COMPOSITIONS COMPRISING AZELASTINE AND METHODS OF USE THEREOF

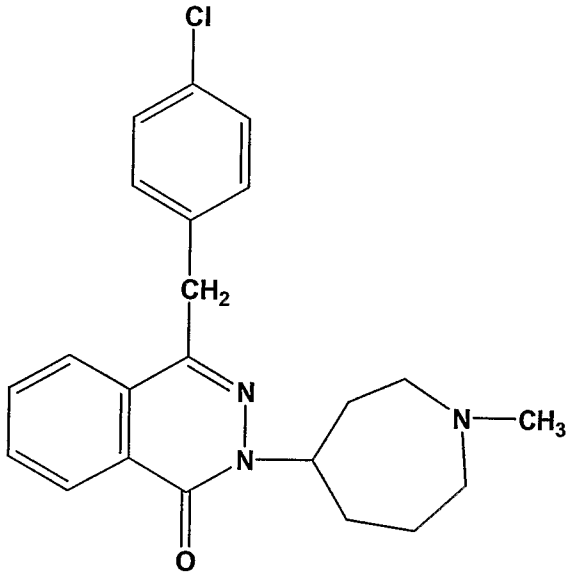
BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention is in the fields of pharmaceuticals, formulations chemistry and pharmacology. The invention generally relates to compositions comprising azelastine or pharmaceutically acceptable salts or esters thereof, including azelastine hydrochloride. In certain embodiments, the invention provides pharmaceutical compositions comprising azelastine hydrochloride formulated for use as nasal sprays and/or ocular solutions or drops, as well as dosage formulations for oral and pulmonary delivery. The invention also relates to methods of use of such compositions in treating, alleviating or preventing symptoms associated with a variety of allergic and non-allergic conditions.

Related Art

[0002] Azelastine is a second-generation H1 antagonist antihistamine which is used for its anti-allergic, anti-asthmatic and antihistamine properties. Azelastine is a phthalazinone derivative having the following structural formula:



(I)

[0003] Azelastine can be produced in a variety of salt forms. The form most frequently used in pharmaceuticals is azelastine hydrochloride, which occurs as a white, almost odorless, crystalline powder with a strong bitter taste. The chemical name for azelastine hydrochloride is (±)-1-(2H)-phthalazinone, 4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride and its molecular formula is $C_{22}H_{24}ClN_3O$•HCl. Other salt forms suitable for use in pharmaceutical compositions include azelastine embonate, which is reduced in bitterness compared to azelastine HCl (*see* U.S. Patent No. 5,232,919 the disclosure of which is incorporated herein by reference), but which may also be less effective than azelastine HCl.

[0004] Research has shown that azelastine and its physiologically acceptable salt forms exhibit beneficial effects when the corresponding formulations are applied directly onto the nasal mucosa and/or the conjunctival sac of the eye (*see* U.S. Patent No. 5,164,194). Elimination of symptoms or noticeable relief has thus been achieved in allergic rhinitis (seasonal and/or nonseasonal), vasomotor rhinitis and allergic conjunctivitis.

[0005] Despite its effectiveness, azelastine hydrochloride possesses a strong bitter taste. This bitter taste is so intense that it was found to be unpleasant

even at a dilution of $1x10^6$ (*see* U.S. Patent No. 5,164,194). The bitter taste was not thought to be a problem in intranasal delivery of azelastine hydrochloride (*see id.*). However, subsequent clinical studies have shown that the bitter taste of azelastine hydrochloride is, indeed, an undesired element as a portion of the medication usually drips down into the pharynx after intranasal administration leading to an unpleasant and undesired taste experience by the patient. For example, MedPointe Pharmaceuticals, Inc. (Somerset, NJ) has reported in the ASTELIN® product label insert that in clinical studies, the bitter taste adverse event occurred statistically more often in patients treated with ASTELIN® brand Nasal Spray (containing 0.10% w/v azelastine hydrochloride) versus vehicle placebo (19.7% vs. 0.6%). Likewise, the fluid formed by a combination of an ocularly administered medication, and induced tears secreted by the lachrymal glands, drains via the nasolachrymal duct into the nose and ultimately down the pharynx (*see* Day, N., "Ophthalmic Dosage Forms," *in: Pharmaceutical Preformulation and Formulation*, Buffalo Grove, IL: Interpharm Press (2002)). Such post-nasal drip caused by the ocular administration of compositions comprising azelastine hydrochloride therefore can also induce a bitter and unpleasant taste experience by the patient. Ukai *et al.* (US Patent No. 6,576,677) disclose the use of polyvinylpyrrolidone and/or copolyvidone to mask the taste of bitter medicaments, including azelastine.

[0006] There remains a need for a therapeutically effective dose of azelastine hydrochloride, particularly for nasal, ocular, or pulmonary delivery, which possesses a more desired taste and/or has a reduced ability to drip down into the pharynx after intranasal or ocular administration, thus improving patient acceptability and compliance.

BRIEF SUMMARY OF THE INVENTION

[0007] The present invention provides compositions, particularly stable pharmaceutical compositions, comprising azelastine and/or one or more pharmacologically acceptable salts or esters thereof, particularly azelastine hydrochloride. In certain embodiments, the pharmaceutical compositions comprise one or more pharmaceutically acceptable carriers or excipients, particularly one or more such carriers or excipients that are useful in formulating the composition into a form suitable for intranasal delivery, *e.g.*, via aerosol or spray approaches, or for ophthalmic delivery, *e.g.*, via ocular drops, or for pulmonary delivery, e.g., via a suitable device.

[0008] In certain additional embodiments, the invention provides pharmaceutical compositions comprising (or consisting essentially of) suitable concentrations of azelastine, or a pharmaceutically acceptable salt or ester thereof (such as azelastine hydrochloride (HCl)) to provide a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of the pharmaceutically acceptable carriers or excipients is a taste-masking agent that masks the bitter taste associated with azelastine or its salts or esters such that the bitter taste experienced by a patient, upon administration of the pharmaceutical composition to the patient, is reduced or eliminated, thus enhancing the organoleptic acceptance of the composition when applied to the nasal, ocular, oral or pharyngeal mucosa. In preferred such embodiments, the taste-masking agent is selected from the group consisting of sucralose, thaumatin (e.g., Talin®) sucrose, saccharin (including the salt forms: sodium, calcium, etc.), fructose, dextrose, corn syrup, aspartame, acesulfame-K, xylitol, sorbitol, erythritol, ammonium glycyrrhizinate, thaumatin, neotame, mannitol, eucalyptus oil, camphor, and natural or artificial flavors or flavoring agents (for example menthol, mints, vanilla, orange, etc.), or combinations of two or more of such agents. Particularly preferred such embodiments provide such pharmaceutical

compositions in which the taste-masking agent is sucralose, at a suitable concentration, for example, from about 0.001% to 1%, preferably from about 0.01% to about 0.5%, more preferably from about 0.02% to about 0.2%, or most preferably from about 0.05% to about 0.15%, of the total composition. Additional such embodiments may further comprise one or more additional flavoring agents, such as menthol, mints, vanilla, orange, etc. The compositions of the present invention preferably can be formulated for administration via any of a variety of routes, including but not limited to intranasal, ocular, oral, buccal, sublingual administration and the like.

[0009] In additional embodiments, the invention provides the intranasal or ocular pharmaceutical compositions described above, which may further comprise one or more agents that reduce or prevent postnasal drip of the compositions into the pharynx upon intranasal or ocular administration of the compositions. Certain such compositions may comprise, for example, one or more viscosity-increasing agents that increase the viscosity of the azelastine-containing composition. Suitable viscosity-increasing agents for use in accordance with this aspect of the invention include, but are not limited to, polyvinylpyrrolidones (PVP) (preferably having a molecular weight of about 10,000 to about 360,000, as well as mixtures containing one or more grades or molecular weight of PVP), cellulose derivatives (including, but not limited to, hydroxyethyl cellulose, carboxymethyl cellulose or its salts, hypromellose, and the like), carrageenan, guar gum, alginates, carbomers, polyethylene glycols, polyvinyl alcohol, xanthan gum, and the like. In certain preferred embodiments, hypromellose is used as a viscosity-increasing agent in the nasal or ocular formulations provided by the present invention.

