that the use of lactose, or other reactive excipients such as other mono-or di-saccharide excipients, in pharmaceutical compositions or formulations containing DCL should be avoided due to the substantial contact with moisture and/or humidity that the compositions experience under normal manufacturing, packaging and storage conditions.

Stability of a pharmaceutical product or composition may be defined as the capability of a particular formulation, in a specific container, to remain within its physical, chemical, microbiological, therapeutic and toxicological specification, although there are exceptions, and to maintain at least about 90% of its labeled potency level. Thus, expiration dating, for example, is defined as the time for which the pharmaceutical product or composition will remain stable when stored under recommended conditions.

Many factors affect the stability of a pharmaceutical product or composition, and include, for example, the stability of the therapeutic ingredient(s), the potential interaction or incompatibility between therapeutic and inactive ingredient(s) (*e.g.*, the interaction between DCL and certain excipients, such as lactose) and the like.

DCL degradation does not occur in the presence of other non-reactive excipients. The terms "inert excipient(s)" and "non-reactive excipient(s)" as used herein are intended to mean excipients, including, but not limited to, binders/fillers, disintegrants, lubricants, anti-caking agents, dispersing agents, preservatives, film coating agents, plasticizers, surface active agents, and the like, which are compatible with and do not interact with DCL under typical manufacturing, packaging and storage conditions. Inert excipients or non-reactive excipients which may be used in the present invention are well known in the

art, and include, but are not limited to, maltodextrin, cellulose, calcium phosphate, calcium phosphate dihydrate, calcium carbonate, talc, calcium stearate, calcium sulfate dihydrate and corn starch. Furthermore, inert or non-reactive excipients provide a pharmaceutical composition that is comparable in manufacturability and therapeutic performance as those utilizing lactose.

The term "inert carrier" as used herein refers to a carrier or vehicle comprising one or more inert excipients or non-reactive excipients.

As used herein, the term "reactive excipient(s)" refers to excipients that react with DCL in the presence of unbound water, and include, for example, lactose and other mono- or di-saccharide excipients. The terms "substantially free of reactive excipient(s)", "substantially free of lactose" and "lactose-free" as used herein are intended to mean that the amount of reactive excipient(s), or lactose as appropriate, present, if any, in the dosage form or pharmaceutical composition of DCL is insufficient to cause the incompatibility between DCL and the particular excipient(s), such as lactose, discovered by the present inventors to detrimentally affect the potency of the DCL below about 90% of its initial potency over the shelf life of the dosage form or pharmaceutical composition. *See*, standards set forth in the USP XXI/NF XVI. Typically, the amount of any reactive excipients that may be present in compositions of the present invention that are substantially free of reactive substituents should be less than about 20% by weight, preferably less than about 10% by weight, and even more preferably, less than about 1 % by weight.

The term "unbound water" as used herein refers to water that is not present in the form of a stable hydrate of one or more components of the pharmaceutical composition, *e.g.*, α-lactose monohydrate. Similarly, the term "anhydrous" as used herein means that the amount of unbound water present, if any, in the dosage form or pharmaceutical composition of DCL is insufficient to initiate and/or accelerate the incompatibility between DCL and reactive excipients, such as lactose. Further, "anhydrous conditions" or nature as used herein means substantially free of unbound water, including moisture. The term "non-hygroscopic" as used herein means the overall formulation or pharmaceutical composition is substantially non-hygroscopic, *i.e.*, it does not provide unbound water sufficient to initiate and/or accelerate the incompatibility between DCL and reactive excipients, such as lactose.

The term "substantially free of unbound water" typically means that less than about 5 weight percent, preferably less than about 1 weight percent, and more preferably, less than about 0.1 weight percent, of water is present.

DCL may be present in pharmaceutical compositions prepared in accordance with the present invention as either a free base or as a pharmaceutically acceptable salt thereof. "Pharmaceutically acceptable salt" refers to a salt prepared from pharmaceutically acceptable non-toxic organic or inorganic, acids or bases. Examples of such organic acids include, for example, aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, such as formic, acetic, propionic, succinic, glycolic, glutamic, glucouronic, maleic, furoic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, stearic, sulfanilic, galacturonic and algenic. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric. Examples of such organic bases include, for example, N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), lysine and procaine. Examples of such inorganic bases include metallic salts made from lithium, aluminum, calcium, magnesium, potassium, sodium and zinc.

