COMPOSITIONS AND METHODS FOR TREATING ALLERGIC AND INFLAMMATORY CONDITIONS WITH COUGH

BACKGROUND OF THE INVENTION

This invention relates to treating and/or preventing allergic and inflammatory conditions with related productive and non-productive cough in humans by administering a combination of a non-sedating antihistamine and an expectorant.

Non-sedating antihistamines are known. See, e.g., Loratadine, disclosed in U.S. Patent No. 4,282,233; Desloratadine, disclosed in U.S. Patent No. 4, 659,716. See also Claritin brand of Loratadine. Product Information Sheet, dated 1/99. Likewise, mucolytic expectorants have been known in the art for some time. See Ambroxol, disclosed in U.S. Patent No. 3,536,712. Although useful, neither the non-sedating antihistamines nor the expectorants, in and of themselves, are capable of effectively treating the multitude of symptoms that may be associated with diseases of the respiratory tract, such as bronchitis and bronchial spasm, seasonal allergic rhinitis, perennial allergic rhinitis, common colds, sinusitis and concomitant symptoms associated with allergic asthma. The symptoms of such diseases may include sneezing, itching runny nose, nasal congestion, redness of the eye, tearing, itching of the ears or palate, and productive and non-productive coughs. It would be highly desirable to provide a formulation of these known separate drugs which enhances their individual efficacy and improves their overall efficacy.

SUMMARY OF THE INVENTION

The present invention provides methods for treating and/or preventing allergic and inflammatory conditions with related cough in

humans in need of such treating and/or preventing which comprises administering an effective amount of a non-sedating antihistamine and an expectorant. In particular embodiments, the non-sedating antihistamine is loratadine and the expectorant is ambroxol. Treatment according to the claimed methods is more effective than treatment with either a non-sedating antihistamine or an expectorant alone, and has a more rapid onset of action than that derived from the non-sedating antihistamine content.

The present invention provides methods for treating and/or preventing allergic or inflammatory conditions with cough in humans 6 years or older in need of such treating and/or preventing comprising administering an effective amount of a non-sedating antihistamine in combination with an expectorant. In preferred embodiments, the antihistamine is loratadine and the expectorant is ambroxol. In particularly preferred embodiments, the amount of loratadine is in the range of about 5.0 mg/day to about 15.0 mg/day in single or divided doses, more preferably about 10 mg/day in single or divided doses, most preferably about 5 mg/twice a day. In further embodiments, the amount of ambroxol is in the range of about 30 mg/day to about 180 mg/day in single or divided doses, more preferably about 30 mg/day to about 90 mg/day or about 60 mg/day in single or divided doses, most preferably about 30 mg/twice a day.

The invention also provides methods for treating and/or preventing allergic or inflammatory conditions with cough in humans aged 6 to 12 years in need of such treating and/or preventing comprising administering an effective amount of a non-sedating antihistamine in combination with an expectorant. In preferred embodiments, the antihistamine is loratadine and the expectorant is ambroxol. In particularly preferred embodiments, the amount of loratadine is in the range of about 0.5 mg to about 15.0 mg in single or divided doses. Preferably, the concentration of loratadine in liquid forms is in the range of about 0.5 mg/ml to about 3.0 mg/ml to be administered in single or divided doses; more preferably about 2.0

mg/ml per day to be administered in single or divided doses, according to body weight, most preferably about 1.0 mg/ml twice a day. The dosage amount of loratadine will preferably range from about 0.1 mg/kg to about 0.3 mg/kg per day, more preferably from about 0.2 mg/kg to about 0.3 mg/kg per day. In further embodiments, the amount of ambroxol is in the range of about 0.6 mg to about 180.0 mg per day in single or divided doses. Preferably, the concentration of ambroxol is in the range of 3.0 mg/ml to 18.0 mg/ml per day to be administered in single or divided doses according to body weight; more preferably about 12.0 mg/ml in single or divided doses, most preferably about 6 mg/ml to be administered according to body weight twice a day. The dosage amount of ambroxol will preferably range from about 0.5 mg/kg per day to about 2.0 mg/kg per day, more preferably from about 1.0 mg/kg per day to about 2.0 mg/kg per day, most preferably from about 1.0 mg/kg per day to about 1.5 mg/kg per day.

Also provided are novel pharmaceutical compositions for treating and/or preventing allergic and inflammatory conditions with cough in humans comprising an effective amount of a non-sedating antihistamine in combination with an expectorant and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel pharmaceutical formulations, which consist essentially of a combination of a non-sedating antihistamine and an expectorant. The formulations of the invention are useful in the prevention and/or treatment of allergic and inflammatory conditions of the skin or airway passages with cough. The formulations are useful for a wide range of patient ages; specific embodiments provided herein include a tablet form for administration to humans 12 years and older, and a pediatric solution for humans aged 6-12 years.

Also provided by the invention are methods for treating and/or preventing allergic and inflammatory conditions with related cough in humans in need of such treating and/or preventing which comprise administering an effective amount of a non-sedating antihistamine in combination with an expectorant.

The phrase "allergic and inflammatory conditions of the skin or airway passages" as used herein means those allergic and inflammatory conditions and symptoms found on the skin and in the upper and lower airway passages from the nose to the lungs. Typical allergic and inflammatory conditions of the skin or upper and lower airway passages include seasonal and perennial allergic rhinitis, non-allergic rhinitis, asthma including allergic and non-allergic asthma, sinusitis, colds, dermatitis, especially allergic and atopic dermatitis, and urticaria and symptomatic dermographism as well as retinopathy, and small vessel diseases, associated with diabetes mellitus.

