Description

Background of the Invention

The present invention relates generally to novel pharmaceutical compositions of matter comprising one or more non-steroidal anti-inflammatory drugs (NSAID) in combination with a non-sedating antihistamine and optionally one or more other active components selected from a sympathomimetic drug (nasal decongestant, bronchodilator) cough suppressant and/or expectorant, optionally in combination with suitable pharmaceutically acceptable non-toxic carriers or excipient, and to methods of using said compositions in the treatment, management or mitigation of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, headache, fever and general malaise associated therewith.

Applicants' earlier application, now U.S. Patent No. 4,619,934 was directed to one or more NSAID's in combination with a conventional antihistamine and other optional components. Applicants have now discovered that the non-sedating antihistamines, which are pharmacologically and chemically distinct from the conventional antihistamines, in combination with one or more NSAID's offers significant advantages in the treatment, management or mitigation of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith. It is well known that the conventional antihistamines may cause drowsiness or marked drowsiness. While this may be an advantage at bedtime, if taken during the day, the label recommends that a patient use caution when driving a motor vehicle or operating machinery. The combination of a non-sedating antihistamine and an NSAID is therefore particularly advantageous for daytime administration.

Non-narcotic analgesics, most of which are also known as non-steroidal anti-inflammatory drugs, are widely administered orally in the treatment of mild to severe pain. Within this class, the compounds vary widely in their chemical structure and in their biological profiles as analgesics, anti-inflammatory agents and antipyretic agents. Among the most commonly used members of the non-narcotic analgesic class of drugs are aspirin and acetaminophen. Aspirin, acetaminophen and salicylamide are among the drugs that have heretofore been included as the pain reliever and fever-reducing component in conventional cough/cold multisymptom alleviating compositions.

However, a number of alternative non-narcotic agents offering a variety of advantages over these conventionally employed non-narcotic analgesic antipyretics have now been developed. The principal advantages of these non-steroidal anti-inflammatory drugs include not only the clinically superior analgesic, anti-inflammatory and antipyretic activity of these agents compared to aspirin and acetaminophen, but also a minimization of the adverse side effects experienced with these conventional agents; more specifically, the gastro-intestinal ulcerations experienced with aspirin and the hepatic toxicity prevalent with the chronic use of acetaminophen.

Exemplary prior art cough/cold formulations containing aspirin or acetaminophen include Coricidin®, Coricidin D®, Comtrex®, Dristan®, Daycare®, Cotylenol®, Sinubid® and the like. These formulations generally contain in addition to aspirin, acetaminophen or salicylamide, one or more conventional antihistaminics, decongestants, cough suppressants, antitussives and expectorants.

While aspirin and acetaminophen have been utilized in these previous compositions, it has not been heretofore proposed to use any of the newer non-steroidal anti-inflammatory drugs (i.e., excluding aspirin, acetaminophen and phenacetin) in the preparation of advantageous cough/cold pharmaceutical compositions.

Summary of the Invention

It is, therefore, a primary object of the present invention to provide pharmaceutical compositions of matter comprising an analgesically effective amount of a non-steroidal anti-inflammatory drug in combination with a non-sedating antihistamine, and optionally one or more active components selected from a decongestant, cough suppressant, expectorant and, further optionally including pharmaceutically acceptable carriers therefor.

It is a further object of the present invention to provide methods for the symptomatic relief of cough, cold, cold-like and flu symptoms and the discomfort, pain, headache, fever and general malaise associated therewith, by the administration of preselected dosages of the pharmaceutical compositions of the present invention. Cold-like symptoms as used herein refers to coryza, nasal congestion, upper respiratory infections, allergic rhinitis, otitis, sinusitis, etc.

An additional object of the present invention is to provide methods for the treatment of an allergic reaction in a mammalian organism in need of such treatment by administering to such organism an allergic

symptom relieving effective amount of a certain non-steroidal anti-inflammatory agent in combination with at least one of the non-sedating antihistamines or pharmaceutically acceptable salt thereof. Typical allergy symptoms involve coryza, rhinitis, and the like.

Another object of the present invention is to provide suitable dosage unit forms of one or more NSAID's in combination with a non-sedating antihistamine and optionally one or more active components selected from a decongestant, cough suppressant or expectorant adapted for convenient oral administration.

Description of the Preferred Embodiments of the Invention

More specifically, the Applicants herein have found that certain non-steroidal anti-inflammatory agents are ideally suited for use in cough/cold formulations by reason of their enhanced analgesic anti-inflammatory and antipyretic activity and low incidence of untoward side effects, particularly at the optimum dosages provided for in the present invention, compared to aspirin or acetaminophen.

For example, the antipyretic effectiveness of ibuprofen in comparison to aspirin and to acetaminophen has been studied. Gaitonde, B.B. et al, "Antipyretic Activity of Ibuprofen (Brufen)", J. ASS. Physicians, India (1973) 21:579-584 describes the results of two randomized, double-blind, parallel studies comparing the antipyretic efficacy of ibuprofen to that of aspirin. In the first study, 17 adult patients with fever of 100°F or more (orally) due to upper respiratory tract infections were given a capsule containing either ibuprofen 200 mg (7 patients) or aspirin 300 mg (10 patients). In the second study, 11 adult patients with resistant, chronic gonococcal urethritis were inoculated with T.A.B. vaccine (containing S. typhosa and paratyphi A + B microorganisms). Once peak temperature was reached as indicated by cessation of rigors, each patient received either ibuprofen 400 mg (5 patients) or aspirin 600 mg (6 patients).

In the patients with upper respiratory tract infections antipyretic effect from both treatments began approximately one hour after dosing. The temperature curves following both treatments were very similar, with the maximum decrease in temperature being reached 3 1/2 hours following aspirin 300 mg and 4 1/2 hours following ibuprofen 200 mg. In the second study, where the fever was induced by the vaccine, the temperature response curves were again very similar with the mean maximum fall in temperature occurring at about three hours with both treatments. The temperature did not rise, however, at five and six hours in the ibuprofen 400 mg treated patients. In the group treated with aspirin 600 mg there was a rise in temperature at five hours and a further rise at six hours although at the six hours observation time there were measurements on only three of the six aspirin patients.

Sheth, U.K. et al, "Measurement of Antipyretic Activity of Ibuprofen and Paracetamol in Children", J. Clin. Pharmacol., 20:672-675 (1980) reported on a randomized, open label study in which the antipyretic activity of ibuprofen was compared to that of acetaminophen in 22 children aged two to eight years suffering from fever due to upper respiratory tract infection and other causes. Both ibuprofen and acetaminophen at the doses used produced a significant fall in the initial temperature, continuing to 12 hours. The rate of fall and maximum effect of the two drugs were similar. Ibuprofen, however, was more effective than acetaminophen at these doses at six and eight hours after drug administration, indicating a longer duration of effect on ibuprofen.