Pharmaceutical compositions of the present invention may also comprise (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically affective amount of at least one non-steroidal antiinflammatory agent or non-narcotic analgesic or a pharmaceutically acceptable salt thereof.

In addition, the disclosed compositions may comprise (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically affective amount of a decongestant or a pharmaceutically acceptable salt thereof.

"Therapeutically effective amount" means that amount, in the case of DCL, or a pharmaceutically salt thereof, which provides a therapeutic benefit in the treatment and management of histamine-induced disorders, including but not limited to, allergic rhinitis and other allergic disorders such as urticaria, symptomatic dermographism, dermatitis, allergic asthma, diabetic retinopathy or other small vessel disorders associated with diabetes mellitus and the symptoms associated with allergic rhinitis such as cough, cold, cold-like and/or flu symptoms including but not limited to, sneezing, rhinorrhea,

lacrimation and dermal irritation.

The magnitude of a prophylactic or therapeutic dose of DCL in the acute or chronic management of disease will vary with the severity of the condition to be treated. The dose, and perhaps the dose frequency, will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range, for the conditions described herein, is from about 0.1 mg to about 10 mg, administered in single or divided doses. Preferably, an oral daily dose range is from about 0.1 mg to about 5 mg, and more preferably, from about 0.2 mg to about 1 mg.

It is further recommended that children, patients over 65 years of age, and those with impaired renal or hepatic function, initially receive a lower dose, and that they then be titrated based upon individual response or blood lever. As will be apparent to those skilled in the art, it may be necessary to use dosages outside these ranges in particular cases. It is further noted that the clinician or treating physician will know how and when to interrupt, adjust or terminate a dosage regimen based upon individual patient response.

"Therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof" is encompassed within the above-described dosages. In addition, the phrases "comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically affective amount of at least one non-steroidal antiinflammatory agent or non-narcotic analgesic or a pharmaceutically acceptable salt thereof" and "comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically affective amount of a decongestant or a pharmaceutically acceptable salt thereof" are also encompassed by the above-described dosages and dose frequency schedules.

Pharmaceutical compositions of the present invention may be administered by any suitable route of administration that provides a patient with a therapeutically effective dosage of DCL. Typically, the DCL pharmaceutical compositions described herein will be formulated for oral administration. Suitable dosage forms include tablets, troches, cachets, caplets, capsules, including hard and soft gelatin capsules, and the like. Tablet forms, however, remain a preferred dosage form because of advantages afforded both the patient (*e.g.*, accuracy of dosage, compactness, portability, blandness of taste and ease of administration) and to the manufacturer (*e.g.*, simplicity and economy of preparation, stability and convenience in packaging, shipping and dispensing).

The pharmaceutical compositions substantially free of reactive excipients may further include a "pharmaceutically acceptable inert carrier" and this expression is intended to include one or more inert excipients, which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like, other than lactose. The anhydrous, non-hygroscopic, and other compositions according to the present invention may include any "pharmaceutically acceptable carrier", and this expression is intended to include one or more inert excipients, as well as reactive excipients, such as α-lactose monohydrate. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques, with the proviso that nonaqueous coatings and coating techniques should be used for tablets of disclosed compositions that are not substantially free of reactive excipients. "Pharmaceutically acceptable carrier" also encompasses controlled release means.

Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, and the like. However, any such optional ingredient must be compatible with DCL to insure the stability of the formulation.

Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to:

BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch (*e.g.*, STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (*e.g.* AVICEL™, such as, AVICEL-PH-101™, -103™ and -105™, sold by FMC Corporation, Marcus Hook, PA, USA), or mixtures thereof;

FILLERS: talc, calcium carbonate (*e.g.*, granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, or mixtures thereof;

DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate , microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums, or mixtures thereof;

LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil *e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof;

ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof;

ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof; and

COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnuba wax, microcrystalline wax, or mixtures thereof.

The disclosed compositions may be prepared to include any of the mentioned ingredients, by any of the methods of pharmacy, with the proviso that the substantially free of reactive excipients, non-hygroscopic or anhydrous nature of a given composition is maintained. Tablets, for example, may be prepared by compression or molding, optionally, with one or more accessory ingredients, consistent with the nature of the particular composition and with the principles of the present invention. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant,

inert diluent, surface active or dispersing agent or other compatible excipient as described herein above. Desirably, each tablet contains from about 0.1 mg to about 10 mg, and more desirably, from about 0.1 to about 5 mg, of the active ingredient, DCL or a pharmaceutically acceptable salt thereof.