The term "a human age 6-12 years" as used herein means a male or female pediatric subject of 6 years of age to 12 years of age. The term "a human of 12 years and older " as used herein means a male or female pediatric subject of greater than 12 years of age to less than 18 years of age and adults of 18 years of age and older.

Although preferred embodiments of the present invention comprise treatment with loratadine and Ambroxol (See Examples 1 and 2), other antihistamines and expectorants are equally applicable in the compositions and methods taught herein. Following are non-inclusive lists of representative antihistamines and expectorants which may be used in the present invention.

I. Antihistamines

Loratadine is a non-sedating antihistamine whose technical name is 11-(4-piperidylidene)-5H-benzo-[5, 6]-cyclohepta-[1, 2-b]-pyridine. The compound is described in U.S. Patent No. 4,282,233. Loratadine is a potent tricyclic and antihistaminic drug with a selective antagonist of

peripheric H_1 receptors activity. The amount of loratadine which can be employed in a unit (*i.e.*, single) dosage form of the present compositions can range from about 1.0 mg to about 15.0 mg, also from about 2.5 mg to about 10.0 mg, preferably from about 5.0 mg. to about 10.0 mg.

Desloratadine is a non-sedating long acting histamine antagonist with potent selective peripheral H1-receptor antagonist activity. Following oral administration, loratadine is rapidly metabolized to descarboethoxyloratadine or desloratadine, a pharmacologically active metabolite. U.S. Patent Nos. 4,659,716, 5,595,997 and 4,804,666 disclose methods of making desloratadine, pharmaceutical compositions containing it and methods for using it to treat various disease states in mammals. The amount of desloratadine which can be employed in a unit (*i.e.*, single) dosage form of the present compositions can range from about 0.75 mg to about 7.5 mg, also from about 1.25 mg to about 5.0 mg, preferably from about 2.5 mg. to about 5.0 mg.

Descarboethoxyloratadine (DCL) is non-sedating antihistamine, whose technical name is 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2]pyridine. This compound is described in Quercia, et al., Hosp. Formul., 28: 137-53 (1993), in U.S. Patent 4,659,716, and in WO 96/20708. DCL is an antagonist of the H-1 histamine receptor protein. The H-1 receptors are those that mediate the response antagonized by conventional antihistamines. H-1 receptors are present, for example, in the ileum, the skin, and the bronchial smooth muscle of man and other mammals. The amount of DCL which can be employed in a unit (i.e. single) dosage form of the present compositions can range from about 2.5 to about 20 mg, also from about 5 to about 10 mg, preferably about 5 or 7.5 mg.

Fexofenadine (MDL 16,455A) is a non-sedating antihistamine, whose technical name is 4-[1-hydroxy-4-(4-hydroxy-diphenylmethyl)-1-piperidinyl)butyl]-α, α-dimethyl-benzene acetic acid. Preferably the pharmaceutically acceptable salt is the hydrochloride, also known as fexofenadine hydrochloride. The amount of fexofenadine which can be

employed in a unit dosage form of the present composition can range from about 40 to 200 mg, also from about 60 to about 180 milligrams, also about 120 milligrams.

II. Expectorants

Ambroxol is a bromhexine metabolite, chemically identified as trans-4(2-amino-3,5-dibromobenzil, amine) ciclohexane hydrochloride, which has been widely used during more than two decades as an expectorant agent or stimulating pulmonary surfactant factor. The compound is described in U.S. Patent No. 3,536,712. The amount of ambroxol which can be employed in a unit dosage form can range from about 30.0 to about 60.0 mg, preferably about 60.0 mg.

Guaiafenesin is an expectorant, whose technical name is 3-(2-methoxyphenoxy)- 1, 2-propanediol. The compound is described in U.S. Patent No. 4,390,732. The amount of guaiafenesin which can be employed in a unit dosage form can range from about 300.0 to about 1200.0 mg, preferably about 1200.0 mg.

Terpin hydrate is an expectorant, whose technical name is 4-hydroxy-α, α, 4-trimethylcyclohexane-methanol. The amount of terpin hydrate that employed in a unit dosage form of the present composition can range from 85.0 to 680.0 milligrams.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable diluents, excipients and carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules (either solid-filled, semi-solid filled or liquid-filled), sachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, sachets and capsules can be used as sold dosage forms suitable for oral administration. Examples of pharmaceutically

acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants that may be mentioned for use in these dosage forms are, metallic stearates, talc, starch powder, stearic acid, different grades of polyethylene-glycol and the like. Disintegrants include starch, methylcellulose, guar gum and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and pacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg preferably from about 0.01 mg to about 750 mg more preferably from about 0.01 mg to about 750 mg and most preferably from about 0.01 mg to about 250 mg according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 5.0 to 10.0 mg/day of loratadine and 30 to 60.0 mg/day of ambroxol, in two to four divided doses.

Dosage form - non-sedating antihistamine and expectorant formulated into a delivery system, *i.e.*, tablet, capsule, oral gel, powder for constitution or suspension in association with inactive ingredients.

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising non-sedating antihistamine and an expectorant. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gels - refers to a non-sedating antihistamine and an expectorant dispersed or solubilized in a hydrophilic semi-solid matrix.

Powders for constitution - refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrants - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures, cross-linked povidones. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binders - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting

point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene-glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glidants - materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidants include silicon dioxide and talc. The amount of glidant in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures.

The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the invention to specific embodiments.