The superiority of the analgesic properties of various of the non-narcotic analgesics belonging to the non-steroidal anti-inflammatory drug class in comparative studies with placebo, aspirin and acetaminophen in patients with various types of pain including headache, aches and pains associated with colds, dental pain, postpartum pain, musculoskeletal pain, menstrual cramping, and so forth, is well documented in the literature.

A report by Busson, M., "A Double Blind Multicentre Comparison of Ibuprofen and Placebo in Colds and Non-specific Headaches", The Boots Company, Ltd. Research Report (1982) presents the results of a double-blind randomized crossover study of the analgesic efficacy of ibuprofen 200 mg or ibuprofen 400 mg compared to placebo in 332 patients with self-diagnosed headaches (161 patients) and colds (171 patients). In addition to a composite analysis of the entire population, subgroup analyses were performed on those patients whose primary complaint was headache and on those patients complaining of colds. The data show that ibuprofen at both doses produced statistically significant improvement both in headache and in aches and pains associated with colds compared with placebo, in all composite and subgroup comparisons except the 200 mg ibuprofen vs. placebo in cold patients in the parallel groups (first treatment only) comparison. Patient preference in the composite, headache, and cold groups was also significantly in favor of both ibuprofen treatments as compared to placebo.

Cooper in 1977 found that for pain relief ibuprofen 400 mg had a greater peak effect and longer duration of action than aspirin 650 mg. Cooper, S.A., Needle, A.E., Kruger, G.O. (1977), "An Analgesic Relative Potency Assay Comparing Aspirin, Ibuprofen and Placebo.", J. Oral Surg., 35:898-903. Cooper in

another study in 1982 found 400 mg of ibuprofen to be more effective than aspirin 650 mg. Cooper, S.A., Engel, J., Ladov, M., Precheur, H., Rosenheck, A., Rauch, D. (1982), "Analgesic Efficacy of an Ibuprofen-codeine Combination.", Pharmacotherapy, 2:162-67. Sunshine et al found ibuprofen to be significantly superior to aspirin in the relief of post-episiotomy pain. Sunshine, A. et al, Clinical Pharmacology and Therapeutics, 24:254-250 (1983).

Dionne in 1982 found ibuprofen to be more effective than acetaminophen in delaying the onset and intensity of post-operative dental pain. Dionne, R.A., Campbell, R.A., Cooper, S.A., Hall, D.L., Buckingham, B., "Suppression of Post operative Pain by Preoperative Administration of Ibuprofen in Comparison to Placebo, Acetaminophen and Acetaminophen Plus Codeine.", J. Clin. Phamacol. (In press).

Naproxen sodium 550 mg was compared with 650 mg of aspirin and was found to provide earlier and better pain relief than aspirin by Sevelius, H., J. Clin. Pharmacol., 20:480-485 (1980), "Comparative Analgesic Effects of Naproxen Sodium, Aspirin and Placebo."

Flurbiprofen 50 and 100 mg was significantly more effective than aspirin 600 mg. Flurbiprofen 25 mg was slightly less effective than aspirin 600 mg. Sunshine, A., Olson N.Z., Laska, E.M., Zighelboim, I., DeCastro, A., Desarrazin, C., Pharmaco Ther., 3:177-181, "Analgesic Effect of Graded Doses of Flurbiprofen in Postepisiotomy Pain."

More recently, ibuprofen 200 mg has become available over-the-counter (OTC) and at 200 to 400 mg is indicated for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever. While these reported findings with respect to the outstanding analgesic properties of the non-steroidal anti-inflammatory drugs compared to aspirin or acetaminophen have prompted the widespread acceptance and usage of these newer non-narcotic analgesics, as single entities, for the treatment and management of acute and chronic pain as well as inflammatory states, notably rheumatoid arthritis and osteoarthritis, the utilization of these agents in cough/cold compositions for multi-symptom relief has not heretofore been considered, this despite the fact that ibuprofen's and other NSAID's antipyretic and analgesic properties have been well known for more than a decade.

The non-steroidal anti-inflammatory drugs for use in the pharmaceutical compositions and methods-of-use of the present invention may be selected from any of the following categories:

(1) The propionic acid derivatives;
(2) The acetic acid derivatives;
(3) The fenamic acid derivatives;
(4) The biphenylcarboxylic acid derivatives; and
(5) The oxicams.

Accordingly, the term "NSAID" as used herein is intended to mean any non-narcotic analgesic non-steroidal anti-inflammatory compound, including the pharmaceutically acceptable non-toxic salts thereof, falling within one of the five structural categories above but excluding aspirin, acetaminophen and phenacetin.

While some of these compounds are primarily used at the present time as anti-inflammatory agents and others are primarily used as analgesics, in fact all of the contemplated compounds have both analgesic and anti-inflammatory activity and can be used at appropriate dosage levels for either purpose in the compositions and methods of the present invention. The compounds in groups (1) through (4) typically contain a carboxylic acid function; however, those acids are sometimes administered in the form of their pharmaceutically acceptable acid addition or alkali metal salts, e.g., sodium salts.

The specific compounds falling within the foregoing definition of the non-steroidal anti-inflammatory drugs for use in the present invention are well known to those skilled in the art and reference may be had to various literature reference sources for their chemical structures, pharmacological activities, side effects, normal dosage ranges, etc. See, for example, Physician's Desk Reference, 35th Edition (1981); The Merck Index, 9th Edition, Merck and Company, Rahway, New Jersey (1976); and Cutting's Handbook of Pharmacology, 6th Edition, Ed. T.Z. Czacky, M.D., Appleton-Century-Crofts, New York (1979), Chapter 49:538-550.

The propionic acid derivatives for use herein include, but are not limited to, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Presently preferred members of the propionic acid group include ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen, and fenbufen.

Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH(CH_3)COOH$ or $-CH_2CH_2COOH$ group (which optionally can be in the

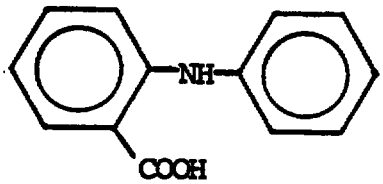
form of a pharmaceutically acceptable salt group, e.g., -CH(CH_3)COO-Na^+ or -CH_2CH_2COO-Na+), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

The acetic acid derivatives for use herein include, but are not limited to, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac and oxpinac. Structurally related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Presently preferred members of the acetic acid group include tolmetin sodium, sulindac and indomethacin.

Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free -CH_2COOH group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g., -$CH_2COO\text{-}Na^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

The fenamic acid derivatives for use herein include, but are not limited to, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Presently preferred members of the fenamic acid group include mefenamic acid and meclofenamate sodium (meclofenamic acid, sodium salt).

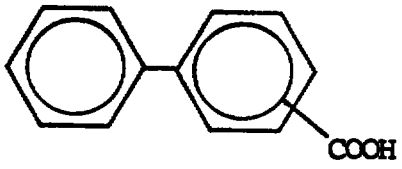
Thus, "fenamic acid derivative" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g, -COO-Na^+.