It is noted that all components comprising the dosage forms of DCL made in accordance with any of the embodiments of the present invention preferably meet or exceed the standards for pharmaceutical ingredients and combinations thereof in the USP/NF. The purpose of the USP/NF is to provide authoritative standards and specifications for materials and substances and their preparations that are used in the practice of the healing arts. The USP/NF establishes titles, definitions, descriptions and standards for the identification, quality, strength, purity, packaging and labeling of such materials and substances. Also, where practicable, provides handling and storage information, formulas for their manufacture and preparation and methods for their examination.

The compositions of DCL described and claimed herein meet the pharmaceutical standards set forth in the USP/NF (*e.g.*, USP XXI/NF XVI) for each of the ingredients and for each of the various dosage forms made with such ingredients. In effect, the disclosed compositions of DCL are said to be pharmaceutically acceptable dosage forms made of pharmaceutically acceptable ingredients in pharmaceutically acceptable combinations and pharmaceutically acceptable amounts to at least meet the standards set forth in the USP XXI/NF XVI.

RESULTS OF EXCIPIENT COMPATIBILITY STUDIES

I. A first study was carried out to determine the chemical compatibilities of DCL with common excipients by differential scanning calorimetry (DSC). The study used descarboethoxyloratadine (Lot 589-YF-15A) as the active drug.

Excipients tested:

AVICEL™ microcrystalline cellulose

STARCH 1500®

Lactose (α-lactose monohydrate)

Procedure: The various excipients were dry blended with DCL (80% excipient to 20% drug). DSC runs were performed on each blend as well as neat drug substance.

Results: The DSC curve for DCL exhibits an endothermic melt peak at 149.82° C. When dry blended with lactose, the low melting endotherm for lactose and the melting

endotherm for DCL combine to produce a single melt indicative of a solid dispersion. The higher melting endotherm for lactose was also reduced to a lower temperature. This behavior is indicative of an active drug/excipient interaction.

The DSC trace for a dry blend of AVICEL™ and DCL shows one endotherm at 147.55° C, the approximate melting point of DCL in the absence of AVICEL™. Since the baseline is affected adversely by the presence of AVICEL™, the slight difference in melting point can be attributed to error in the extrapolated onset temperature. Therefore, the endotherm for the blend appears to be the same as for neat DCL and no interaction with AVICEL™ is apparent.

As for the AVICEL™ blend, the dry blending of STARCH 1500® and DCL produce one peak at 147.75° C. Thus, there does not appear to be a DCL/STARCH 1500® interaction. These results are presented in Table 1, below.

Table 1

SUBSTANCE	COMMENTS
DCL	one peak 149.82°C
AVICEL™	no peak (does not melt)
STARCH 1500®	no peak (does not melt)
α-LACTOSE monohydrate	two peaks 140.81°C, 210.47°C
DCL/AVICEL™	one peak 147.55°C - no interaction
DCL/STARCH 1500®	one peak 147.75°C - no interaction
DCL/α-LACTOSE monohydrate	two peaks 145.04°C, 195.17°C solid dispersion

II. A second study was carried out to determine the stability of a formulation comprised of DCL and lactose, in the presence and absence of 5% water. The study used descarboethoxyloratadine (Lot 589-YF-15A).

Procedure: A series of amber 20 ml crimp-topped vials were prepared to contain DCL and lactose. The contents of the vials were (1) dry DCL; (2) 20% dry DCL and 80% lactose; and (3) 20% DCL, 80% lactose and 5% H_2O. The vials were placed in a 60° C oven for 16 days and then assayed via high-performance liquid chromatography (HPLC) at 256 nanometers.

Results: The only significant degradation seen was in the vial containing 5% H_2O. This sample represents the worst case scenario for a drug/excipient interaction as stated in *Drug Stability* (Carstensen *et al.*, pp. 379-380). Thus, these data indicate that under

common accelerated conditions for excipient interaction studies, the presence of α-lactose monohydrate has been shown to adversely affect the stability of DCL, while a solid dose DCL/lactose composition in the absence of 5% moisture does not show this high degree of degradation. These results are presented in Table 2, below.