EXAMPLE I
Novel Pharmaceutical Compositions

The present invention provides a novel combination of a slow release non-sedating antihistamine such as loratadine, and an expectorant and mucolytic agent such as ambroxol, in a new pharmaceutical preparation. The combination is indicated primarily in the treatment of those patients who show bronchopulmonary conditions of allergic origin associated with cough, where viscosity and mucous adherence are increased, obstructing permeability of the airways. The principal indications include but are not limited to allergic rhinitis associated with cough; acute, chronic, spasmodic and asthmatic bronchitis; bronchial asthma; bronchiectasis; sinusitis; otitis media; pneumonia; bronchopneumonia; atelectasis by mucous obstruction; tracheotomy and as a pre and post prophylactic agent.

The formulas for each pharmaceutical form presented in the following examples are as follows:

Tablets

Name of Ingredients	Concentration (mg/tablet)	Rationale	% Variation
Loratadine	5.00	Active	
Ambroxol Hydrochloride	30.00	Active	
Lactose Anhydrous	84.75	Filler	±20
Corn Starch	12.00	Disintegrant	±20
Cellulose Microcrystalline	16.75	Disintegrant	±10
Colloidall Silicon Dioxide	0.75	Glidant	±10
Magnesium Stearate	0.75	Lubricant	±10
Tablet Weight	150.00mg		

Manufacturing procedure:

The tablets are prepared by a direct compression process, mixing into a blender the powder ingredients the specific time to assure content uniformity, the blend is compressed into tablets.

Solution

Name of Ingredients	Concentration mg/ml	Rationale	% Variation
Loratadine	1.00	Active	
Ambroxol Hydrochloride	6.00	Active	
Citric Acid	0.40	Buffer	±10
Glycerin	150.00	Solvent	±20
Propylene Glycol	200.00	Solvent	±20
Saccharin Sodium	0.40	Sweetener	±10
Sorbitol solution 70%	315.00	Solvent	±20
Peach Flavor No. 609	2.50	Flavor	±10
Purified Water	q.s.	Solvent	±20
To make	1.00 ml		

Manufacturing procedure:

The solution is prepared by the addition of Loratadine and Saccharin to the propylene glycol, the citric acid is dissolved in water and added to the batch. Ambroxol is added to the batch and dissolved. Glycerin, Sorbitol and Flavor are added to the batch and mixed until homogeneous.

EXAMPLE 2
Clinical Studies

The safety and efficacy of each separate component of the loratadine/ambroxol combination is well established. Studies of acute toxicity carried out with loratadine (in extensive clinical and preclinical programs) and ambroxol components have confirmed the low potential for systemic toxicity, which was expected for this combination.

Loratadine is a potent tricyclic and antihistaminic drug of slow release, with a selective antagonist of peripheric H_1 receptors activity. It is completely absorbed after being orally administered. The plasma elimination half life is of 9 hours. Nevertheless, its antihistaminic effect

persists during 24 hours. The onset of action is very early, estimated at approximately 30 minutes. Afterwards, loratadine is extensively metabolized in the liver and it is excreted through urine and feces.

Ambroxol is a bromhexine metabolite, chemically identified as trans-4(2-amino-3,5-dibromobenzil, amine) ciclohexane hydrochloride, which has been widely used for more than two decades as an expectorant agent or stimulating pulmonary surfactant factor. After oral administration, the absorption rate is rapid and complete. The elimination half life has been estimated at 20-25 hours in man, and it is excreted almost completely in urine. It has been found that the biotransformation routes are similar in all species studied. Ambroxol is metabolized predominantly by the conjugation with glucuronic acid and in less extension by reactions which carry dibromoanthranilic acid. Ambroxol has a wide distribution, crosses the placenta barrier and fetal concentrations have been detected 15 minutes after the administration, with a concentration that amounts 3 times the levels in maternal plasma. An accumulation in liver and lungs, with maximum values at 90 minutes after its administration, has been detected.

The clinical efficacy and safety of the new combination of the invention is to be documented in 3 clinical trials: Study one is a six-month controlled, prospective, longitudinal study including 120 adult patients who exhibit symptoms of bronchitis with bronchoconstriction; Study Two is a six month prospective, double-blind, controlled, randomized and comparative study including 120 patients to evaluate the efficacy and safety of a loratadine/ambroxol solution versus the single active ingredients, loratadine and ambroxol, in children between 6 and 12 years old with allergic rhinitis and cough; and Study Three is a single-center, randomized, open-label, three-way crossover single dose bioavailability study of the Loratadine-Ambroxol tablet of this invention vs. 30-mg Ambroxol tablet) and 10-mg Loratadine tablet in 30 healthy volunteers. The results of these clinical studies will demonstrate that the combination of loratadine and ambroxol is safer

and more effective for the treatment and/or prevention of allergic and inflammatory conditions of the skin or airway passage with related cough than its single ingredients separately.

CLINICAL STUDY DESIGNS

The following three clinical protocols were designed to (a) compare the safety and efficacy of the loratadine/ambroxol combination in adult patients with bronchitis with bronchoconstriction (Study 1); (b) to evaluate the safety and efficacy of the loratadine/ambroxol combination in pediatric patients with allergic rhinitis and cough (Study 2); and (c) to compare the relative bioavailability of the loratadine/ambroxol combination with each administered separately to healthy volunteers (Study 3).

STUDY NO. 1

This study is a six-month doubled-blind, controlled, prospective, longitudinal study including 120 adult patients who exhibit symptoms of bronchitis with bronchoconstriction.

STUDY OBJECTIVE

The objective of this study is to evaluate the efficacy and safety of the administration of the loratadine/ambroxol combination in adult patients presenting bronchitis with bronchoconstriction.

INVESTIGATIONAL PLAN

Overall Study Design and Plan: Description

The study calls for enrollment of a total of 120 adult subjects having bronchitis with bronchoconstriction. A combination of loratadine/ambroxol is administered orally in tablet form twice a day (every 12 hours) for fourteen days.