[0010] Certain compositions of the invention may further comprise one or more additional components or agents, including one or more solvents, one or more preservatives, one or more stabilizers, one or more solubility-improving agents, one or more isotonicity agents, one or more buffers or buffering agents, one or more synthetic, semi-synthetic or natural bioadhesives, and the like.

[0011] The invention also provides methods of treating or preventing a variety of allergy-related and/or vasomotor-related conditions, or symptoms thereof, including allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis and the like. According to this aspect of the invention, the compositions may be administered to the patient via any suitable mode of administration, including intranasal, ocular, oral, buccal, sublingual, pulmonary or the like. Suitably, the compositions are administered directly to the nasal mucosa (*i.e.*, intranasally, *e.g.*, in the form of a nasal spray or drops) or to the conjunctival sac of the eye (*i.e.*, ocularly, *e.g.*, in the form of ocular drops).

[0012] The present invention also provides oral dosage pharmaceutical compositions comprising (or consisting essentially of) a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, at a concentration of from about 0.05% to about 5.0% by weight, or to provide about 0.5 mg to about 10 mg per dose, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of the pharmaceutically acceptable carriers or excipients is a taste masking agent, e.g., sucralose. In certain such embodiments, the amount of azelastine, or a pharmaceutically acceptable salt thereof (e.g., azelastine HCl) is in the range of about 0.05 mg to about 10 mg. Suitably the concentration of sucralose is about 0.05% to about 0.15% by weight. Exemplary forms of oral dosage compositions include, but are not limited to, liquid solutions, suspensions, tablets, capsules, chewable tablets, orally disintegrating tablets, effervescent compositions and orally dissolving/consumable films.

[0013] The present invention also provides pharmaceutical compositions comprising (or consisting essentially of) a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, at a concentration of from about 0.05% to about 5.0% by weight, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of the pharmaceutically acceptable carriers or excipients is sucralose, and wherein the pharmaceutical composition further comprises one or more additional active agents. Suitable additional active agents for use in such compositions

include, but are not limited to, antihistamines (such as cetirizine, fexofenadine, olopatadine, terfenadine and loratadine), steroids (such as fluoromethalone, fluticasone, mometasone, triamcinolone, betamethasone, flunisolide, budesonide, beclomethasone, budesonide, rimexolone, loteprednol, beloxil, prednisone, loteprednol and dexamethasone), leukotriene antagonists (such as montelukast), decongestants (such as pseudoephedrine, phenylephedrine, phenylephrine, phenylpropanolamine, oxymetazoline, propylhexedrine, xylometazoline, epinephrine, ephedrine, desoxyephedrine, naphazoline, and tetrahydrozoline), expectorants (such as guaifenesin, sodium cromoglycate, codeine phosphate, and isoproternol hydrochloride) and non-steroidal anti-inflammatory agents (such asibuprofen, diclofenac, aceclofenac, naproxen, etodolac, flurbiprofen, fenoprofen, ketoprofen, suprofen, fenbufen, fluprofen, tolmetin sodium, oxaprozin, zomepirac, sulindac indomethacin, piroxicam, mefenamic acid, nabumetone, meclofenamate sodium, diflunisal, flufenisal, piroxicam, ketorolac, sudoxicam and isoxicam). Suitably the amount of sucralose in such compositions is about 0.05% to about 0.15% by weight. The pharmaceutical compositions can also comprise combinations of azelastine and multiple additional active agents, for example, azelastine, one or more steroids and one or more decongestants; or azelastine, one or more steroids and one or more leukotriene antagonists. Such combination compositions can also further comprise sucralose and/or other additional carriers or excipients.

[0014] In another embodiment, the present invention provides sustained release pharmaceutical compositions for oral delivery comprising (or consisting essentially of) a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of the pharmaceutically acceptable carriers or excipients is sucralose, and wherein the azelastine, or the pharmaceutically acceptable salt or ester thereof, is: 1) coated with one or more sustained release components; 2) bound to a cation exchanger; 3) reacted with one or more osmotically active substances and coated with a semi-permeable membrane and a hole is bored into the

membrane; or 4) embedded in, or is bound to, one or more substances selected from of the group consisting of digestible fats, indigestible fats, polymers and swelling agents. Suitably, the amount of azelastine in such sustained release compositions is about 0.05% to about 10.0% by weight and the amount of sucralose in such sustained release compositions is about 0.05% to about 0.15% by weight. In certain such embodiments, the amount of azelastine or salt thereof (e.g., azelastine HCl) is about 0.5 mg to about 10 mg.

[0015] In another embodiment, the present invention provides liquid pharmaceutical compositions for ocular administration, comprising (or consisting essentially of) a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of the pharmaceutically acceptable carriers or excipients is sucralose, wherein the composition is free, or substantially free of preservatives, and wherein the composition is provided in a single unit-dose container. Suitably, the amount of azelastine in such liquid, unit-dose pharmaceutical compositions is about 0.05% to about 0.15% by weight and the amount of sucralose in such liquid, unit-dose pharmaceutical compositions is about 0.05% to about 0.15% by weight. Suitable unit-dose containers include, but are not limited to, high density polyethylene containers, for example, high density polyethylene containers produced using a blow-fill-seal manufacturing technique with a volume capacity of about 1 mL.

[0016] In another embodiment, the present invention provides liquid pharmaceutical compositions for nasal administration in unit-dose or multi-dose configurations, comprising (or consisting essentially of) a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of the pharmaceutically acceptable carriers or excipients is sucralose, wherein the composition is free, or substantially free of preservatives, and wherein the composition is provided in either a unit-dose or multi-dose container. Suitably, the amount of azelastine in such liquid, unit-

dose or multi-dose pharmaceutical compositions is about 0.05% to about 0.15% by weight and the amount of sucralose in such liquid, unit-dose or multi-dose pharmaceutical compositions is about 0.05% to about 0.15% by weight. Suitable unit-dose or multi-dose containers include, but are not limited to, high density polyethylene bottles with a volume capacity of about 1ml to 10 mL fitted with a spray pump specifically designed for use with preservative free formulations.

[0017] The present invention also provides inhalable powder pharmaceutical compositions comprising (or consisting essentially of), a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers or excipients, wherein the azelastine is in the form of micronized particles and wherein at least one of the pharmaceutically acceptable carriers or excipients is sucralose, for example, micronized particles of sucralose. Suitable such inhalable powder pharmaceutical compositions comprise micronized particles of azelastine with an average particle size of about 1 μm to about 5 μm, and micronized particles of sucralose with an average particle size of about 1 μm to about 20 μm. Such inhalable powder pharmaceutical compositions of the present invention can be formulated for pulmonary delivery using, for example, a dry powder inhaler. Suitably, the amount of azelastine in such inhalable powder pharmaceutical compositions is about 0.1% to about 20.0% by weight and the amount of sucralose in such inhalable powder pharmaceutical compositions is about 0.05% to about 20.0% by weight.

[0018] The present invention also provides inhalable spray pharmaceutical compositions comprising (or consisting essentially of), a suitable concentration to provide a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carrier, stabilizer or excipient, wherein the azelastine is in a solution form and wherein at least one of the pharmaceutically acceptable carriers or excipients is sucralose dissolved in the solution. Such inhalable spray pharmaceutical compositions when used with a

suitable device provide a fine spray of the components (including active and non-active components) having an average particle size of about 1 μm to about 5 μm. Such inhalable spray pharmaceutical compositions of the present invention can be formulated for pulmonary delivery using, for example, a suitable device or inhaler. Suitably the amount of azelastine in such inhalable spray pharmaceutical compositions is about 0.1% to about 10% by weight and the amount of sucralose in such inhalable spray pharmaceutical compositions is about 0.05% to about 0.15% by weight.

[0019] The present invention also provides methods of treating snoring in an animal, comprising administering to the animal a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of the pharmaceutically acceptable carriers or excipients is sucralose. The amount of azelastine in such compositions suitably is about 0.05% to about 0.15% by weight, and the amount of sucralose in such compositions is suitably about 0.05% to about 0.15% by weight.

[0020] The present invention also provides methods of treating or preventing allergic rhinitis, non-allergic vasomotor rhinitis or allergic conjunctivitis in an animal, such as a human, suffering from or predisposed thereto, comprising administering to said animal a pharmaceutical composition comprising an effective amount azelastine and a taste-masking amount of sucralose, thereby avoiding the bitter taste associated with the azelastine.