The biphenylcarboxylic acid derivatives for use herein include, but are not limited to, diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Preferred members of this group are diflunisal and flufenisal.

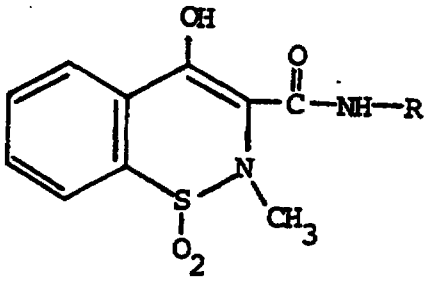
Thus, "biphenylcarboxylic acid derivative" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., -COO-Na+.

The oxicams for use herein include, but are not limited to piroxicam, sudoxicam, isoxicam and CP-14,304. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. A preferred member of this group is piroxicam.

Thus, "oxicams" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula



where R is an aryl or heteroaryl ring system.

Of course, it will be appreciated by those skilled in the art, that any of the foregoing compounds may be utilized in the form of their pharmaceutically acceptable salt forms, e.g., -COO-Na+, -COO-K+, and the like.

Of the foregoing non-steroidal anti-inflammatory drugs, in the practice of the preferred embodiments of the present invention, ibuprofen and naproxen are most preferred.

With respect to the dosage amount of the non-steroidal anti-inflammatory drugs in the compositions of the invention, although the specific dose will vary depending upon the age and weight of the patient, the severity of the symptoms, the incidence of side effects and the like, for humans, typical effective analgesic amounts of presently preferred NSAID's for use in unit dose compositions of the invention are about 100 - 500 mg diflunisal, about 50 - 600 mg ibuprofen, most preferably 100 - 400 mg, about 125 - 500 mg naproxen, about 25 - 100 mg flurbiprofen, about 50 - 100 mg fenoprofen, about 10 - 20 mg piroxicam, about 125 - 250 mg mefenamic acid, about 100 - 400 mg fenbufen or about 25 - 50 mg ketoprofen; however, greater or lesser amounts may be employed if desired or necessary. With respect to the compounds set forth hereinabove falling within the propionic acid derivative category, suitable dosage ranges for these compounds will generally fall within the range of 25 mg to 600 mg in each unit dose.

In any event, the amounts of NSAID and non-steroidal anti-inflammatory agent to be administered in a total daily dose should not exceed the generally recognized as safe limits established for the particular NSAID and non-steroidal anti-inflammatory agent when administered alone for their respective usual therapeutic indications.

The non-sedating antihistamines are pharmacologically and chemically distinct from the conventional antihistamines. The non-sedating antihistamines represent a new generation of drugs which specifically block H_1-histamine receptors and do not cause sedation. The sedative properties of conventional antihistamines are well known and for daytime use especially represent a significant disadvantage during treatment. The FDA's Tentative Final Monograph has proposed that the labeling for category I OTC antihistamines, in general, carry the warning, "May cause drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution while driving a motor vehicle or operating machinery." The non-sedating antihistamines are only peripherally active, that is, they do not penetrate the blood-brain barrier in significant amounts to cause drowsiness. Thus, unlike the conventional antihistamines, the labeling for the non-sedating antihistamines do not carry warnings to patients to refrain from driving a car or operating machinery during therapy or concomitantly using alcohol or other central nervous system depressants as they do for conventional antihistamines. Nor are the non-sedating antihistamines contraindicated in patients who are suffering from glaucoma, bronchial asthma, or prostatic hypertrophy.

In vivo studies have shown that the non-sedating antihistamines preferentially bind to peripheral rather than central H_1-histamine receptors. Since conventional antihistamines which produce sedation have greater affinities for central H_1-histamine receptors, the lesser penetration of the non-sedating antihistamines into the central nervous system may be responsible for their apparent lack of central nervous system effects. In addition, as a general rule, the non-sedating antihistamines possess minimal or no antiserotoninergic, anticholinergic or antiadrenergic activity. Psychomotor and visual function tests in man have shown that the non-sedating antihistamines do not impair psychomotor performance or adversely affect subjective feelings, in contrast to conventional antihistamines which were active in these tests. The non-sedating antihistamines neither affect the EEG as sedative antihistamines are known to do, nor interact with other depressant drugs (such as alcohol or benzodiazepines) to produce enhanced depressant effects.

The lack of sedative effects from the non-sedating antihistamines may be especially useful in children, where prescribing of conventional antihistamines is often hindered because of the daytime sedation they

produce.

The non-sedating antihistamines include but are not limited to AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine and terfenadine. Representative chemical structures for many of the non-sedating antihistamines are presented in Table I.

TABLE I

Non-Sedating Antihistamines

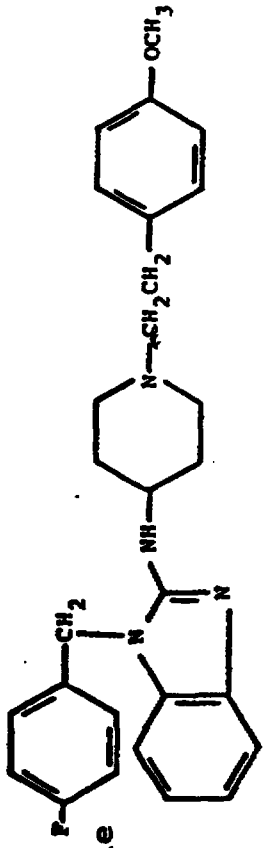
Common Name or Generic Name	Chemical Structure	Chemical Name
astemizole		4-(2-(4-((1-((4-fluorophenyl)methyl)-1H-benzimidazol-2-yl)amino)-1-piperidinyl)ethyl)-phenol

TABLE I (continued)

Non-Sedating Antihistamines

Common Name or Generic Name	Chemical Structure	Chemical Name
ketotifen		4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo(4,5)cyclohepta(1,2-b)-thiophen-10-one [(E)-2-butenedioate (1:1)]

TABLE I (continued)

Non-Sedating Antihistamines

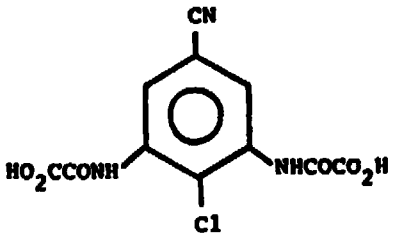
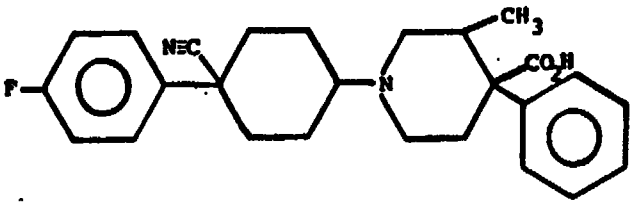
Common Name or Generic Name	Chemical Structure	Chemical Name
lodoxamide		2,2'-((2-chloro-5-cyano-1,3-phenylene)diimino)bis(2-oxo-acetic acid) compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:2)
levocabastine		1-(4-cyano-4-(4-fluorophenyl)cyclohexyl)-3-methyl-4-phenyl-4-piperidinecarboxylic acid