During clinical evaluation of the disorder, time of evolution of symptoms will be determined and the symptoms and clinical signs will

be recorded. Patients will be seen by the specialist at the beginning of the study (day 1- Basal Measurement), and through 3 follow up visits at 7 days (visit 2), 14 days(final visit). At each visit, global evaluations must be made about changes in the disease, comparing all results with what was recorded in the first and subsequent visits. Subjects will be observed at each visit and questioned throughout the study for possible occurrence of adverse events. Type of reaction, severity, temporal and causal relationship with treatment will be documented. In the final visit, subjects will be asked to make an evaluation about the efficacy of the medicine used.

Each subject will randomly receive one of the following three treatments:

Treatment 1: One loratadine 5 mg/ambroxol 30 mg combination tablet orally administered every 12 hours for fourteen days.

Treatment 2: One placebo tablet orally administered every 12 hours for fourteen days.

Study Population/ Inclusion Criteria/ Exclusion Criteria

Inclusion Criteria:

- Adult males or females between the ages of 18 to 70 years inclusive.
- Subjects presenting bronchitis diagnosis with bronchoconstriction
- Otherwise clinically healthy.
- Subjects understand the requirements and restrictions of the study and agree to attend evaluation visits.
- Subjects must give written informed consent prior to any study-related procedures being performed.

Exclusion Criteria:

- Subjects who are pregnant or lactating.

- Subjects with allergy or hypersensitivity to the drugs used in the study.
- Subjects who have received a treatment with antihistamines, expectorants or mucolytic agents 8 days before entrance to study.
- Subjects with background of cardiac, hepatic or renal disease.
- Subjects receiving immunotherapy.
- Subjects who do not comply with the requirement that he or she should not use any prescription or over the counter drugs other than those given for the study protocol for the duration of the study.

Early termination of Treatment and Exclusions

The investigator has the right and obligation to interrupt the treatment of any patient whose welfare or physical health is compromised with the continuation of the study. Such patients must be withdrawn from the study and they must not continue under a modified scheme.

If treatment is prematurely ceased for reasons other than previously specified, the subject must be considered as "dropout" and another subject must be included in his or her place. A Case Report Form must be filled out for all "dropouts".

Study Treatments

At visit 1 of the study, each subject receive a treatment bottle containing enough tablets for one of the above-listed three treatments (1 or 2). Patients must return the bottle (empty or partially used) on the last visit.

The first drug dose is administered in the doctor's office, after completion of the initial evaluations of the disease. At each subsequent visit, the subject must be carefully questioned to assure treatment adherence according to protocol requirements. Variations, such as forgetting to take one or several doses or exceeding the number of doses, must be recorded in the Case Report Form.

Any adverse event that risks patient's safety requires withdrawal of treatment and exclusion of the subject from the study. The patient must return for additional clinical evaluations until the adverse event resolves.

Efficacy Parameters

The following parameters are to be monitored:

Loratadine:

- Bronchoconstriction relief
- Inflammation

Ambroxol:

- Cough qualitative measurement
- Secretion fluidity

These parameters will be graded with an analogue scale of 3 grades, to be evaluated with non parametric statistical methods.

Safety Parameters

All adverse events will be recorded in the adverse events sheet. Some adverse events necessitate early termination of treatment. If the appearance of an adverse event requires administration of an additional therapeutic, this must be recorded in the case report in the section entitled "Concomitant Therapy." The patient's progress during the subsequent visits must also be recorded.

Documentation of each adverse event should include time of initial manifestation, place and the duration of the adverse event; and definition of the relationship with the study drug.

Any patient who experiences a serious adverse event must be withdrawn immediately from the study. All serious adverse events, whether they are or not related to the drug, must be communicated by telephone to Schering Plough's monitor, in the following 48 hours. This written report must be delivered within the following five days.

A serious adverse event is the one that suggests a significative risk or danger, contraindication, collateral effect or precaution. With

regard to clinical experience in human beings, this includes any event that:

- Results in patient's death
- Imposes an immediate health risk.
- Results in hospitalization or prolongs a present hospitalization.
- Causes permanent, persistent or significant disability.
- Results in organic toxicity, including hematological, hepatic, gastrointestinal and central nervous system toxicity. In addition, abnormalities in laboratory tests which show changes more than 3 times the normal limits are also considered as organic toxicity. If the values of tests taken at the beginning are out of normal limits, any change $\geq$ 25% in relation to basal values, must be reported.
- Is cancer
- Is an overdose, rather intentional or unnoticed
- Is a congenital defect

Protocol Deviations

The protocol must be carried out exactly, following the written indications. Any change in the protocol must be made under a mutual written agreement between the investigator and Schering Plough. Before any change is implemented, an amendment to protocol must be signed by the investigator as well as by Schering Plough.

The following are examples of protocol deviations that disqualify the patients for the subsequent visits:

- Use of prohibited medicines or treatments.
- Modification in dosage: Failure to take more than one doses or taking extra doses in treatment days.

Statistical Analysis:

A comparison of the qualification of signs and symptoms, including the sum of them (total sum of symptoms and signs) will be

evaluated, as well as the percentage of improvement in total qualification of symptoms and signs, with respect to basal evaluation; in the same way, the results in the global response to treatment obtained by the doctor and the evaluation carried out by the patient himself/herself (mother/father/tutor), will be compared and used as an efficacy criteria.

STUDY NO. 2.

This study is a six month prospective, double-blind, controlled, randomized and comparative study to evaluate the efficacy and safety of a loratadine/ambroxol solution versus the single active ingredients, loratadine and ambroxol, in children between 6 and 12 years old with allergic rhinitis and cough.