[0021] In suitable embodiments, the present invention provides pharmaceutical compositions comprising (or consisting essentially of) the following:

[0022] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; and about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone.

[0023] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of

fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; and about 0.1% to about 0.15% (w/v) sucralose.

[0024] About 0.1% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; and about 0.1% (w/v) sucralose.

[0025] About 0.1% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; and about 0.15% (w/v) sucralose.

[0026] About 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; and about 0.1% (w/v) sucralose.

[0027] About 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; and about 0.15% (w/v) sucralose.

[0028] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; and about 0.1% to about 5.0% (w/v) montelukast.

[0029] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 5.0% (w/v) montelukast; and about 0.1% to about 0.15% (w/v) sucralose.

[0030] About 0.1% (w/v) azelastine hydrochloride; about 0.1% to about 5.0% (w/v) montelukast; and about 0.1% (w/v) sucralose.

[0031] About 0.1% (w/v) azelastine hydrochloride; about 0.1% to about 5.0% (w/v) montelukast; and about 0.15% (w/v) sucralose.

[0032] About 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 5.0% (w/v) montelukast; and about 0.1% (w/v) sucralose.

[0033] About 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 5.0% (w/v) montelukast; and about 0.15% (w/v) sucralose.

[0034] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; and about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine.

[0035] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and about 0.1% to about 0.15% (w/v) sucralose.

[0036] About 0.1% (w/v) azelastine hydrochloride; about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and about 0.1% (w/v) sucralose.

[0037] About 0.1% (w/v) azelastine hydrochloride; about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and about 0.15% (w/v) sucralose.

[0038] About 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and about 0.1% (w/v) sucralose.

[0039] About 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and about 0.15% (w/v) sucralose.

[0040] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; and about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen.

[0041] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen; and about 0.1% to about 0.15% (w/v) sucralose.

[0042] About 0.1% (w/v) azelastine hydrochloride; about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen; and about 0.1% (w/v) sucralose.

[0043] About 0.1% (w/v) azelastine hydrochloride; about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen; and about 0.15% (w/v) sucralose.

[0044] About 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen; and about 0.1% (w/v) sucralose.

[0045] About 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen; and about 0.15% (w/v) sucralose.

[0046] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; and about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine.

[0047] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and about 0.1% to about 0.15% (w/v) sucralose.

[0048] About 0.1% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and about 0.1% (w/v) sucralose.

[0049] About 0.1% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; about 0.1% to about 1.0% (w/v) decongestant selected from the

group consisting of pseudoephedrine and phenylephrine; and about 0.15% (w/v) sucralose.

[0050] About 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and about 0.1% (w/v) sucralose.

[0051] About 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and about 0.15% (w/v) sucralose.

[0052] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; and about 0.1% to about 5.0% (w/v) montelukast.

[0053] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; about 0.1% to about 5.0% (w/v) montelukast; and about 0.1% to about 0.15% (w/v) sucralose.

[0054] About 0.1% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; about 0.1% to about 5.0% (w/v) montelukast; and about 0.1% (w/v) sucralose.

[0055] About 0.1% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and

triamcinolone; about 0.1% to about 5.0% (w/v) montelukast; and about 0.15% (w/v) sucralose.

[0056] About 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; about 0.1% to about 5.0% (w/v) montelukast; and about 0.1% (w/v) sucralose.

[0057] About 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 1.0% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; about 0.1% to about 5.0% (w/v) montelukast; and about 0.15% (w/v) sucralose.

[0058] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; about 0.001% to about 5.00% (w/v) of a water-soluble polymer; about 0.01 % to about 2 % of a suspending agent; about 0.01 % to about 0.2 % of a wetting agent; about 0.01% to about 0.1% (w/v) disodium edetate; about 0.001% to about 0.5% (w/v) of a preservative such as benzalkonium chloride and/or phenethyl alcohol; about 0.1% to about 0.15% sucralose; a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4; a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and QS water.

[0059] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 5% (w/v) montelukast; about 0.001% to about 5.00% (w/v) of a water-soluble polymer; about 0.01% to about 0.1% (w/v) disodium edetate; about 0.001% to about 0.5% (w/v) benzalkonium chloride; about 0.1% to about 0.15% sucralose; a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5

to about 7.4; a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and QS water.

[0060] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 1% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; about 0.001% to about 5.00% (w/v) of a water-soluble polymer; about 0.01% to about 0.1% (w/v) disodium edetate; about 0.001% to about 0.5% (w/v) benzalkonium chloride; about 0.1% to about 0.15% sucralose; a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4; a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and QS water.

[0061] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.1% to about 10% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen; about 0.001% to about 5.00% (w/v) of a water-soluble polymer; about 0.01% to about 0.1% (w/v) disodium edetate; about 0.001% to about 0.5% (w/v) benzalkonium chloride; about 0.1% to about 0.15% sucralose; a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4; a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and QS water.

[0062] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; about 0.1% to about 1% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; about 0.001% to about 5.00% (w/v) of a water-soluble polymer; about 0.01 % to about 2 % of a suspending agent; about 0.01 % to about 0.2 % of a wetting agent; about 0.01% to about 0.1% (w/v) disodium edetate; about 0.001% to about 0.5% (w/v) of a preservative such as benzalkonium chloride and/or phenylethyl alcohol; about 0.1% to about 0.15% sucralose; a sufficient amount of a

pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4; a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and QS water.

[0063] About 0.05% to about 0.15% (w/v) azelastine hydrochloride; about 0.01% to about 1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; about 0.1% to about 1% (w/v) montelukast; about 0.001% to about 5.00% (w/v) of a water-soluble polymer; about 0.01 % to about 2% of a suspending agent; about 0.01 % to about 0.2% of a wetting agent; about 0.01% to about 0.1% (w/v) disodium edetate; about 0.001% to about 0.5% (w/v) of a preservative such as benzalkonium chloride and/or phenylethyl alcohol; about 0.1% to about 0.15% sucralose; a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4; a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and QS water.

[0064] In another embodiment, the present invention provides methods of treating or preventing a physical disorder in an animal suffering from or predisposed thereto, comprising administering to said animal an effective amount of any one of the pharmaceutical compositions described herein. Suitably the animal is a human, and the physical disorder is selected from the group consisting of allergic rhinitis, non-allergic vasomotor rhinitis and allergic conjunctivitis.

[0065] Other features and advantages of the invention will be apparent from the following detailed description, and from the claims. The disclosed materials, methods, and examples are for illustrative purposes only and are not intended to be limiting. Skilled artisans will appreciate that methods and materials similar or equivalent to those described herein can be used to practice the invention.

[0066] Unless otherwise defined, all technical and scientific terms used herein have the meaning commonly understood by one skilled in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

DETAILED DESCRIPTION OF THE INVENTION

Overview

[0067] As used herein when referring to any numerical value, the term "about" means a value falling within a range that is ±10% of the stated value. For example, "about 50°C" encompasses a range of temperatures from 45°C to 55°C, inclusive; similarly, "about 100 mM" encompasses a range of concentrations from 90 mM to 110 mM, inclusive.

[0068] As used herein, the articles "a," "an" and "one" mean "at least one" or "one or more" of the object to which they refer, unless otherwise specified or made clear by the context in which they appear herein.

[0069] The present invention provides compositions, particularly pharmaceutical compositions, comprising azelastine and/or one or more of its pharmacologically acceptable salts or esters thereof, particularly azelastine hydrochloride. Preferred such compositions of the invention comprise azelastine hydrochloride as the active ingredient, and may further comprise one or more additional components, such as one or more solvents, one or more preservatives, one or more stabilizers, one or more buffers or buffering agents, one or more bioadhesives, one or more suspending agents (e.g., microcrystalline cellulose, sodium carboxy methyl cellulose, hypromellose carbopol and the like), one or more surfactants or wetting agents and/or one or more isotonicity agents. To reduce or eliminate the bitter taste associated with azelastine (or a salt or ester thereof, such as azelastine hydrochloride), the compositions of the present invention further comprise one or more stable taste-masking, flavoring, or sweetening agents, or a combination of such

agents. To reduce the post-nasal drip of the compositions of the present invention for intranasal or ocular administration, the compositions of the present invention may further comprise one or more stable viscosity-increasing agents, one or more stable bioadhesive agents, and/or a combination of viscosity-increasing agents and bioadhesive agents. In other embodiments, the pharmaceutical compositions can comprise one or more additional active agents, such as those described herein, in addition to azelastine, including, but not limited to, additional antihistamines (including H_1, H_3 and H_4 receptor antagonists), steroids (e.g., safe steroids), leukotriene antagonists, prostaglandin D2 receptor antagonists, decongestants, anti-fungal agents, triamcinolone and triamcinolone derivatives, non-steroidal immunophilin-dependent immunosuppressants (NSIDIs), anti-inflammatory agents, non-steroidal anti-inflammatory agents (NSAIDs), COX-2 inhibitors, anti-infective agents, mucolytic agents, anticholinergic agents, mast cell stabilizers, non-antibiotic anti-microbial agents, anti-viral agents, antiseptics, neurokinin antagonists, platelet activating factor (PAF) and 5-lipoxygenase (5-LO) inhibitors.