TABLE I (continued)

Non-Sedating Antihistamines

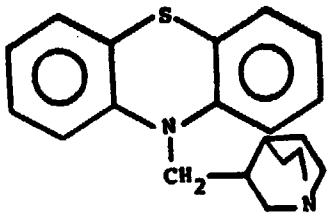
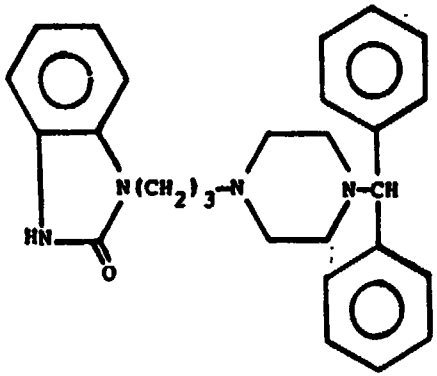
Common Name or Generic Name	Chemical Structure	Chemical Name
mequitazine		10-(1-azabicyclo(2.2.2)oct-3-yl-methyl)-10H-phenothiazine
oxatomide		1-(3-(4-(diphenylmethyl)-1-piperazinyl)propyl)-1,3-dihydro-2H-benzimidazol-2-one

TABLE I (continued)

Non-Sedating Antihistamines

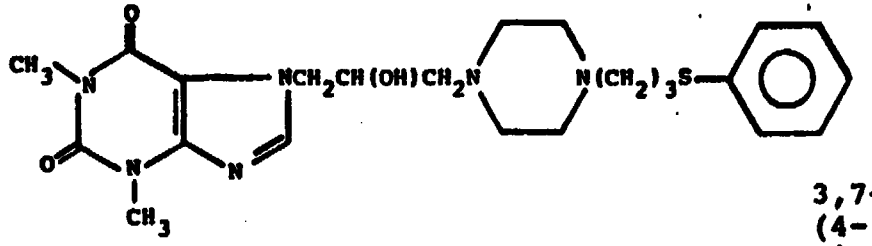
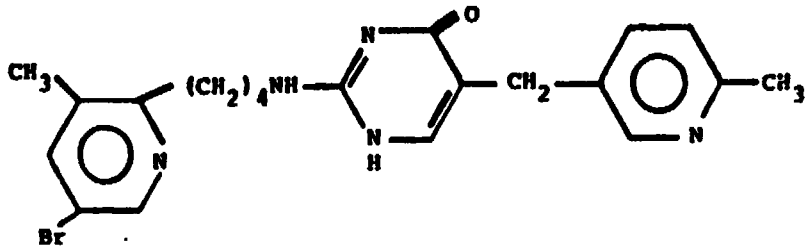
Common Name or Generic Name	Chemical Structure	Chemical Name
tazifylline		3,7-dihydro-7-(2-hydroxy-3-(4-(3-(phenylthio)propyl)-1-piperazinyl)propyl)-1,3-dimethyl-1H-purine-2,6-dione
temelastine		2-((4-(5-bromo-3-methyl-2-pyridinyl)butyl)amino)-5-((6-methyl-3-pyridinyl)methyl)-4(1H)-pyrimidinone

TABLE I (continued)

Non-Sedating Antihistamines

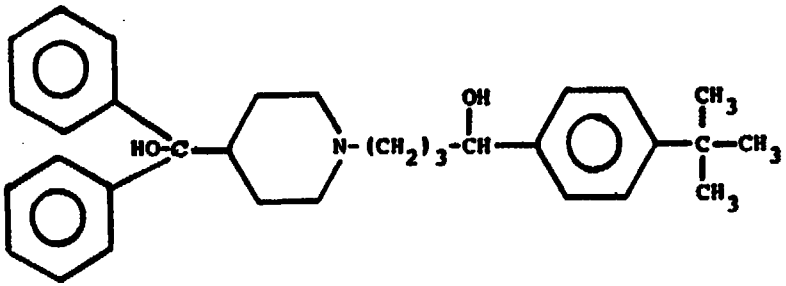
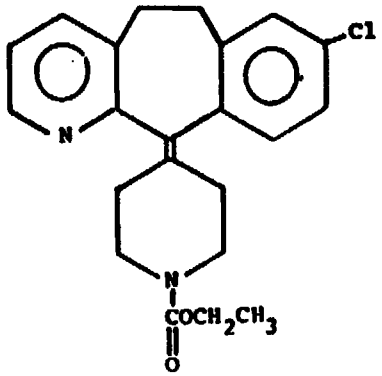
Common Name or Generic Name	Chemical Structure	Chemical Name
terfenadine		alpha-(4-(1,1-dimethylethyl)phenyl)-4-(hydroxydiphenylmethyl)-1-piperidinebutanol
loratidine		(8-chloro(6,11-dihydro-11-(1-carboethoxy-4-piperidylidene)-5-H-benzo(5,6]cyclohepta(1,2-b]-pyridine)

TABLE I (continued)

Non-Sedating Antihistamines

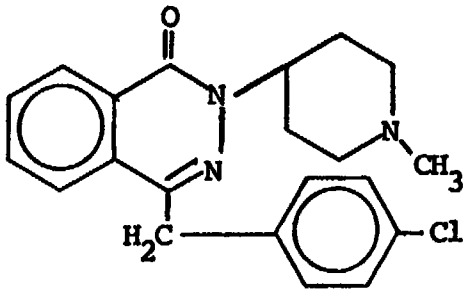
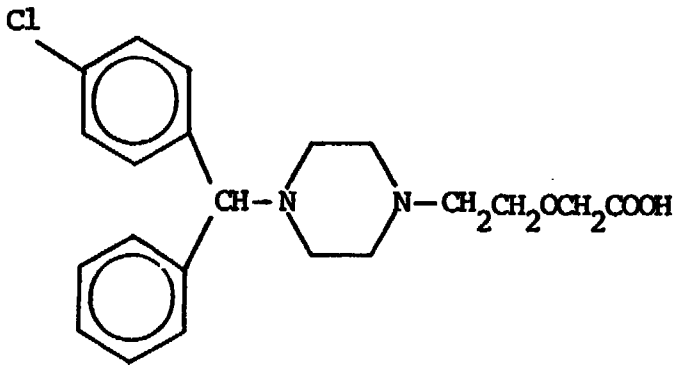
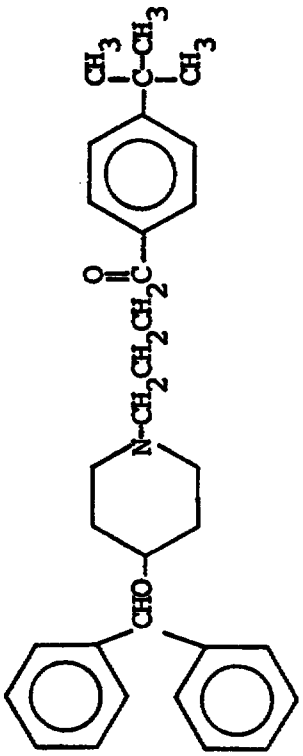
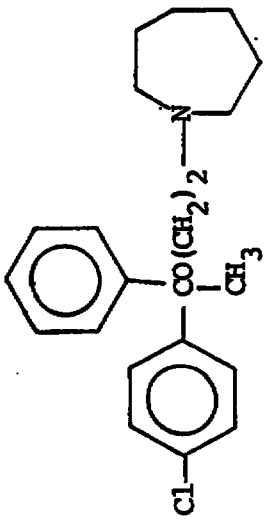
Common Name or Generic Name	Chemical Structure	Chemical Name
azelastine		4-6-chlorobenzyl)-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone
cetirizine		(I)-[2-[4-(p-chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy]-acetic acid