STUDY OBJECTIVE

The objective of this study is to evaluate the efficacy and safety of the administration of the loratadine/ambroxol combination in children between 6 and 12 years old, with diagnoses of allergic rhinitis and cough.

INVESTIGATION PLAN

Overall Study Design and Plan: Description

This study calls for enrollment of a total of 120 children between the ages of 6 and 12 years inclusive, who exhibit symptoms of allergic rhinitis and cough. A pediatric solution consisting of a combination of loratadine/ambroxol will be administered twice a day (every 12 hours), for ten days, for comparison to its own ingredients separately, loratadine and ambroxol.

The diagnosis of allergic rhinitis will be done based on the presence of nasal congestion, hyaline rhinorrhea, sneezing, lacrimation, conjunctival pruritus, and it must be associated with cough.

Among the clinical evaluation of the disorder, time of evolution of symptoms will be determined and the symptoms and clinical signs will be recorded. Patients will be seen by the specialist at the beginning of the study (day 1- Basal Measurement), and through 3 follow up visits, at 5 days (visit 2), at 10 day (final visit). At each visit, global evaluations will be made about changes in the disease, comparing all results with what was recorded in the first and subsequent visits. Subjects will be observed at each visit and questioned throughout the study for possible occurrence of adverse events. Type of reaction, severity, and temporal and causal relationship with treatment will be documented. In the final visit, parents or patient's tutor will be asked to make an evaluation about the efficacy of the medicine used.

Each subject will randomly receive one of the following three treatments:

Treatment 1: One oral dose of a pediatric solution of a loratadine 1.0 mg/ml and ambroxol 6.0 mg/ml combination administered every 12 hours for ten days.

Treatment 2: One oral dose of a pediatric solution of loratadine 1.0 mg/ml administered every 12 hours for ten days.

Treatment 3: One oral dose of a pediatric solution of ambroxol 6.0 mg/ml administered every 12 hours for ten days.

Dosage will be determined according to age and body weight, as shown in the following table:

Age	Body Weight (Kg)	Volumen every 12 hours (ml)	Loratadine 12 hours (mg)	Loratadine 24 hours (mg)	Ambroxol 12 hour (mg)	Ambroxol 24 hours (mg)
6 to 9	20.3 to 29.9	2.5	2.5	5.0	15	30
10 to 12	30.0 to 44.0	5	5.0	10.0	30	60

Recommended doses per kilogram of body weight are as follows:

Loratadine:
6 to 9 years of age: Average body weight: 25.1 Kg. Dosage: 0.199 mg/kg.
10 to 12 years of age: Average body weight: 37 Kg. Dosage: 0.27 mg/kg.

Ambroxol:
6 to 9 years of age: Average body weight: 25.1 Kg. Dosage: 1.19 mg/kg.
10 to 12 years of age: Average body weight: 37 Kg. Dosage: 1.62 mg/kg.

For this study, subjects weighing less than 30 kg will be administered 2.5 ml of solution every 12 hours, while subjects weighing 30 kg and over will be administered 5 ml of solution every 12 hours.

Study Population/Inclusion Criteria/Exclusion Criteria

Inclusion Criteria:

- Males or females between the ages of 6 and 12 years inclusive.
- Subjects with diagnosis of allergic rhinitis and cough.
- Otherwise clinically healthy.
- Parents or tutors must understand the requirements and restrictions of the study and agree to attend to evaluation visits.
- Parents or tutors must give written informed consent (prior to any study-related procedure being performed).

Exclusion Criteria:

- Subjects with allergy or hypersensitivity to the drugs used in the study.
- Clinical evidence of bacterial infections in nasopharynges.
- Subjects who have received a treatment with antihistaminics, vasoconstrictors or corticoesteroids 8 days before entrance to study.
- Subjects with background of cardiac, hepatic or renal disease.
- Subjects who, according to the investigator, have any vital sign, weight or height clinically abnormal for the age.
- Subjects receiving immunotherapy.

- Subjects who do not comply with the requirement that he or she should not use any prescription or over the counter drugs other than those for the study protocol for the duration of the study.

Early termination of Treatment and Exclusions

The investigator has the right and obligation to interrupt the treatment of any patient whose welfare of physical health is compromised with the continuation of the study. Such patients must be withdrawn from the study and they must not continue under a modified scheme.

If treatment is prematurely ceased for reasons other than those previously specified (for example, failure to go to controls), the patient must be considered as "dropout" and in its place, another patient must be included in his or her place. A Case Report Form must be filled out for all "dropouts".

Study Treatments

At visit 1 of the study each subject will receive a formulation bottle containing fourteen days of treatment according to one of the above-listed three treatments. Patients must return the bottle (empty or partially used) on the last visit. The first drug dose must be

administered in the doctor's office, after completing the initial evaluations of the disease.

The first drug dose must be administered in the doctor's office, after completing the initial evaluations of the disease. At each subsequent visit, the patient (parent or tutor) must be carefully questioned to assure treatment adherence according to protocol requirements. Variations, such as forgetting to take one or several doses or to exceed the number of doses, must be recorded in the Case Report Form.

Any adverse event that risks patient's safety requires the withdrawal of treatment, and exclusion of the patient from the study. The patient must return for additional clinical evaluations until the adverse event resolves.

Efficacy Parameters

The following parameters will be monitored:

Loratadine:

- Sneezing
- Aqueous Rhinorrhea
- Lacrimation
- Conjunctival pruritus

Ambroxol:

- Decrease in cough frequency and intensity
- Secretion fluidity

These parameters will be graded with an analogue scale of 3 grades, to be evaluated with non parametric statistical methods.

Safety Parameters

All adverse events will be recorded in the adverse events sheet. Some adverse events necessitate early termination of treatment. If the appearance of an adverse event requires administration of an additional therapeutic, this must be recorded in the case report in the section

entitled "Concomitant Therapy." The patient's progress during the subsequent visits must also be recorded.