[0070] In certain embodiments, the pharmaceutical compositions comprise one or more pharmaceutically carriers or excipients, particularly one or more such carriers or excipients that are useful in formulating the composition into a form suitable for delivery intranasally via aerosol or spray approaches, or for delivery ocularly via drops. In related embodiments, the invention provides such pharmaceutical compositions in which at least one of the carriers or excipients is a taste-masking agent, such as sucralose, and other compositions in which at least one of the carriers or excipients is a viscosity-increasing agent, such as hypromellose. In certain preferred embodiments, the pharmaceutical compositions provided by the invention comprise at least one taste-masking agent such as sucralose, and at least one viscosity-increasing agent such as hypromellose. The compositions of the invention are particularly useful in treating the symptoms associated with a variety of

conditions such as allergic rhinitis (seasonal and/or nonseasonal), non-allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis and the like.

Compositions and Modes of Administration

[0071] In certain embodiments, the invention provides compositions, particularly pharmaceutical compositions, comprising (or consisting essentially of) a therapeutically or pharmacologically effective amount of azelastine or a pharmaceutically acceptable salt or ester thereof and one or more pharmaceutically acceptable carriers or excipients. Particularly preferred for use in the compositions of the invention is azelastine hydrochloride (*see* U.S. Patent Nos. 3,813,384, 4,704,387 and 5,164,194, the disclosures of which are incorporated herein by reference in their entireties). By "pharmaceutically acceptable carrier or excipient" is meant a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

[0072] The compositions of the present invention can be administered to a patient via any suitable mode of administration, including oral, intranasal, ocular, buccal, sublingual, pulmonary or the like. In certain embodiments, the compositions are administered directly to the nasal mucosa (*i.e.*, intranasally, *e.g.*, in the form of a nasal spray or drops) or to the conjunctival sac of the eye (*i.e.*, ocularly, *e.g.*, in the form of ocular drops). In alternative embodiments, the compositions are administered topically to the buccal or sublingual cavity or intrapulmonarily. Regardless of their mode of administration, the compositions provided by the present invention suitably comprise from about 0.0001% to about 1.0%, and more suitably from about 0.005% to about 0.5% or most suitably from about 0.05% to about 0.15% (e.g., about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09%, about 0.10%, about 0.11%, about 0.12%, about 0.13%, about 0.14% or about 0.15%), of pure azelastine salt based on weight (calculated as the free azelastine base) as the active ingredient. The percentage of azelastine in a given composition of the invention is calculated as a percentage of the weight of the composition for

solid dosage forms (*i.e.*, weight/weight) or as a percentage of the volume of the composition for solution or liquid dosage forms (*i.e.*, weight/volume). The amount of a given salt form of azelastine (*e.g.*, azelastine hydrochloride) to be included in a given composition of the invention is calculated so that the composition contains the amount of pure azelastine noted above. In certain compositions of the invention, *e.g.*, nasal spray formulations, a solution formulated at a higher concentration of azelastine (or salt thereof) can be delivered at a smaller volume to provide a given dosage of azelastine (or salt thereof), thus minimizing the possibility of postnasal drip of the solution into the pharynx which leads to an unpleasant taste sensation by the person to whom the azelastine-containing nasal spray is administered.

[0073] In certain embodiments, the compositions of the invention may be formulated into forms for oral administration, including solid dosage forms or liquid dosage forms. In alternative embodiments, the compositions of the invention may be formulated into forms for direct administration to the mucosa, including the nasal mucosa (*i.e.*, intranasal administration), ocular tissue or conjunctival sac (*i.e.*, ocular administration), buccal mucosa (*i.e.*, buccal administration) or oral mucosa under the tongue (*i.e.*, sublingual administration).

[0074] Solid dosage forms for oral administration include capsules, tablets, pills, powders, particles and granules. In such solid dosage forms, the active azelastine compound(s) are mixed with at least one pharmaceutically acceptable excipient or carrier such as (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, dicalcium phosphate and microcrystalline cellulose; (b) binders such as sodium carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, and acacia; (c) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium carboxymethyl cellulose, pregelatinized starch and sodium starch glycolate; (d) lubricants such as calcium stearate, magnesium stearate, stearic acid, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and/or (e) glidants such as talc, silicon dioxide and starch. In the case

of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols, oils and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings, which may in themselves provide taste-masking, and shells such as enteric coatings and other coatings that are well known in the pharmaceutical formulating art. The solid dosage forms also may optionally contain opacifying, coloring and/or flavoring agents, and can also be formulated such that they release the active azelastine ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally in a delayed manner (*see* U.S. Patent No. 5,271,946, the disclosure of which is incorporated herein by reference in its entirety). Examples of embedding compositions which can be used include polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0075] Liquid dosage forms for nasal, ocular or oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active azelastine compound(s), the liquid dosage forms may contain inert diluents and/or solvents commonly used in the art. Water is the solvent of choice for the formulations of the invention; however, combinations of water with other physiologically acceptable solvents as required are also satisfactory for use. Other solvents, solubilizing agents and emulsifiers suitable for use in place of, or in addition to, water include but are not limited to saturated aliphatic mono- and polyvalent alcohols which contain 2-6 carbon atoms (including, but not limited to, ethanol, 1,2-propylene glycol, sorbitol, and glycerine), polyglycols such as polyethylene glycols, and surfactants/emulsifiers like the fatty acid esters of sorbitan, and mixtures thereof. Oils, in particular, cottonseed, peanut, or corn oils, may also be added to the compositions. The combination of the additional solvents in the aqueous solution should preferably not exceed about 15% (w/v) of the total

composition. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents (e.g., microcrystalline cellulose, sodium carboxymethyl cellulose, hypromellose, carbopol and the like), surfactants, sweetening, flavoring, and perfuming agents, including those described in further detail herein below. Liquid dosage forms that provide the active ingredient in suspension may comprise, in addition to the active azelastine compound(s), one or more suspending agents such as microcrystalline cellulose, magnesium aluminum silicate, bentonite, agar-agar, hypromellose, sodium carboxymethyl cellulose, carbopol/carbomer, pectin, acacia, tragacanth or their mixtures.

[0076] Certain liquid compositions of the invention may further comprise one or more preservatives and/or one or more stabilizers. Preservatives that are suitable for use in the compositions of the invention include, but are not limited to, edetic acid and their alkali salts such as disodium EDTA (also referred to as "disodium edetate" or "the disodium salt of edetic acid") and calcium EDTA (also referred to as "calcium edetate"), benzyl alcohol, methylparaben, propylparaben, butylparaben, chlorobutanol, phenylethyl alcohol, benzalkonium chloride, thimerosal, propylene glycol, sorbic acid, and benzoic acid derivatives. The preservatives should be used at a concentration of from about 0.001% to about 0.5% (w/v) in the final composition. The combination of benzalkonium chloride, used at a concentration of from about 0.001% to about 0.5% or preferably from about 0.005% to about 0.1% (w/v), and edetic acid (as a disodium salt), used at a concentration of from about 0.005% to about 0.1% (w/v), are the preferred preservative/stabilizer combination used in the compositions of the present invention.

[0077] Certain compositions of the invention may further comprise one or more solubility-enhancing agents that are used to improve the solubility of the azelastine compound used as an active ingredient. Solubility-enhancing agents that are suitable for use in the compositions of the invention include, but are not limited to, polyvinylpyrrolidone (preferably grades 25, 30, 60, or

90), poloxamer, polysorbate 80, sorbitan monooleate 80, and polyethylene glycols (molecular weights of 200 to 600).