TABLE I (continued)

Non-Sedating Antihistamines

Common Name or Generic Name	Chemical Structure	Chemical Name
ebastine		4'-tert-butyl-4-[4-(diphenyl-methoxy)piperidino]butyrophenone
setastine		1-[2-[(p-chloro-α-methyl-α-phenylbenzyl)oxy]ethyl]hexahydro-1H-azepine

The preferred non-sedating antihistamines for use in the practice of the present invention are astemizole and terfenadine. Terfenadine is marketed in the United States as Seldane, a registered trademark of Merrill Dow Pharmaceuticals.

The amount of the non-sedating antihistamine useful in the practice of the present invention generally ranges from about 1 mg to about 1000 mg depending on the specific non-sedating antihistamine selected;

however, greater or lesser amounts may be employed if desired or necessary.

The recommended dosage of terfenadine, for instance, is 60 mg orally (1 tablet or 10 ml of suspension) once or twice daily. In children aged 6 to 12 years, the dosage is 30 mg (5 ml of suspension) to 60 mg twice daily depending on body weight. In children aged 3 to 5 years, the dosage is 15 mg twice daily. Some studies suggest doses ranging from 20 mg thrice daily to 200 mg thrice daily. Terfenadine has also been demonstrated to be of value in exercise-induced asthma when given orally in a single dose of 120 mg or 180 mg.

The usual dose of astemizole is 10 mg to 25 mg once daily. Astemizole has a half-life of several days and thus it may be given as a single tablet daily, which is an important advantage in obtaining greater patient compliance; therefore, it can advantageously be added to one of the longer acting NSAID's. The recommended dose of mequitazine is 5 mg twice daily. Temelastine is being evaluated in humans at a dose of 100 mg once or twice daily.

The cough/cold pharmaceutical compositions of the present invention comprise, in addition to the non-steroidal anti-inflammatory drugs, at least one non-sedating antihistamine as an active ingredient and optionally one or more active ingredients from the following pharmacological classes: sympathomimetics (decongestants), cough suppressants-antitussives and expectorants. Typical therapeutically active components from these categories, along with their usual adult dosage, for use in the pharmaceutical compositions and methods of the invention are set forth in the following Table II. Of course, sustained release formulations would contain higher doses than those set forth in Table II.

These non-sedating antihistamines could enhance the analgesic properties of the NSAID's, such as ibuprofen and naproxen, as has been observed for conventional antihistamines. Notably, diphenhydramine, a conventional antihistamine, in combination with a non-steroidal anti-inflammatory drug, ibuprofen, has already been demonstrated by Applicants to produce a synergistically enhanced analgesic response in a mammalian organism. As noted earlier, the non-sedating antihistamines could also be useful for the treatment of an allergic reaction.

TABLE II

DRUG (FORM-SALT)	ACTION	PREPARATIONS	USUAL SINGLE DOSE (ADULT)
pseudoephedrine (sulfate, HCl)	D	Tablet, Capsule, 30 mg, 60 mg, 120 mg (sustained action)	30-120 mg
phenylpropanolamine	D	Tablet, Capsule, Elixir, 25 mg, 50 mg, 12.5 mg/5cc	5-50 mg
phenylephrine (bitartrate, tannate, HBr, HCl	D	Tablet, Capsule, Elixir, 5 mg, 10 mg, 25 mg, 5 mg/5cc	5-25 mg
caramiphen (edisylate)	CS	Capsule, Elixir, 20 mg, 5 mg/5cc	5-20 mg
dextromethorphan (HBr)	CS	Tablet, Capsule, Elixir, 15 mg, 30 mg, 15 mg/5cc	2.5-30 mg
codeine (phosphate, sulfate)	CS	Tablet, Elixir, 10 mg, 10 mg/5cc	10-20 mg
benzonatate	CS	Capsule, 100 mg	100 mg
chlophedianol (HCl)	CS	Elixir, 25 mg/5cc	25 mg
terpin hydrate	E	Tablet, Elixir, 300 mg	85-300 mg
quaifenesin (glyceryl, guaiacolate)	E	Tablet, Capsule, Elixir, 100 mg, 100 mg/5cc	25-200 mg
potassium (Iodide, citrate)	E	Tablet, Elixir, 100 mg, 100 mg/5cc	150-300 mg
potassium guaicolsulfonate	E	Elixir, 80 mg/5cc	45-300 mg
D = decongestant CS = cough suppressant E = expectorant			

In the pharmaceutical compositions and methods of the present invention, the foregoing active ingredients will typically be administered in admixture with suitable pharmaceutical diluents, excipients or

carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, i.e., oral tablets, capsules, elixirs, syrups, suspensions, etc. and consistent with conventional pharmaceutical practices. For instance, for oral administration in the form of tablets or capsules, the active drug components may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can 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 there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, etc. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, etc. Sweetening and flavoring agents and preservatives can also be included where appropriate.

Of course, 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 to optimize the therapeutic effects, i.e., analgesia, antihistaminic, etc. while minimizing undesirable side 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.

As representative suitable formulations consistent with the objects, features and advantages of the present invention, the following non-limiting examples are provided.

EXAMPLE 1

Ibuprofen	200 mg
Dextromethorphan hydrobromide	30 mg
Guaifenesin	100 mg
Terfenadine	60 mg
Triturate active ingredients and q.s. with lactose to selected capsule size.	

EXAMPLE 2

In each fluid ounce:

Naproxen (sodium)	250 mg
Dextromethorphan hydrobromide	30 mg
Astemizole	10 mg
Orange flavoring and alcohol 10% v/v.	

EXAMPLE 3

Ibuprofen	200 mg
Terfenadine	60 mg
Triturate active ingredients and q.s. with lactose to selected capsule size.	

From the foregoing, other typical acceptable pharmaceutical formulations will be apparent to those skilled in the art of pharmaceutical formulations.