Documentation of each adverse event should include time of the initial manifestation, the place and the duration of the adverse event, and the relationship with the study drug. A serious adverse event is the one that suggests a significant risk or danger, contraindication, collateral effect or precaution. With regard to clinical experience in human beings, this includes any event that:

- Results in patient's death
- Imposes an immediate health risk.
- Results in hospitalization or prolongs a present hospitalization.
- Causes permanent, persistent or significant disability.
- Results in organic toxicity, including hematological, hepatic, gastrointestinal and central nervous system toxicity. In addition, abnormalities in laboratory tests which show changes more than 3 times the normal limits are also considered as organic toxicity. If the values of tests taken at the beginning are out of normal limits, any change $\geq$ 25% in relation to basal values, must be reported.
- Is cancer
- Is an overdose, rather intentional or unnoticed
- Is a congenital defect

Any subject who experiences a serious adverse event must be withdrawn immediately from the study. All serious adverse events, whether they are or not related to the drug, must be communicated by telephone to Schering Plough's monitor in the following 24 hours. This written report must be delivered within the following five days.

Protocol Deviations

The protocol must be carried out exactly, following the written indications. Any change in the protocol must be made under a mutual

written agreement between the investigator and Schering Plough. Before any change is implemented, an amendment to protocol must be signed by the investigator as well as by Schering Plough.

The following are examples of protocol deviations that disqualify the patients for the subsequent visits:

- Use of prohibited medicines or treatments.
- Modification in dosage: Failure to take more than one doses or taking extra doses in treatment days.

Statistical Analysis:

A comparison of the qualification of signs and symptoms, including the sum of them (total sum of symptoms and signs) will be evaluated, as well as the percentage of improvement in total qualification of symptoms and signs, with respect to basal evaluation; in the same way, the results in the global response to treatment obtained by the doctor and the evaluation carried out by the patient himself/herself (mother/father/tutor), will be compared and used as an efficacy criteria.

STUDY NO. 3

This study is a single-center, randomized, open-label, three-way crossover single dose bioavailability study of tablet vs. 30-mg Ambroxol tablet and 10-mg Loratadine tablet in 24 healthy volunteers.

STUDY OBJECTIVE

The objective of this study is to compare the relative bioavailability of the combination Loratadine/Ambroxol tablet with each of one administered separately to healthy volunteers.

INVESTIGATION PLAN

Overall Study Design and Plan: Description

Thirty healthy male volunteers between the ages of 18 and 50 years will be empanelled and enrolled at a single center in accordance with a random crossover design and the subject inclusion criteria into this three-way crossover study. All the subjects will be determined to be in good health through medical history, physical examination, electrocardiogram and laboratory test. Subjects must meet the inclusion and exclusion criteria listed below.

This study will require approximately 36 days to be clinically complete. Subjects will be screened within two days of treatment. Each treatment period will require 2 days to complete and each treatment will be separated by a washout period of at least two weeks. Prior to initial dosing, the study monitor or her/his designee must review all screening data, to ensure all subjects are eligible.

Treatments

In the morning (approximately 8 a.m.), following an overnight fast, each subject will receive one of the followings treatments according to a computer-generated code.

Treatment A: Two Loratadine-Ambroxol tablets starting at 8:00 a.m.

Treatment B: Two 30-mg Ambroxol tablets starting at 8:00 a.m.

Treatment C: One x 10-mg Loratadine tablet starting at 8:00 a.m.

TABLE 1

Period I	Period II	Period III
Treatment A	Treatment B	Treatment C
Treatment B	Treatment C	Treatment A
Treatment C	Treatment A	Treatment B

*All treatments will be administered with 240 ml of water. There will be fifteen days washout time between the treatments.

Dosage Form and Study Design

The following drug products will be employed:

Loratadine-Ambroxol (30-mg Ambroxol and 5-mg Loratadine) tablets.

Mucosolvan® (30-mg Ambroxol) tablets

Clarityne ® (10-mg Loratadine) tablets

All drug supplies are to be stored in a secure location within the storage conditions specified on the labels.

Study Population/Inclusion Criteria/Exclusion

Inclusion Criteria:

Males between the ages of 18 and 50 years having weights in accordance to Metropolitan Life Insurance Company 1983 Height and Weight tables (± 10%) will be selected for this study. Each patient will undergo a physical examination within two weeks prior to entering the study. Furthermore, a complete medical history will be taken, an electrocardiogram will be obtained, and the following laboratory tests performed:

1) Complete blood count (including differential)
2) Hepatitis B Surface Antigen Test
3) HIV Antibody test
4) Blood chemistries.

5) Total protein
6) Albumin
7) Calcium
8) Inorganic Phosphorus
9) Cholesterol
10) Triglycerides
11) Fasting blood sugar
12) Blood urea nitrogen
13) Uric acid
14) Total bilirubin
15) Alkaline phosphate
16) Lactic dehydrogenase
17) Serum Glutamic Pyruvic Transaminase
18) Serum Glutamic Oxalacetic Transaminase
19) Gamma Glutamyl Transpeptidase
20) Serum creatinine
21) Electrolytes (Na, K, Cl, Bicarbonate as CO2)
22) Urinalysis

Prior to initial dosing, the clinical laboratory test performed for screening purposes and physical examination results must be reviewed by the study monitor or his/her designee. Subjects must be able to understand the requirements of the study, be willing to abide by the restrictions, and return for the required examinations and treatments.

Upon entering the study, each patient will be assigned a random number and written informed consent will be obtained. This information will be noted on the patient's case report form.