[0078] Certain compositions of the invention may further comprise one or more agents that are used to render the composition isotonic, particularly in those compositions in which water is used as a solvent. Such agents are particularly useful in compositions formulated for nasal or ocular application, since they adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal or ocular secretions. Agents that are suitable for such a use in the compositions of the invention include, but are not limited to, sodium chloride, sorbitol, propylene glycol, dextrose, sucrose, and glycerine, and other isotonicity agents that are known in the art (*see, e.g.*, Reich *et al.*, "Chapter 18: Tonicity, Osmoticity, Osmolality and Osmolarity," *in: Remington: The Science and Practice of Pharmacy*, 20th Edition, Lippincott Williams and Wilkins, Philadelphia, PA (2000)).

[0079] It is desirable that the compositions of the present invention that are to be administered in liquid form (including intranasally, orally or ocularly applied formulations) have a pH of about 4.5 to about 7.4, and preferably have a pH of about 5.5 to 7.1, for physiological reasons. Accordingly, in additional embodiments, the compositions of the invention may further comprise one or more buffering agents or combinations thereof, that are used to adjust and/or maintain the compositions into the desired pH range. Adjustment of pH or buffering agents that are suitable for use in the compositions of the invention include, but are not limited to, citric acid, sodium citrate, sodium phosphate (dibasic, heptahydrate form), and boric acid or equivalent conventional buffers, or combinations thereof. The appropriate amounts of buffers and buffering agents, or combinations thereof, that are to be used in the compositions of the invention are readily determined by those of ordinary skill without undue experimentation, particularly in view of the guidance contained herein and in standard formularies such as the United States Pharmacopoeia, *Remington: The Science and Practice of Pharmacy*, and the like, the disclosures of which are incorporated herein by reference in their entireties.

[0080] As noted above, azelastine salts, particularly azelastine hydrochloride, have a strong bitter taste when the compounds or compositions comprising them are administered intranasally, ocularly, or orally. Thus, in certain embodiments, the liquid formulations of the invention, particularly those that are to be administered intranasally, ocularly, or orally, preferably further comprise one or more taste-masking agents, one or more flavoring agents, and/or one or more sweetening agents, or a combination of such agents. Non-limiting examples of such substances include sucralose (about 0.001 to about 1%), sucrose (about 0.5 to about 10%), saccharin (including the salt forms: sodium, calcium, etc.) (about 0.01 to about 2%), fructose (about 0.5 to about 10%), dextrose (about 0.5 to about 10%), corn syrup (about 0.5 to about 10%), aspartame (about 0.01 to about 2%), acesulfame-K (about 0.01 to about 2%), xylitol (about 0.1 to about 10%), sorbitol (about 0.1 to about 10%), erythritol (about 0.1 to about 10%), ammonium glycyrrhizinate (about 0.01 to about 4%), thaumatin (Talin™) (about 0.01 to about 2%), neotame (about 0.01 to about 2%) mannitol (about 0.5 to about 5%), menthol (about 0.01 to about 0.5%), eucalyptus oil (about 0.01 to about 0.5%), camphor (about 0.01 to about 0.5%), natural and/or artificial flavors such as Artificial Custard Cream Flavor #36184 from International Flavors and Fragrances, Inc. (New York, NY) (about 0.01 to about 1.0%), and the like. Sucralose, an intense sweetener marketed for food and beverage use as SPLENDA® by McNeil Nutritionals LLP (Fort Washington, PA), is especially effective as a sweetening and taste-masking agent in the compositions of the present invention, particularly when used at concentrations of from about 0.001% to about 1%, preferably at concentrations of from about 0.01% to about 0.5%, and more preferably at concentrations of from about 0.02% to about 0.2%, and most preferably from about 0.05% to about 0.15% (e.g., about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09%, about 0.10%, about 0.11%, about 0.12%, about 0.13%, about 0.14%, or about 0.15%), of the total composition. Sucralose has been shown to be useful as a taste modifying agent in oral delivery of certain pharmaceutical compositions, for example in sore throat spray products (*see*

U.S. Patent No. 6,319,513), oral suspensions (*see* U.S. Patent Nos. 5,658,919 and 5,621,005), solid dosage forms (*see* U.S. Patent No. 6,149,941), quick melt dosage forms (*see* U.S. Patent No. 6,165,512) and mucosal delivery (*see* U.S. Patent No. 6,552,024), but has not heretofore been shown to be useful in intranasally or ocularly applied compositions such as those of the present invention. Additional such compositions of the invention may comprise one or more additional taste-masking or flavoring agents such as those described herein, for example menthol at a concentration of from about 0.01% to about 1%, preferably at a concentration of from about 0.05% to about 0.1%. Suitable compositions of the invention include, for example, about 0.1%-0.15% azelastine and about 0.05%-0.15% sucralose, for example, about 0.1% azelastine and about 0.05%-0.15% sucralose, or about 0.125%-0.15% azelastine and about 0.05%-0.15% sucralose, or about 0.10% azelastine and about 0.15% sucralose, or about 0.15% azelastine and about 0.15% sucralose.

[0081] As noted above, intranasal or ocular application of azelastine-containing compositions, particularly those containing azelastine hydrochloride, is often complicated by the postnasal drip of the composition into the pharynx following intranasal or ocular administration. Such postnasal drip can induce a very bitter and unpleasant taste experience by the patient. Thus, to avoid, reduce or minimize such issues arising from postnasal drip, certain compositions of the present invention may alternatively or further comprise one or more water-soluble viscosity-increasing agents. Such agents are preferably used at the concentration of about 0.01% to about 5.0% (w/v), in order to typically produce a viscosity of the final solution between about 2 and about 300 centipoise. Use of such viscosity-increasing agents extends the mucocilliary clearance time, increases retention in the nasal cavity, and reduces post nasal drip, of intranasally applied compositions (*see* U.S. Patent No. 5,897,858, the disclosure of which is incorporated herein by reference in its entirety) such as those of the present invention. Viscosity-increasing agents that are suitable for use in accordance with the present invention include, but are not limited to, polyvinylpyrrolidones, cellulose derivatives including, but

not limited to, hydroxyethyl cellulose, carboxymethyl cellulose or its salts, hypromellose, carrageenan, guar gum, alginates, carbomers, polyethylene glycols, polyvinyl alcohol, and xanthan gum. Particularly preferred is hypromellose, at a concentration of about 0.001% to about 5.00%, preferably at a concentration of about 0.01% to about 1%, more preferably at a concentration of about 0.1% to about 0.5%, and most preferably at a concentration of about 0.1% to about 0.3%.

[0082] The compositions of the present invention that are provided in solution form may be preserved, aseptically manufactured and/or sterilized, for example, by filtration through a bacterial-retaining filter.

Compositions Comprising Additional Active Agents

[0083] In addition to azelastine (e.g., azelastine HCl) and the various excipients, taste masking agents, viscosity-increasing agents and the like disclosed herein, the pharmaceutical compositions of the invention can further comprise (or consist essentially of) one or more additional active agents, such as those disclosed throughout U.S. Patent Publication No. 2005/0148562, the disclosure of which is herein incorporated by reference in its entirety. Exemplary additional active agents include, but are not limited to, additional antihistamines (including H_1, H_3 and H_4 receptor antagonists), steroids (e.g., safe steroids), leukotriene antagonists, prostaglandin D2 receptor antagonists, decongestants, expectorants, anti-fungal agents, triamcinolone and triamcinolone derivatives, non-steroidal immunophilin-dependent immunosuppressants (NsIDIs), anti-inflammatory agents, non-steroidal anti-inflammatory agents (NSAIDs), COX-2 inhibitors, anti-infective agents, mucolytic agents, anticholinergic agents, mast cell stabilizers, non-antibiotic anti-microbial agents, anti-viral agents, antiseptics, neurokinin antagonists, platelet activating factor (PAF) and 5-lipoxygenase (5-LO) inhibitors.

[0084] Examples of antihistamines in addition to azelastine (e.g., H_1 receptor antagonists) suitable for inclusion in the present compositions include, but are not limited to, acrivastine, cyclizine, carebastine, cyproheptadine,

carbinoxamine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, ketotifen, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, olopatadine, picumast, tripelenamine, temelastine, trimeprazine, triprolidine, bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine, pyrilamine, astemizole, terfenadine, loratadine, cetirizine, levocetirizine, fexofenadine, descarboethoxyloratadine, desloratadine, dimenhydrinate and hydroxyzine.