Table 2

SAMPLE	T_0 wt. DCL (mg)	T_{16} wt. DCL (mg)	%DEGRADATION
DCL	28.70	28.70	0
DCL/LACTOSE	19.82	19.74	0.40
DCL/LACTOSE/5% H_2O	39.70	19.51	50.86

III. A third study was carried out to evaluate the reactivity of DCL with lactose, in the presence and absence of intentionally introduced water. The effects of reduced particle size were also evaluated by comminuting blends of DCL/lactose in a mortar and pestle prior to storage. Samples were stored in crimp-topped vials (as above), under accelerated conditions (60° C at 75% RH) for various time periods and then tested for reactivity of DCL with lactose. The results are shown in Table 3, below.

Table 3
Reactivity of DCL with Lactose

Storage Time (60° C / 75% RH)	Treatment	% Initial
4 weeks	neat	99.70
4 weeks	80% lactose	68.58
4 weeks	80% lactose / 5% H_2O	49.57
1 week	80% lactose / 5% H_2O*	90.35
2 weeks	80% lactose / 5% H_2O*	49.07
4 weeks	80% lactose / 5% H_2O*	48.80
4 weeks	80% lactose **	46.95
4 weeks	80% lactose **	49.52

* DCL and lactose particle sizes reduced with mortar and pestle
** High surface area Fast Flo® lactose

As can be seen from the results, the reaction rate and/or the extent of DCL/lactose interaction, is reduced in the absence of added water. In addition, a reduction in the

particle size of DCL and lactose led to the same extent of reaction after 2 and 4 weeks of storage under accelerated conditions. It is not possible to determine if this rate was accelerated relative to the material that was not reduced in size because of the lack of comparative data. It is noteworthy, however, that samples containing high surface area lactose led to reaction even in the absence of added water. This result indicates that the reaction rate is surface area dependent beyond some threshhold value, as Fast Flo® lactose, despite its desirable flow and compressability characteristics, led to a faster degradation rate.

As shown in Table 4, below, the reactivity of loratadine with lactose was negligible under similar conditions, including samples where 5% water was introduced .

Table 4
Reactivity of Loratadine with Lactose

Storage Time (60° C / 75% RH)	Treatment	% Initial
4 weeks	neat	99.35
4 weeks	80% lactose	100.33
4 weeks	80% lactose / 5% H_2O	100.37

EXAMPLES

Various embodiments of the present invention are hereinafter described in more detail by means of the following examples of pharmaceutical compositions of DCL, substantially free of reactive excipients, that are provided by way of illustration and not by way of limitation.

Example 1

Compressed DCL tablets may be prepared using conventional wet granulation techniques, such that each dosage unit contains 0.1 mg to 10 mg of DCL.

	Per tablet	Per 10,000 tablets
DCL	10 mg	100 g
Starch	60 mg	600 g
Talc	12 mg	120 g
Acacia	12 mg	120 g
Stearic Acid	1 mg	10 g

The acacia and an equal weight of starch is blended to form a paste which is used to granulate the DCL. The mixture is dried and placed through a mesh screen. The remainder of the material is added and mixed thoroughly. The resulting mixture is compressed into tablets using a 9/32-inch (7 mm) punch.

Example 2

Compressed DCL tablets may be prepared using conventional dry granulation techniques, such that each dosage unit contains 0.1 mg to 10 mg of DCL.

	Per tablet	Per 10,000 tablets
DCL	10 mg	100 g
Starch	85 mg	850 g

The starch is dried to a moisture content of 10% and then thoroughly mixed with the DCL. The resulting mixture is compressed into slugs and then ground to fine mesh size. Tablets are then compressed, using a 9/32-inch (7mm) punch.

Example 3

Compressed DCL tablets may be prepared using conventional direct compression techniques, such that each dosage unit contains 0.1 mg to 10 mg of DCL.

	Per tablet	Per 10,000 tablets
DCL	10 mg	100 g
Microcrystalline Cellulose	80 mg	800 g
Stearic Acid	5 mg	50 g
Colloidal Silica	1 mg	10 g

All of the ingredients are blended in a suitable blender. The resulting mixture is compressed into tablets, using a 9/32-inch (7mm) punch.

Example 4

Chewable DCL tablets may also be prepared using conventional direct compression techniques, such that each dosage unit contains 0.1 mg to 10 mg of DCL.

	Per tablet	Per 10,000 tablets
DCL	10 mg	100 g
Mannitol, USP	70 mg	700 g
Microcrystalline Cellulose	7 mg	70 g
Corn starch	3 mg	30 g
Calcium stearate	2 mg	20 g
Flavoring agent	qs	qs

All of the ingredients are blended in a suitable blender. The mixture is compressed into tablets using a 9/32-inch (7mm) flat-face bevel-edge punch.