No other drugs (either prescription, investigational or OTC) shall be taken for two weeks prior to the study or during the course of the study.

The subject's smoking history will be obtained and recorded on the case report forms.

Exclusion Criteria

1) Individuals with a history of cardiovascular, neurologic, hematological, gastrointestinal, cerebrovascular, respiratory, hepatic or renal disease, or any other disorder that requires a physician's care.
2) Individuals with a laboratory test results outside the normal range (for that laboratory) which are:
   - 2.1) Not expected as a reflection of known underlying disease and considered by the investigator and Schering project Director/Project Physician to contraindicate study participation.
   - 2.2) In the investigator's judgment, clinically significant based on clinical evaluation and based on other test with clinical relevance to the abnormal lab test.
3) Individuals who have a history of any local or systemic infectious disease and urinary tract infection within four weeks prior to drug administration.
4) Any individual who does not comply with the requirement that he should not have used any drug for at least two weeks prior to the study nor alcohol within 24 hours, nor caffeine or marijuana within 24 hours prior to treatment administration.
5) Individuals who have participated in a clinical trial and have received an investigational drug within two months prior to the start of the study.
6) Individuals who are or are known to be former narcotic addicts or alcoholics.
7) Individuals who have a known allergy to Ambroxol or Loratadine or a strong history of food or drug allergy.
8) Individuals who are positive to HIV antibodies.
9) Individuals who are positive for Hepatitis B surface antigen or hepatitis C antibody.

Randomization

Subjects will be randomized to receive treatment A, B, or C in one of three possible sequences, (ABC, BCA, and CAB) respectively according to a computer-generated code supplied to the investigator by Schering Plough M-PDL.

Replacement of Subjects

All subjects who discontinue the study early and meet the following criteria may be replaced:

10) Any discontinuation due to administrative reasons (e.g., subject preference)
11) Failure to meet entry criteria
12) Subject fails to follow protocol requirements

The replacement subject will be numbered using the original subject's assigned number plus an "R" (e.g., 1 is replaced by 1R). The dosing regimen for the new subject will be according to the original subject's dosing regimen.

Study Treatments

A. Drug Administration

Periods of the cross-over

After the written informed consent, the subjects will take the Treatment A, or Treatment B, or Treatment C after which the study starts (Day one, Period I) and continue until the day thirty-six. After 15-days washout period, on day eighteen (Period II) the subjects will take the complimentary treatment A or B or C according to the sequence previously described. After 15-days washout period, on day thirty-five (Period III) the subjects will take the complimentary treatment A or B or C according to the sequence previously described.

All treatments will be administered in the morning at approximately 8 AM. On days 1, 18, and 35, volunteers will be administered following an overnight fast, and no food or fluid for four hours after dosing will be permitted.

At the completion of each study period volunteers will be examined and may then released from the study site. Volunteers will be advised when to report back to the study for period II, and III. The dose administrations must be separated by a washout period of at least 15-days.

At the completion of the study (after the last blood sample on day 36), the physical examination, blood chemistries, urinalysis, and electrocardiogram performed at screening for each volunteer will be repeated. If any laboratory test is outside the reference range (except for tests expected to be outside the reference range) and is considered to be clinically significant by the investigator, it should be repeated at appropriate time intervals until it returns to baseline or becomes a clinically insignificant finding.

Meals

On the day of dosing, breakfast will be omitted. No food or fluid (including water) will be consumed during the four-hour period after treatment administration.

Meals will be standardized so that the same meals will be served on the same day during each respective treatment period to all volunteers. Since grapefruit juice has been reported to inhibit first-pass metabolism of some drugs, no grapefruit juice, grapefruit or products containing grapefruit will be consumed during the confinement period for each treatment phase of the study.

Blood Samples

Blood samples will be collected on day 1 to 2, day 18 to 19, and day 35 to 36 at specified time following each treatment for subsequent analysis of Ambroxol, and Loratadine in human plasma. Laboratory tests, physical examinations, and EKGs will be performed before the study. In addition, vital signs will be recorded daily prior to the 8:00 a.m. drug administration during each treatment day, and all subjects will be continuously observed throughout the study for possible adverse experiences. Any adverse experience will be recorded on the case report forms.

Clinical Observation

Prior to drug administration during each period of the study of sampling time, vital signs (BP, HR, respiratory rate, and oral body temperature) will be obtained and recorded on the case report form. Vital signs will also be obtained and recorded. The subjects will be observed and questioned during the study for the possible occurrence of side effects. Medically acceptable terminology should be used when recording any symptom.

The severity of adverse experiences should be assessed according to the following definitions:

Mild: Experience was rather trivial and did not cause any real problem to the volunteer.

Moderate: Experience was a problem to the volunteer but did not interfere significantly with the daily activities or clinical status of the volunteer.

Severe: Experience caused a significant interference with the normal daily activities or clinical status of the volunteer.

Clinical Observations

The results of pre-study and post-study tests will be evaluated.

Pharmacokinetic and Bioequivalence

Pharmacokinetic Analysis will be performed on Loratadine and Ambroxol plasma concentration using a Non-Compartmental Approach with the WinNonlin Professional Program. The maximum plasma concentration (Cmax) and time to reach the maximum plasma concentration (Tmax) will be obtained directly from the data. The terminal phase rate constant (lambda Z) will be calculated as the negative of the slope of the log-linear terminal portion of the plasma concentration-time curve using linear regression. The terminal phase half-life (T1/2) will be calculated as 0.693/lambda Z.

For Ambroxol the area under the plasma-concentration curve from time 0 to infinity (AUC_inf ng*Hr/ml) will be calculated using the linear trapezoidal rule then the log trapezoidal rule. All the pharmacokinetic parameters will be calculated according to the model 200 of the WinNonlin Library.