While this invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit of the invention. For example, effective dosages other than

the preferred ranges set forth hereinabove with respect to the active ingredients may be applicable as a consequence of variations of the responsiveness of the mammal treated, severity of symptoms, dosage related adverse effects, if any, observed and similar considerations. Accordingly, such expected variations or differences in the practice of the present invention and the results obtained are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow.

Claims

1. A pharmaceutical composition of matter for use in the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith, in a mammalian organism, and adapted for unit dosage oral administration, said composition comprising (i) an analgesically and anti-inflammatory effective amount of at least one non-steroidal anti-inflammatory drug comprising a propionic acid derivative, an acetic acid derivative, a fenamic acid derivative, a biphenylcarboxylic acid derivative, an oxicam or pharmaceutically acceptable salt thereof, in combinatory immixture with (ii) an antihistaminically effective amount of at least one of the non-sedating antihistamines.

2. A pharmaceutical composition according to claim 1, said non-sedating antihistamine comprising AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, terfenadine or pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition according to claim 1 or 2, said non-steroidal anti-inflammatory drug comprising a propionic acid derivative.

4. A pharmaceutical composition according to claim 3, said propionic acid derivative comprising ibuprofen, naproxen, benoxaprofen, flurbibrofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, alminoprofen, tiaprofenic acid, fluprofen, bucloxic acid or pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition according to any one of the preceding claims, comprising at least 25 mg of said non-steroidal anti-inflammatory drug.

6. A pharmaceutical composition according to claim 5, comprising from 25 mg to 600 mg of said non-steroidal anti-inflammatory drug.

7. A pharmaceutical composition according to claim 4, comprising from 50 mg to 600 mg of ibuprofen or pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition according to claim 4, comprising from 125 mg to 500 mg of naproxen or pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition according to claim 1 or 2, said non-steroidal anti-inflammatory drug comprising an acetic acid derivative.

10. A pharmaceutical composition according to claim 9, said acetic acid derivative comprising indomethacin, silindac, tolmetin, diclofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac or pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition according to claim 1 or 2, said non-steroidal anti-inflammatory drug comprising a fenamic acid derivative.

12. A pharmaceutical composition according to claim 11, said fenamic acid derivative comprising mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid or pharmaceutically acceptable salt thereof.

the preferred ranges set forth hereinabove with respect to the active ingredients may be applicable as a consequence of variations of the responsiveness of the mammal treated, severity of symptoms, dosage related adverse effects, if any, observed and similar considerations. Accordingly, such expected variations or differences in the practice of the present invention and the results obtained are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow.

Claims

1. A pharmaceutical composition of matter for use in the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith, in a mammalian organism, and adapted for unit dosage oral administration, said composition comprising (i) an analgesically and anti-inflammatory effective amount of at least one non-steroidal anti-inflammatory drug comprising a propionic acid derivative, an acetic acid derivative, a fenamic acid derivative, a biphenylcarboxylic acid derivative, an oxicam or pharmaceutically acceptable salt thereof, in combinatory immixture with (ii) an antihistaminically effective amount of at least one of the non-sedating antihistamines.

2. A pharmaceutical composition according to claim 1, said non-sedating antihistamine comprising AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, terfenadine or pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition according to claim 1 or 2, said non-steroidal anti-inflammatory drug comprising a propionic acid derivative.

4. A pharmaceutical composition according to claim 3, said propionic acid derivative comprising ibuprofen, naproxen, benoxaprofen, flurbibrofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, alminoprofen, tiaprofenic acid, fluprofen, bucloxic acid or pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition according to any one of the preceding claims, comprising at least 25 mg of said non-steroidal anti-inflammatory drug.

6. A pharmaceutical composition according to claim 5, comprising from 25 mg to 600 mg of said non-steroidal anti-inflammatory drug.

7. A pharmaceutical composition according to claim 4, comprising from 50 mg to 600 mg of ibuprofen or pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition according to claim 4, comprising from 125 mg to 500 mg of naproxen or pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition according to claim 1 or 2, said non-steroidal anti-inflammatory drug comprising an acetic acid derivative.

10. A pharmaceutical composition according to claim 9, said acetic acid derivative comprising indomethacin, silindac, tolmetin, diclofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac or pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition according to claim 1 or 2, said non-steroidal anti-inflammatory drug comprising a fenamic acid derivative.

12. A pharmaceutical composition according to claim 11, said fenamic acid derivative comprising mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid or pharmaceutically acceptable salt thereof.

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13. A pharmaceutical composition according to claim 1 or 2, said non-steroidal anti-inflammatory drug comprising a biphenylcarboxylic acid derivative.

14. A pharmaceutical composition according to claim 13, said biphenylcarboxylic acid derivative comprising diflunisal, flufenisal or pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition according to claim 1 or 2, said non-steroidal anti-inflammatory drug comprising an oxicam.

16. A pharmaceutical composition according to claim 15, said oxicam comprising piroxicam, sudoxicam, isoxicam or pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition according to any one of the preceding claims, comprising from 1 mg to 1000 mg of said non-sedating antihistamine.

18. A pharmaceutical composition according to any one of the preceding claims, wherein said non-sedating antihistamine is terfenadine or pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition according to any one of claims 1 to 17, wherein said non-sedating antihistamine is astemizole or pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition according to any one of the preceding claims, further comprising (iii) a pharmaceutically acceptable non toxic carrier.

21. A pharmaceutical composition of matter for use in the treatment of an allergic reaction in a mammalian organism in need of such treatment, comprising an allergic symptom relieving effective amount of (i) at least one non-steroidal anti-inflammatory drug comprising a propionic acid derivative, an acetic acid derivative, a fenamic acid derivative, a biphenylcarboxylic acid derivative, an oxicam or pharmaceutically acceptable salt thereof, in combinatory immixture with (ii) at least one of the non-sedating antihistamines.

22. A pharmaceutical composition-of-matter for use in the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith, in a mammalian organism, and adapted for unit dosage oral administration, said composition comprising (i) an analgesically and anti-inflammatory effective amount of at least one non-steroidal anti-inflammatory drug comprising a propionic acid derivative, an acetic acid derivative, a fenamic acid derivative, a biphenylcarboxylic acid derivative, an oxicam or pharmaceutically acceptable salt thereof, in combinatory immixture with (ii) an antihistaminically effective amount of at least one of the non-sedating antihistamines, AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, terfenadine or pharmaceutically acceptable salt thereof and (iii) one or more active components selected from a decongestant, cough suppressant and expectorant.