[0085] Examples of H_3 receptor antagonists suitable for inclusion in the present compositions include, but are not limited to, thioperamide, impromidine, burimamide, clobenpropit, impentamine, mifetidine, clozapine, S-sopromidine, R-sopromidine and ciproxifam.

[0086] Examples of leukotriene antagonists (e.g., leukotriene D4 antagonists) suitable for inclusion in the present compositions include, but are not limited to, albuterol sulfate, aminophylline, amoxicillin, ampicillin, astemizole, attenuated tubercle bacillus, azithromycin, bacampicillin, beclomethasone dipropionate, budesonide, bupropion hydrochloride, cefaclor, cefadroxil, cefixime, cefprozil, cefuroxime axetil, cephalexin, ciprofloxacin hydrochloride, clarithromycin, clindamycin, cloxacillin, doxycycline, erythromycin, ethambutol, fenoterol hydrobromide, fluconazole, flunisolide, fluticasone propionate, formoterol fumarate, gatifloxacin, influenza virus vaccine, ipratropium bromide, isoniazid, isoproterenol hydrochloride, itraconazole, ketoconazole, ketotifen, levofloxacin, minocycline, montelukast (e.g., montelukast sodium), moxifloxacin, nedocromil sodium, nicotine, nystatin, ofloxacin, orciprenaline, oseltamivir, oseltamivir sulfate, oxtriphylline, penicillin, pirbuterol acetate, pivampicillin, pneumococcal conjugate vaccine, pneumococcal polysaccharide vaccine, prednisone, pyrazinamide, rifampin, salbutamol, salmeterol xinafoate, sodium cromoglycate (cromolyn sodium), terbutaline sulfate, terfenadine, theophylline, triamcinolone acetonide, zafirlukast and zanamivir.

[0087] Examples of decongestants suitable for inclusion in the present compositions include, but are not limited to, pseudoephedrine, phenylephedrine, phenylephrine, phenylpropanolamine, oxymetazoline, propylhexedrine, xylometazoline, epinephrine, ephedrine, desoxyephedrine, naphazoline, and tetrahydrozoline.

[0088] Examples of expectorants suitable for inclusion in the present compositions include, but are not limited to, guaifenesin, codeine phosphate, and isoproternol hydrochloride.

[0089] Examples of anti-fungal agents suitable for inclusion in the present compositions include, but are not limited to, amphotericin B, nystatin, fluconazole, ketoconazole, terbinafine, itraconazole, imidazole, triazole, ciclopirox, clotrimazole, and miconazole.

[0090] Examples of NSAIDs suitable for inclusion in the present compositions include, but are not limited to, ibuprofen, aceclofenac, diclofenac, naproxen, etodolac, flurbiprofen, fenoprofen, ketoprofen, suprofen, fenbufen, fluprofen, tolmetin sodium, oxaprozin, zomepirac, sulindac, indomethacin, piroxicam, mefenamic acid, nabumetone, meclofenamate sodium, diflunisal, flufenisal, piroxicam, ketorolac, sudoxicam and isoxicam.

[0091] By "non-steroidal immunophilin-dependent immunosuppressant" or "NsIDI" is meant any non-steroidal agent that decreases proinflammatory cytokine production or secretion, binds an immunophilin, or causes a down regulation of the proinflammatory reaction. NsIDIs suitable for inclusion in the present compositions include, but are not limited to, calcineurin inhibitors, such as cyclosporine, tacrolimus, ascomycin, pimecrolimus, as well as other agents (peptides, peptide fragments, chemically modified peptides, or peptide mimetics) that inhibit the phosphatase activity of calcineurin. NsIDIs also include rapamycin (sirolimus) and everolimus, which bind to an FK506-binding protein, FKBP-12, and block antigen-induced proliferation of white blood cells and cytokine secretion.

[0092] Examples of COX-2 inhibitors suitable for inclusion in the present compositions include, but are not limited to, rofecoxib, celecoxib, valdecoxib, lumiracoxib, meloxicam, and nimesulide.

[0093] Examples of steroids suitable for inclusion in the present compositions include but are not limited to, fluoromethalone, fluticasone, mometasone, triamcinolone, betamethasone, flunisolide, budesonide, beclomethasone, budesonide, rimexolone, beloxil, prednisone, loteprednol, dexamethasone and its analogues (e.g., dexamethasone beloxil) described in U.S. Pat. Nos. 5,223,493 and 5,420,120, incorporated herein by reference in their entireties.

[0094] Examples of anti-infective agents suitable for inclusion in the present compositions include, but are not limited to, penicillins and other beta lactam antibiotics, cephalosporins, macrolides, ketolides, sulfonamides, quinolones, aminoglycosides, and linezolid.

[0095] Examples of non-antibiotic antimicrobials suitable for inclusion in the present compositions include, but are not limited to, taurolidine.

[0096] Examples of mast cell stabilizers suitable for inclusion in the present compositions include, but are not limited to, cromolyn and nedcromil sodium.

[0097] Examples of mucolytic agents suitable for inclusion in the present compositions include, but are not limited to, acetylcysteine and dornase alpha.

[0098] Examples of antibiotic agents suitable for inclusion in the present compositions include, but are not limited to, cefuroxime, vancomycin, amoxicillin and gentamicin.

[0099] Examples of antiseptics suitable for inclusion in the present compositions include, but are not limited to, iodine, chlorhexidine acetate, sodium hypochlorite, and calcium hydroxide.

[0100] Examples of anticholinergics suitable for inclusion in the present compositions include, but are not limited to, ipratropium, atropine, and scopolamine.

[0101] Examples of neurokinin antagonists suitable for inclusion in the present compositions include, but are not limited to, oximes, hydrazones, piperidines, piperazines, aryl alkyl amines, hydrazones, nitroalkanes, amides,

isoxazolines, quinolines, isoquinolines, azanorbornanes, naphthyridines, and benzodiazepines, such as those disclosed in U.S. Pat. Nos. 5,798,359; 5,795,894; 5,789,422; 5,783,579; 5,719,156; 5,696,267; 5,691,362; 5,688,960; 5,654,316, incorporated by reference herein in their entireties.

[0102] Examples of 5-lipoxygenase (5-LO) inhibitors suitable for inclusion in the present compositions include, but are not limited to, zileuton, docebenone, piripost and tenidap.

[0103] The concentrations, absolute amounts and relative amounts (i.e., relative to the concentration or absolute amount of azelastine or a salt thereof, e.g. azelastine HCl) of the additional one or more active agents will be familiar to one of ordinary skill in the art. For example, the amounts of additional active agents (e.g., one or more steroid(s), leukotriene antagonist(s), anithistaminte(s), decongestant(s), NSAIDs, etc), can be present in any amount, for example about 0.01% to about 99% (e.g., about 0.01%, about 0.1%, about 1%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%).

[0104] In one embodiment, the pharmaceutical compositions comprise (or consisting essentially of) an effective amount of azelastine (suitably azelastine hydrochloride) along with an effective amount of one or more steroids. Exemplary steroids include those discussed above. In certain suitable embodiments, the compositions further comprise one or more additional ingredients, such as one or more excipients, one or more taste-masking agents and/or one or more viscosity-increasing agents. Such compositions can be formulated as intranasal or ocular suspensions or solutions, with a pH of about 6.0 to 8.0. In other embodiments, the compositions can be formulated as oral (e.g., tablets or capsules) or topical delivery formulations, such as those disclosed throughout. While the amount of azelastine can be varied and adjusted appropriately by the ordinarily skilled artisan, it is suitably contained in the intranasal or ocular formulations in an amount of about 0.0001% to about 1.0% by weight, and more suitably from about 0.005% to about 0.5% or most suitably from about 0.05% to about 0.15% (e.g., 0.05%, 0.06%, 0.07%,

0.08%, 0.09%. 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%), of pure azelastine (calculated as the free azelastine base). The amount of steroid(s) present in the various formulations can be varied and adjusted appropriately by the ordinarily skilled artisan, and can be present in any amount, for example about 0.01% to about 99% (e.g., about 0.01%, about 0.1%, about 1%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%). Suitably the amount of steroid is about 0.01% to about 1.5% by weight, more suitably about 0.01% to about 1.0% by weight, or even more suitably about 0.05% to about 0.1% by weight (e.g., about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09%, or about 0.1% by weight). Preferred steroids for use in the formulations of the present invention are "safe steroids." As used herein, the term "safe steroid" means a steroid which treats eosinophil and neurotrophil associated inflammation, reduces papillae formation, and which is effective in treating inflammation, without causing a clinically significant elevation in intraocular pressure (IOP). Exemplary safe steroids that can be used in the various formulations of the present invention, particularly for delivery using nasal spray or ocular drop delivery systems include, but are not limited to, any glucocorticoid which meets the safe steroid definition, including but not limited to, fluoromethalone, fluticasone (and its conjugates, e.g., fluticasone propionate), rimexolone, loteprednol, dexamethasone beloxil and its analogues described in U.S. Pat. Nos. 5,223,493 and 5,420,120, the disclosures of which are incorporated by reference herein in their entireties. Additional "safe steroids" and methods for determining appropriate amounts of such agents for inclusion in the present compositions are disclosed in U.S. Patent No. 6,649,602, the disclosure of which is incorporated by reference herein in its entirety. Exemplary compositions of the present invention comprising azelastine and a safe steroid comprise about 0.1%-0.15% azelastine, about 0.01%-0.1% of a safe steroid, and optionally about 0.05%-0.15% sucralose.