Cmax: For single dose data: the maximum concentration between 0 and last measurable amount.

Tmax: Time of maximum observed concentration.

AUC_0-tmax Area under the curve from time of dosing (Dosing_time) to Tmax hours.

AUC_0-48: Area under the curve from time zero (Dosing_time) to 48 hours.

AUC_0-inf Area under the curve from the time of dosing (Dosing_time) to infinity.

T1/2 _lambda z (hr) Terminal half-life =Ln(2)/ λz, where λz (hr-1) is the First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration.

The test product will be the data obtained from the Loratadine-Ambroxol

It will be described the Ratio of the means for the parameters used to test for the Bioequivalence of the products ($Tablet_{test}$ / $Tablet_{Reference}$) and the Confidence Intervals calculated from the ANOVA analysis

For loratadine, the Area under the plasma-concentration curve from time zero to 48 hrs (AUC_0-48 ng*Hr/ml), Area under the plasma-concentration curve from time 0 to infinity (AUC_inf ng*Hr/ml) will be calculated and adjusted by dose using the linear trapezoidal rule then the log trapezoidal rule. All the pharmacokinetic parameters will be calculated according to the model 200 of the WinNonlin Library and the analysis will be identical to previously describe.

Statistical Analysis

Pharmacokinetic data will be statistically analyzed using an Analysis of Variance (ANOVA) model extracting the effects due to Sequence, Subject, Period, Formulation, that is:

Seq +Subject(Seq) + Period + Form

The Subject (Seq) term is equivalent in this model to the nested effect Subject within Seq.

The sequence effect will be tested using the Subject (Seq) mean square from the ANOVA as an error term. All other main effects will be tested against the residual error (error mean square) from the ANOVA.

The two one-sided hypotheses at the α=0.05 level of significance will be tested for, Tmax, Cmax, and AUC_0-inf by constructing the 90% confidence interval for the ratio between the test (Loratadine-Ambroxol tablets) and reference (Loratadine tablets and Ambroxol tablets) averages.

The Analysis will be carried out according to the FDA Guidance ("Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design, July 1992) for each of the actives relations and considering the four periods.

Rationale of the Study

Treatment according to the claimed methods is expected to be effective than treatment with either a non-sedating antihistamine or an expectorant alone, and to have a more rapid onset of action than that derived from the non-sedating antihistamine content.

All references cited herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated herein by reference.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

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What is claimed is:

(1) The use of a non-sedating antihistamine in combination with an an expectorant for the preparation of a medicament for the treatment and/or prevention of allergic and inflammatory conditions with cough in humans in need of such treatment and/or prevention which comprises an effective amount of a non-sedating antihistamine in combination with an effective amount of an expectorant.

(2) A pharmaceutical composition for treating and/or preventing allergic and inflammatory conditions with cough in humans comprising an effective amount of a non-sedating antihistamine in combination with an expectorant and a pharmaceutically acceptable carrier.

(3) The use of claim 1 or the pharmaceutical composition of claim 2 wherein the non-sedating antihistamine is loratadine.

(4) The use or the pharmaceutical composition of claim 3 wherein the human is 12 years of age or older and amount of loratadine is 5.0 mg/day to 15 mg/day, preferably 10 mg/day, in single or divided doses.

(5) The use or the pharmaceutical composition of claim 3 wherein the human is 12 years of age or older and the amount of loratadine is about 5 mg/ twice a day.

(6) The use of claim 1 or the pharmaceutical composition of claim 2 wherein the expectorant is ambroxol.

(7) The use or the pharmaceutical composition of claim 6 wherein wherein the human is 12 years of age or older and the amount of

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ambroxol is 30 mg/day to 180 mg/day, preferably 60 mg/day or 30 mg/day to 90 mg/day in single or divided doses.

(8) The use or the pharmaceutical composition of claim 6 wherein wherein the human is 12 years of age or older and the amount of ambroxol is about 30 mg twice a day.

(9) The use of claim 1 or the pharmaceutical composition of claim 2, wherein

a) the non-sedating antihistamine is loratadine; and

b) the expectorant is ambroxol.

(10) The use of claim 1 or the pharmaceutical composition of claim 2 wherein the allergic or inflammatory condition is allergic rhinitis associated with cough, bronchial asthma, bronchitis, bronchiectasis, sinusitis, otitis media, pneumonia, bronchopneumonia, atelectasis by mucous obstruction, or bronchoconstriction.

(11) The use of claim 1 or the pharmaceutical composition of claim 2 wherein the human is 6 to less than 12 years of age and the amount of loratadine is 0.1 mg/kg to 0.3 mg/kg per day, preferably 0.2 mg/kg to 0.3 mg/kg per day, in single or divided doses.

(12) The use of claim 1 or the pharmaceutical composition of claim 2 wherein the human is 6 to less than 12 years of age and the amount of loratadine is 0.1 mg/kg twice a day.

(13) The use of claim 1 or the pharmaceutical composition of claim 2 the human is 6 to less than 12 years of age and wherein the amount of ambroxol is 0.5 mg/kg to 2.0 mg/kg per day, preferably 1.0 mg/kg per day to 2.0 mg/kg per day, in single or divided doses.

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[14] The use of claim 1 or the pharmaceutical composition of claim 2 the human is 6 to less than 12 years of age and wherein the amount of ambroxol is 0.7 mg/kg twice a day.

(15) The use of claim 1 or the pharmaceutical composition of claim 2 the human is 6 to less than 12 years of age and wherein one oral dose of a solution of a loratadine 1.0 mg/ml-ambroxol 6.0 mg/ml combination is administered every 12 hours for 14 days.