Patentansprüche

1. Pharmazeutische Stoffzusammensetzung zur Verwendung bei der Behandlung von Husten, Erkältung, erkältungsähnlichen Symptomen und/oder Grippesymptomen, und Beschwerden, Schmerz, Fieber und dem allgmeinen Unbehagen, die damit verbunden sind, bei einem Säugerorganismus, und hergerichtet für eine orale Einheitsdosisverabreichung, welche Zusammensetzung umfaßt: (i) eine analgesisch- und entzündungshemmend-wirkende Menge mindestens eines entzündungshemmenden Nicht-Steroid-Arzneimittels, umfassend ein Propionsäurederivat, ein Essigsäurederivat, ein Fenaminsäurederivat, ein Biphenylcarbonsäurederivat, ein Oxicam, oder ein pharmazeutisch akzeptables Salz davon, in Kombinationsvermischung mit (ii) einer antihistaminisch wirksamen Menge mindestens eines der nicht-sedierenden Antihistaminika.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei das nicht-sedierende Antihistaminikum AHR-11325, Astemizol, Azelastin, Cetirizin, Ebastin, Ketotifen, Lodoxamid, Loratidin, Levocabastin, Mequitazin, Oxatomid, Setastin, Tazifyllin, Temelastin, Terfenadin, oder ein pharmazeutisch akzeptables

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Salze davon umfaßt.

3. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, wobei das entzündungshemmende Nicht-Steroid-Arzneimittel ein Propionsäurederivat umfaßt.

4. Pharmazeutische Zusammensetzung nach Anspruch 3, wobei das Propionsäurederivat umfaßt: Ibuprofen, Naproxen, Benoxaprofen, Flurbiprofen, Fenoprofen, Fenbufen, Ketoprofen, Indoprofen, Pirprofen, Carprofen, Oxaprozin, Pranoprofen, Miroprofen, Tioxaprofen, Alminoprofen, Tiaprofensäure, Fluprofen, Bucloxasäure, oder ein pharmazeutisch akzeptables Salze davon.

5. Pharmazeutische Zusammensetzung nach einem der vorhergehenden Ansprüche, welche mindestens 25 mg des entzündungshemmenden Nicht-Steroid-Arzneimittels umfaßt.

6. Pharmazeutische Zusammensetzung nach Anspruch 5, welche 25 mg bis 600 mg des entzündungshemmenden Nicht-Steroid-Arzneimittels umfaßt.

7. Pharmazeutische Zusammensetzung nach Anspruch 4, welche 50 mg bis 600 mg Ibuprofen oder ein pharmazeutisch akzeptables Salz davon umfaßt.

8. Pharmazeutische Zusammensetzung nach Anspruch 4, welche 125 bis 500 mg Naproxen oder ein pharmazeutisch akzeptables Salz davon umfaßt.

9. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, wobei das entzündungshemmende Nicht-Steroid-Arzneimittel ein Essigsäurederivat umfaßt.

10. Pharmazeutische Zusammensetzung nach Anspruch 9, wobei das Essigsäurederivat umfaßt: Indomethacin, Silindac, Tolmetin, Diclofenac, Tiopinac, Zidometacin, Acemetacin, Fentiazac, Clidanac, Oxpinac, oder ein pharmazeutisch akzeptables Salz davon.

11. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, wobei das entzündungshemmende Nicht-Steroid-Arzneimittel ein Fenaminsäurederivat umfaßt.

12. Pharmazeutische Zusammensetzung nach Anspruch 11, wobei das Fenaminsäurederivat umfaßt: Mefenaminsäure, Meclofenaminsäure, Flufenaminsäure, Nifluminsäure, Tolfenaminsäure, oder ein pharmazeutisch akzeptables Salz davon.

13. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, wobei das entzündungshemmende Nicht-Steroid-Arzneimittel ein Biphenylcarbonsäurederivat umfaßt.

14. Pharmazeutische Zusammensetzung nach Anspruch 13, wobei das Biphenylcarbonsäurederivat umfaßt: Diflunisal, Flufenisal, oder ein pharmazeutisch akzeptables Salz davon.

15. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, wobei das entzündungshemmende Nicht-Steroid-Arzneimittel ein Oxicam umfaßt.

16. Pharmazeutische Zusammensetzung nach Anspruch 15, wobei das Oxicam umfaßt: Piroxicam, Sudoxicam, Isoxicam, oder ein pharmazeutisch akzeptables Salz davon.

17. Pharmazeutische Zusammensetzung nach einem der vorhergehenden Ansprüche, welche 1 mg bis 1000 mg nicht-sedierendes Antihistaminikum umfaßt.

18. Pharmazeutische Zusammensetzung nach einen, der vorhergehenden Ansprüche, wobei das nicht-sedierende Antihistaminikum Terfenadin oder ein pharmazeutisch akzeptables Salz davon umfaßt.

19. Pharmazeutische Zusammensetzung nach einem, der Ansprüche 1 bis 17, wobei das nicht-sedierende Antihistaminikum Astemizol oder ein pharmazeutisch akzeptables Salz davon ist.

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20. Pharmazeutische Zusammensetzung nach einem der vorhergehenden Ansprüche, welche ferner (iii) einen pharmazeutisch akzeptablen, nicht-toxischen Träger umfaßt.

21. Pharmazeutische Stoffzusammensetzung zur Verwendung bei der Behandlung einer allergischen Reaktion in einem Säugerorganismus, welcher eine solche Behandlung braucht, umfassend eine zur Linderung allergischer Symptome wirksame Menge von (i) mindestens einem entzündungshemmenden Nicht-Steroid-Arzneimittel, umfassend ein Propionsäurederivat, ein Essigsäurederivat, ein Fenaminsäurederivat, ein Biphenylcarbonsäurederivat, ein Oxicam oder ein pharmazeutisch akzeptables Salz davon, in Kombinationsvermischung mit (ii) mindestens einem der nicht-sedierenden Antihistaminika.

22. Pharmazeutische Stoffzusammensetzung zur Verwendung bei der Behandlung von Husten, Erkältung, erkältungsähnlichen Symptomen und/oder Grippesymptomen, und Beschwerden, Schmerz, Fieber und dem allgmeinen Unbehagen, die damit verbunden sind, bei einem Säugerorganismus, und hergerichtet für eine orale Einheitsdosisverabreichung, welche Zusammensetzung umfaßt: (i) eine analgesisch- und entzündungshemmend-wirkende Menge mindestens eines entzündungshemmenden Nicht-Steroid-Arzneimittels, umfassend ein Propionsäurederivat, ein Essigsäurederivat, ein Fenaminsäurederivat, ein Biphenylcarbonsäurederivat, ein Oxicam oder ein pharmazeutisch akzeptables Salz davon, in Kombinationsvermischung mit (ii) einer antihistaminisch wirksamen Menge mindestens eines der nicht-sedierenden Antihistaminika AHR-11325, Astemizol, Azelastin, Cetirizin, Ebastin, Ketotifen, Lodoxamid, Loratidin, Levocabastin, Mequitazin, Oxatomid, Setastin, Tazifyllin, Temelastin, Terfenadin oder einem pharmazeutisch akzeptablen Salze davon, und (iii) eine oder mehrere aktive Komponenten, gewählt aus einem Dekongestionsmittel, Hustenunterdrückungsmittel und Expektorans.