[0105] In another embodiment, the pharmaceutical compositions comprise (or consist essentially of) an effective amount of azelastine (suitably azelastine hydrochloride) along with an effective amount of one or more steroids, and also an effective amount of one or more decongestants. In suitable such embodiments, the compositions further comprise one or more additional ingredients, such as one or more excipients, one or more taste-masking agents and/or one or more viscosity-increasing agents. Such compositions can be formulated as intranasal or ocular suspensions or solutions, with a pH of about 6.0 to 8.0. In other embodiments, the compositions can be formulated as oral or topical delivery formulations, such as those disclosed throughout. The appropriate amounts of azelastine, steroid and decongestant can be readily determined by those or ordinary skill in the art. Suitably, the amount of steroid and azelastine used will be in the ranges disclosed herein. The amount of decongestant can be present in any amount, for example about 0.01% to about 99% (e.g., about 0.01%, about 0.1%, about 1%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%). Suitably the amount of decongestiant is about 0.05% to about 1.5% by weight, or more suitably in an amount of about 0.1% to about 1.0% by weight. In addition, the compositions can also comprise sucralose at about 0.05%-0.15%.

[0106] In an additional embodiment, the pharmaceutical compositions comprise (or consist essentially of) an effective amount of azelastine (suitably azelastine hydrochloride) along with an effective amount of one or more additional anti-allergic and/or one or more anti-asthmatic agents. Exemplary anti-allergics and anti-asthmatics include those discussed herein, including, but not limited to, H_1 receptor antagonists, H_3 receptor antagonists and leukotriene antagonists (e.g., leukotriene D4 antagonists). In suitable such embodiments, the compositions further comprise one or more additional ingredients, such as one or more excipients, one or more taste-masking agents and/or one or more viscosity-increasing agents. Such compositions can be formulated as intranasal or ocular suspensions or solutions, with a pH of about

6.0 to 8.0. In other embodiments, the compositions can be formulated for oral or pulmonary delivery, such as those described herein. While the amount of azelastine can be varied and adjusted appropriately by the ordinarily skilled artisan, it is suitably contained in the intranasal or ocular formulations in an amount of about 0.0001% to about 1.0% by weight, and more suitably from about 0.005% to about 0.5% or most suitably from about 0.05% to about 0.15% (e.g., about 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%), of pure azelastine (calculated as the free azelastine base). The amount of one or more additional anti-allergic and/or anti-asthmatics present in the various formulations can be varied and adjusted appropriately by the ordinarily skilled artisan and can be present in any amount, for example about 0.01% to about 99% (e.g., about 0.01%, about 0.1%, about 1%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%). Suitably the amount of these additional compounds will be in an amount of about 0.01% to about 10% by weight, or more suitably in an amount of about 0.1% to about 5.0% by weight. In addition, the compositions can also comprise sucralose at about 0.05%-0.15%.

[0107] Suitable compositions of the present invention comprise (or consist essentially of), for example (percentages of azelastine refer to weight percentages of azelastine HCl or other suitable salt):

[0108] About 0.05% azelastine and about 0.05% sucralose;

[0109] About 0.05% azelastine and about 0.1% sucralose;

[0110] About 0.05% azelastine and about 0.15% sucralose;

[0111] About 0.1% azelastine and about 0.05% sucralose;

[0112] About 0.1% azelastine and about 0.1% sucralose;

[0113] About 0.1% azelastine and about 0.15% sucralose;

[0114] About 0.125% azelastine and about 0.05% sucralose;

[0115] About 0.125% azelastine and about 0.1% sucralose;

[0116] About 0.125% azelastine and about 0.15% sucralose;

[0117] About 0.15% azelastine and about 0.05% sucralose;

[0118] About 0.15% azelastine and about 0.1% sucralose;

[0119] About 0.15% azelastine and about 0.15% sucralose;

[0120] About 0.05% azelastine and about 0.01% steroid;

[0121] About 0.1% azelastine and about 0.01% steroid;

[0122] About 0.125% azelastine and about 0.01% steroid;

[0123] About 0.15% azelastine and about 0.01% steroid;

[0124] About 0.05% azelastine and about 0.05% steroid;

[0125] About 0.1% azelastine and about 0.05% steroid;

[0126] About 0.125% azelastine and about 0.05% steroid;

[0127] About 0.15% azelastine and about 0.05% steroid;

[0128] About 0.05% azelastine and about 0.1% steroid;

[0129] About 0.1% azelastine and about 0.1% steroid;

[0130] About 0.125% azelastine and about 0.1% steroid;

[0131] About 0.15% azelastine and about 0.1% steroid;

[0132] About 0.05% azelastine, about 0.01% steroid and about 0.05% sucralose;

[0133] About 0.1% azelastine, about 0.01% steroid and about 0.05% sucralose;

[0134] About 0.125% azelastine, about 0.01% steroid and about 0.05% sucralose;

[0135] About 0.15% azelastine, about 0.01% steroid and about 0.05% sucralose;

[0136] About 0.05% azelastine, about 0.05% steroid and about 0.05% sucralose;

[0137] About 0.1% azelastine, about 0.05% steroid and about 0.05% sucralose;

[0138] About 0.125% azelastine, about 0.05% steroid and about 0.05% sucralose;

[0139] About 0.15% azelastine, about 0.05% steroid and about 0.05% sucralose;

[0140] About 0.05% azelastine, about 0.1% steroid and about 0.05% sucralose;

[0141] About 0.1% azelastine, about 0.1% steroid and about 0.05% sucralose;

[0142] About 0.125% azelastine, about 0.1% steroid and about 0.05% sucralose;

[0143] About 0.15% azelastine, about 0.1% steroid and about 0.05% sucralose;

[0144] About 0.05% azelastine, about 0.01% steroid and about 0.1% sucralose;

[0145] About 0.1% azelastine, about 0.01% steroid and about 0.1% sucralose;

[0146] About 0.125% azelastine, about 0.01% steroid and about 0.1% sucralose;

[0147] About 0.15% azelastine, about 0.01% steroid and about 0.1% sucralose;

[0148] About 0.05% azelastine, about 0.05% steroid and about 0.1% sucralose;

[0149] About 0.1% azelastine, about 0.05% steroid and about 0.1% sucralose;

[0150] About 0.125% azelastine, about 0.05% steroid and about 0.1% sucralose;

[0151] About 0.15% azelastine, about 0.05% steroid and about 0.1% sucralose;

[0152] About 0.05% azelastine, about 0.1% steroid and about 0.1% sucralose;

[0153] About 0.1% azelastine, about 0.1% steroid and about 0.1% sucralose;

[0154] About 0.125% azelastine, about 0.1% steroid and about 0.1% sucralose;

[0155] About 0.15% azelastine, about 0.1% steroid and about 0.1% sucralose;

[0156] About 0.05% azelastine, about 0.01% steroid and about 0.15% sucralose;

[0157] About 0.1% azelastine, about 0.01% steroid and about 0.15% sucralose;

[0158] About 0.125% azelastine, about 0.01% steroid and about 0.15% sucralose;

[0159] About 0.15% azelastine, about 0.01% steroid and about 0.15% sucralose;

[0160] About 0.05% azelastine, about 0.05% steroid and about 0.15% sucralose;