Example 5

Soft gelatin DCL capsules may be prepared with a mixture of DCL in a digestible oil such as soybean oil, lecithin, cottonseed oil, or olive oil wherein the mixture is injected by means of a positive pressure pump into gelatin, such that each dosage unit contains 0.1 mg to 10 mg of DCL. The capsules are washed and dried.

Example 6

This example is provided as an illustration of an anhydrous pharmaceutical composition of DCL that includes lactose. Compressed DCL tablets may be prepared using conventional dry granulation techniques, such that each dosage unit contains 0.1 mg to 10 mg of DCL.

	Per tablet	Per 10,000 tablets
DCL	10 mg	100 g
Lactose (granular, 12-mesh)	35 mg	350 g
Starch	25 mg	250 g
Talc	25 mg	250 g
Magnesium stearate	0.2 mg	2 g

All of the ingredients are mixed thoroughly and then compressed into slugs. The slugs are then ground and screened to 14- to 16-mesh granules, which are then compressed into tablets, using a 9/32-inch (7mm) concave punch.

Tablets and capsules of other strengths may be prepared by altering the ratio of active ingredient to the excipients or to the final weight of the tablet.

While this invention has been described in terms of specific embodiments, it should be understood that these embodiments are presented by way of illustration only, and that the invention is not necessarily limited thereto. Modifications and variations within the spirit and scope of the claims that follow will be readily apparent from this disclosure, as those skilled in the art will appreciate.

We claim:

CLAIMS

1. A pharmaceutical composition in blended or granulated form for the treatment of histamine-induced disorders, comprising a therapeutically effective amount of descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable inert carrier.

2. The pharmaceutical composition of claim 1 wherein the pharmaceutical composition is substantially free of reactive excipients.

3. The pharmaceutical composition of claim 2 wherein the pharmaceutical composition is substantially free of lactose.

4. The pharmaceutical composition of claim 1 wherein the therapeutically effective amount of descarboethoxyloratadine is about 0.1 mg to 10 mg.

5. The pharmaceutical composition of claim 4 wherein the therapeutically effective amount of descarboethoxyloratadine is about 0.1 mg to 5 mg.

6. The pharmaceutical composition of claim 1 further comprising a therapeutically effective amount of an analgesic.

7. The pharmaceutical composition of claim 6 wherein the analgesic is selected from the group consisting of acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, naproxen or a pharmaceutically acceptable salt thereof.

8. The pharmaceutical composition of claim 1 further comprising a therapeutically effective amount of a decongestant.

9. The pharmaceutical composition of claim 1 wherein the composition is present in one of tablet or capsule form.

10. The pharmaceutical composition of claim 7 wherein the composition is present in tablet form.

11. A method of treating cough, cold, cold-like and flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, comprising administering a pharmaceutical composition according to claim 1.

12. A method of treating diabetic retinopathy or other small vessel disorders associated with diabetes melitis, comprising administering a pharmaceutical composition according to claim 1.

13. A method of treating symptomatic dermographism or dermatitis, comprising administering a pharmaceutical composition according to claim 1.

14. A method of treating allergic rhinitis, comprising administering a pharmaceutical composition according to claim 1.

15. A method of treating histamine-induced disorders, comprising administering a pharmaceutical composition according to claim 1.

16. An anhydrous pharmaceutical composition for the treatment of histamine-induced disorders, comprising a therapeutically effective amount of descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. The anhydrous pharmaceutical composition of claim 16 wherein the therapeutically effective amount of descarboethoxyloratadine is about 0.1 mg to 10 mg.

18. The anhydrous pharmaceutical composition of claim 17 wherein the therapeutically effective amount of descarboethoxyloratadine is about 0.1 mg to 5 mg.

19. The anhydrous pharmaceutical composition of claim 16 further comprising a therapeutically effective amount of an analgesic.

20. The anhydrous pharmaceutical composition of claim 19 wherein the analgesic is selected from the group consisting of acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, naproxen or a pharmaceutically acceptable salt thereof.

21. The anhydrous pharmaceutical composition of claim 16 further comprising a therapeutically effective amount of a decongestant.

22. The anhydrous pharmaceutical composition of claim 16 wherein the composition is present in one of tablet or capsule form.