Revendications

1. Composition pharmaceutique destinée à être utilisée dans le traitement de la toux, du rhume, de symptômes analogues à ceux du rhume et/ou de symptômes grippaux et de l'inconfort, de la douleur, de la fièvre et du malaise général associés à ces symptômes, dans l'organisme d'un mammifère, et apte à l'administration orale d'une dose unitaire, ladite composition comprenant (i) une quantité à effet analgésique et anti-inflammatoire d'au moins un médicament anti-inflammatoire non stéroïdien comprenant un dérivé d'acide propionique, un dérivé d'acide acétique, un dérivé d'acide fénamique, un dérivé d'acide biphénylcarboxylique, un oxicam ou un de leurs sels pharmaceutiquement acceptables, en mélange avec (ii) une quantité à effet anti-histaminique d'au moins un des anti-histaminiques non sédatifs.

2. Composition pharmaceutique suivant la revendication 1, dans laquelle l'anti-histaminique non sédatif comprend le AHR-11325, l'astémizole, l'azélastine, la cétirizine, l'ébastine, le kétotifène, le lodoxamide, la loratidine, la lévocabastine, la méquitazine, l'oxatomide, la sétastine, la tazifylline, la témélastine, la terfénadine ou un de leurs sels pharmaceutiquement acceptables.

3. Composition pharmaceutique suivant la revendication 1 ou 2, dans laquelle le médicament anti-inflammatoire non stéroïdien comprend un dérivé d'acide propionique.

4. Composition pharmaceutique suivant la revendication 3, dans laquelle le dérivé d'acide propionique comprend l'ibuprofène, le naproxène, le bénoxaprofène, le flurbibrofène, le fénorofène, le fenbufène, le kétoprofène, l'indoprofène, le pirprofène, le carprofène, l'oxaprozine, le pranoprofène, le miroprofène, le tioxaprofène, l'alminoprofène, l'acide tiaprofénique, le fluprofène, l'acide bucloxique ou un de leurs sels pharmaceutiquement acceptables.

5. Composition pharmaceutique suivant l'une quelconque des revendications précédentes, comprenant au moins 25 mg du médicament anti-inflammatoire non stéroïdien.

6. Composition pharmaceutique suivant la revendication 5, comprenant 25 mg à 600 mg du médicament anti-inflammatoire non stéroïdien.

7. Composition pharmaceutique suivant la revendication 4, comprenant 50 mg à 600 mg d'ibuprofène ou d'un de ses sels pharmaceutiquement acceptables.

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8. Composition pharmaceutique suivant la revendication 4, comprenant 125 mg à 500 mg de naproxène ou d'un de ses sels pharmaceutiquement acceptables.

9. Composition pharmaceutique suivant la revendication 1 ou 2, dans laquelle le médicament anti-inflammatoire non stéroïdien comprend un dérivé d'acide acétique.

10. Composition pharmaceutique suivant la revendication 9, dans laquelle le dérivé d'acide acétique comprend l'indométhacine, le silindac, la tolmétine, le diclofénac, le tiopinac, la zidométacine, l'acémétacine, le fentiazac, le clidanac, l'oxpinac ou un de leurs sels pharmaceutiquement acceptables.

11. Composition pharmaceutique suivant la revendication 1 ou 2, dans laquelle le médicament anti-inflammatoire non stéroïdien comprend un dérivé d'acide fénamique.

12. Composition pharmaceutique suivant la revendication 11, dans laquelle le dérivé d'acide fénamique comprend l'acide méfénamique, l'acide méclofénamique, l'acide flufénamique, l'acide niflumique, l'acide tolfénamique ou un de leurs sels pharmaceutiquement acceptables.

13. Composition pharmaceutique suivant la revendication 1 ou 2, dans laquelle le médicament anti-inflammatoire non stéroïdien comprend un dérivé d'acide biphénylcarboxylique.

14. Composition pharmaceutique suivant la revendication 13, dans laquelle le dérivé d'acide biphénylcarboxylique comprend le diflunisal, le flufénisal ou un de leurs sels pharmaceutiquement acceptables.

15. Composition pharmaceutique suivant la revendication 1 ou 2, dans laquelle le médicament anti-inflammatoire non stéroïdien comprend un oxicam.

16. Composition pharmaceutique suivant la revendication 15, dans laquelle l'oxicam consiste en piroxicam, sudoxicam, isoxicam ou un de leurs sels pharmaceutiquement acceptables.

17. Composition pharmaceutique suivant l'une quelconque des revendications précédentes, comprenant 1 mg à 1000 mg de l'anti-histaminique non sédatif.

18. Composition pharmaceutique suivant l'une quelconque des revendications précédentes, dans laquelle l'anti-histaminique non sédatif est la terfénadine ou un de ses sels pharmaceutiquement acceptables.

19. Composition pharmaceutique suivant l'une quelconque des revendications 1 à 17, dans laquelle l'anti-histaminique non sédatif est l'astémizole ou un de ses sels pharmaceutiquement acceptables.

20. Composition pharmaceutique suivant l'une quelconque des revendications précédentes, comprenant en outre (iii) un support non toxique pharmaceutiquement acceptable.

21. Composition pharmaceutique destinée à être utilisée dans le traitement d'une réaction allergique dans l'organisme d'un mammifère nécessitant un tel traitement, comprenant une quantité, ayant pour effet de soulager les symptômes allergiques, (i) d'au moins un médicament anti-inflammatoire non stéroïdien comprenant un dérivé d'acide propionique, un dérivé d'acide acétique, un dérivé d'acide fénamique, un dérivé d'acide biphénylcarboxylique, un oxicam ou un de leurs sels pharmaceutiquement acceptables, en mélange avec (ii) au moins un des anti-histaminiques non sédatifs.

22. Composition pharmaceutique destinée à être utilisée dans le traitement de la toux, du rhume, de symptômes analogues à ceux du rhume et/ou de symptômes grippaux et de l'inconfort, de la douleur, de la fièvre et du malaise général associés à ces symptômes, dans l'organisme d'un mammifère, et aptes à l'administration orale d'une dose unitaire, ladite composition comprenant (i) une quantité à effet analgésique et anti-inflammatoire d'au moins un médicament anti-inflammatoire non stéroïdien comprenant un dérivé d'acide propionique, un dérivé d'acide acétique, un dérivé d'acide fénamique, un dérivé d'acide biphénylcarboxylique, un oxicam ou un de leurs sels pharmaceutiquement acceptables, en mélange avec (ii) une quantité à effet anti-histaminique d'au moins un des anti-histaminiques non sédatifs consistant en AHR-11325, astémizole, azélastine, cétirizine, ébastine, kétotifène, lodoxamide, loratidine, lévocabastine, méquitazine, oxatomide, sétastine, tazifylline, témélastine, terfénadine ou leurs

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sels pharmaceutiquement acceptables, et (iii) un ou plusieurs constituants actifs choisis entre un décongestionnant, un agent anti-tussif et un expectorant.

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