23. The anhydrous pharmaceutical composition of claim 22 wherein the composition is present in tablet form.

24. A method of treating cough, cold, cold-like and flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, comprising administering an anhydrous pharmaceutical composition according to claim 16.

25. A method of treating diabetic retinopathy or other small vessel disorders associated with diabetes melitis, comprising administering an anhydrous pharmaceutical composition according to claim 16.

26. A method of treating symptomatic dermographism or dermatitis,comprising administering an anhydrous pharmaceutical composition according to claim 16.

27. A method of treating allergic rhinitis, comprising administering an anhydrous pharmaceutical composition according to claim 16.

28. A method of treating histamine-induced disorders, comprising administering an anhydrous pharmaceutical composition according to claim 16.

29. A non-hygroscopic pharmaceutical composition comprising descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, lactose and one or more pharmaceutically acceptable inert excipients wherein the composition is substantially free of unbound water.

30. The non-hygroscopic pharmaceutical composition of claim 29 wherein the one or more pharmaceutically acceptable inert excipients is selected from the group consisting of non-hygroscopic excipients and low-moisture excipients.

31. A solid, non-hygroscopic pharmaceutical composition comprising descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

32. An uncoated pharmaceutical composition substantially free of reactive excipients comprising descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

33. A chemically stable pharmaceutical composition in blended or granulated dosage form and substantially free of reactive excipients comprising about 1 % to about 50% by weight of descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, and about 99% to about 50% by weight of a pharmaceutically acceptable inert carrier.

34. A pharmaceutical composition for the treatment of histamine-induced disorders comprising large particles of descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

35. The pharmaceutical composition of claim 34 wherein the descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, present in the composition has a particle size distribution in which greater than about 40% by weight of the descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, comprises particles having a size of 250 μm or larger.

36. A solid pharmaceutical composition for the treatment of histamine-induced disorders comprising a therapeutically effective amount of coated descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, which comprises descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, coated with an inert coating agent, and a pharmaceutically acceptable carrier.

37. The solid pharmaceutical composition of claim 36 wherein the coated descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, further comprises a granulated formulation of descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable inert excipient, wherein the granulated formulation is coated with an inert coating agent.

38. The solid pharmaceutical composition of claim 36 or 37 wherein the inert coating agent comprises an inert film-forming agent in a solvent.

39. The solid pharmaceutical composition of claim 38 wherein the inert film-forming agent is selected from the group consisting of methylcellulose, hydroxymethyl cellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, methylhydroxyethylcellulose and sodium carboxymethylcellulose.

40. An instant release solid pharmaceutical dosage form for treating histamine-induced disorders, comprising an open matrix network carrying a therapeutically effective amount of descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof, wherein the open matrix network comprises a pharmaceutically acceptable water-soluble or water-dispersible carrier that does not interact with the descarboethoxyloratadine, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Inter. ›nal Application No
PCT/US 98/02328

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445

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 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 20708 A (SEPRACOR INC) 11 July 1996 cited in the application see abstract see page 5, line 1 - page 7, line 24 see page 16, line 1 - page 17, line 12; claims; examples 7-9 & US 5 595 997 A (ABERG ET AL.) ---	1-34,40
X	EP 0 396 404 B (SCHERING CORP) 16 February 1994 see the whole document --- -/--	1-11, 14-24, 27,28, 31,33, 34,36-40

[X] Further documents are listed in the continuation of box C.

[X] 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
8 June 1998	24.06.98

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	Hoff, P

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

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/US 98/02328

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 659 716 A (VILLANI FRANK J ET AL) 21 April 1987 see abstract see column 6, line 62 - column 8, line 46 see column 9, line 14 - line 16 see column 22, line 25 - column 25, line 31; claims ---	1-5, 8-10, 14-18, 21-23, 27-34,40
X	WO 85 03707 A (SCHERING CORP) 29 August 1985 see abstract see page 3, paragraph 3 - page 6, paragraph 2; claims; examples A-D ---	1-5,9, 10, 14-18, 22,23, 27-34,40
X	WO 96 16641 A (HEXAL AG ;KLOKKERS KARIN (DE); FISCHER WILFRIED (DE)) 6 June 1996 see the whole document ---	1-5, 14-18, 27-34
A	US 4 371 516 A (GREGORY GEORGE K E ET AL) 1 February 1983 cited in the application see the whole document -----	40

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/02328

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:

Although claims 11-15, 24-28 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.

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

Interr nal Application No
PCT/US 98/02328

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