[0161] About 0.1% azelastine, about 0.05% steroid and about 0.15% sucralose;

[0162] About 0.125% azelastine, about 0.05% steroid and about 0.15% sucralose;

[0163] About 0.15% azelastine, about 0.05% steroid and about 0.15% sucralose;

[0164] About 0.05% azelastine, about 0.1% steroid and about 0.15% sucralose;

[0165] About 0.1% azelastine, about 0.1% steroid and about 0.15% sucralose;

[0166] About 0.125% azelastine, about 0.1% steroid and about 0.15% sucralose;

[0167] About 0.15% azelastine, about 0.1% steroid and about 0.15% sucralose;

[0168] About 0.05% azelastine and about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0169] About 0.1% azelastine and about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0170] About 0.125% azelastine and about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0171] About 0.15% azelastine and about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0172] About 0.05% azelastine and about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0173] About 0.1% azelastine and about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0174] About 0.125% azelastine and about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0175] About 0.15% azelastine and about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0176] About 0.05% azelastine and about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0177] About 0.1% azelastine and about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0178] About 0.125% azelastine and about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0179] About 0.15% azelastine and about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone;

[0180] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0181] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0182] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0183] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0184] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0185] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0186] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0187] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0188] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0189] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0190] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0191] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0192] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0193] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0194] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0195] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0196] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0197] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0198] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0199] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0200] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0201] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0202] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0203] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0204] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0205] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0206] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0207] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.05% sucralose;

[0208] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0209] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0210] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0211] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% sucralose;

[0212] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0213] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0214] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0215] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.15% sucralose;

[0216] About 0.05% azelastine and about 0.1% leukotriene antagonist;

[0217] About 0.1% azelastine and about 0.1% leukotriene antagonist;

[0218] About 0.125% azelastine and about 0.1% leukotriene antagonist;

[0219] About 0.15% azelastine and about 0.1% leukotriene antagonist;

[0220] About 0.05% azelastine and about 0.5% leukotriene antagonist;

[0221] About 0.1% azelastine and about 0.5% leukotriene antagonist;

[0222] About 0.125% azelastine and about 0.5% leukotriene antagonist;

[0223] About 0.15% azelastine and about 0.5% leukotriene antagonist;

[0224] About 0.05% azelastine and about 5.0% leukotriene antagonist;

[0225] About 0.1% azelastine and about 5.0% leukotriene antagonist;

[0226] About 0.125% azelastine and about 5.0% leukotriene antagonist;

[0227] About 0.15% azelastine and about 5.0% leukotriene antagonist;

[0228] About 0.05% azelastine, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0229] About 0.1% azelastine, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0230] About 0.125% azelastine, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0231] About 0.15% azelastine, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0232] About 0.05% azelastine, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0233] About 0.1% azelastine, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0234] About 0.125% azelastine, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0235] About 0.15% azelastine, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0236] About 0.05% azelastine, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0237] About 0.1% azelastine, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0238] About 0.125% azelastine, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0239] About 0.15% azelastine, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0240] About 0.05% azelastine, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0241] About 0.1% azelastine, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0242] About 0.125% azelastine, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0243] About 0.15% azelastine, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0244] About 0.05% azelastine, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0245] About 0.1% azelastine, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0246] About 0.125% azelastine, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0247] About 0.15% azelastine, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0248]

[0249] About 0.05% azelastine, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0250] About 0.1% azelastine, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0251] About 0.125% azelastine, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0252] About 0.15% azelastine, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0253] About 0.05% azelastine, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0254] About 0.1% azelastine, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0255] About 0.125% azelastine, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0256] About 0.15% azelastine, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0257] About 0.05% azelastine, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0258] About 0.1% azelastine, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0259] About 0.125% azelastine, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0260] About 0.15% azelastine, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0261] About 0.05% azelastine, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0262] About 0.1% azelastine, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0263] About 0.125% azelastine, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0264] About 0.15% azelastine, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0265] About 0.05% azelastine and about 0.1% montelukast;

[0266] About 0.1% azelastine and about 0.1% montelukast;

[0267] About 0.125% azelastine and about 0.1% montelukast;

[0268] About 0.15% azelastine and about 0.1% montelukast;

[0269] About 0.05% azelastine and about 0.5% montelukast;

[0270] About 0.1% azelastine and about 0.5% montelukast;

[0271] About 0.125% azelastine and about 0.5% montelukast;

[0272] About 0.15% azelastine and about 0.5% montelukast;

[0273] About 0.05% azelastine and about 5.0% montelukast;

[0274] About 0.1% azelastine and about 5.0% montelukast;

[0275] About 0.125% azelastine and about 5.0% montelukast;

[0276] About 0.15% azelastine and about 5.0% montelukast;

[0277] About 0.05% azelastine, about 0.1% montelukast and about 0.05% sucralose;

[0278] About 0.1% azelastine, about 0.1% montelukast and about 0.05% sucralose;

[0279] About 0.125% azelastine, about 0.1% montelukast and about 0.05% sucralose;

[0280] About 0.15% azelastine, about 0.1% montelukast and about 0.05% sucralose;

[0281] About 0.05% azelastine, about 0.1% montelukast and about 0.1% sucralose;

[0282] About 0.1% azelastine, about 0.1% montelukast and about 0.1% sucralose;

[0283] About 0.125% azelastine, about 0.1% montelukast and about 0.1% sucralose;

[0284] About 0.15% azelastine, about 0.1% montelukast and about 0.1% sucralose;

[0285] About 0.05% azelastine, about 0.1% montelukast and about 0.15% sucralose;

[0286] About 0.1% azelastine, about 0.1% montelukast and about 0.15% sucralose;

[0287] About 0.125% azelastine, about 0.1% montelukast and about 0.15% sucralose;

[0288] About 0.15% azelastine, about 0.1% montelukast and about 0.15% sucralose;

[0289] About 0.05% azelastine, about 0.5% montelukast and about 0.05% sucralose;

[0290] About 0.1% azelastine, about 0.5% montelukast and about 0.05% sucralose;

[0291] About 0.125% azelastine, about 0.5% montelukast and about 0.05% sucralose;

[0292] About 0.15% azelastine, about 0.5% montelukast and about 0.05% sucralose;

[0293] About 0.05% azelastine, about 0.5% montelukast and about 0.1% sucralose;

[0294] About 0.1% azelastine, about 0.5% montelukast and about 0.1% sucralose;

[0295] About 0.125% azelastine, about 0.5% montelukast and about 0.1% sucralose;

[0296] About 0.15% azelastine, about 0.5% montelukast and about 0.1% sucralose;

[0297] About 0.05% azelastine, about 0.5% montelukast and about 0.15% sucralose;

[0298] About 0.1% azelastine, about 0.5% montelukast and about 0.15% sucralose;

[0299] About 0.125% azelastine, about 0.5% montelukast and about 0.15% sucralose;

[0300] About 0.15% azelastine, about 0.5% montelukast and about 0.15% sucralose;

[0301] About 0.05% azelastine, about 5.0% montelukast and about 0.05% sucralose;

[0302] About 0.1% azelastine, about 5.0% montelukast and about 0.05% sucralose;

[0303] About 0.125% azelastine, about 5.0% montelukast and about 0.05% sucralose;

[0304] About 0.15% azelastine, about 5.0% montelukast and about 0.05% sucralose;

[0305] About 0.05% azelastine, about 5.0% montelukast and about 0.1% sucralose;

[0306] About 0.1% azelastine, about 5.0% montelukast and about 0.1% sucralose;

[0307] About 0.125% azelastine, about 5.0% montelukast and about 0.1% sucralose;

[0308] About 0.15% azelastine, about 5.0% montelukast and about 0.1% sucralose;

[0309] About 0.05% azelastine, about 5.0% montelukast and about 0.15% sucralose;

[0310] About 0.1% azelastine, about 5.0% montelukast and about 0.15% sucralose;

[0311] About 0.125% azelastine, about 5.0% montelukast and about 0.15% sucralose;

[0312] About 0.15% azelastine, about 5.0% montelukast and about 0.15% sucralose;

[0313] About 0.05% azelastine and about 0.1% decongestant;

[0314] About 0.1% azelastine and about 0.1% decongestant;

[0315] About 0.125% azelastine and about 0.1% decongestant;

[0316] About 0.15% azelastine and about 0.1% decongestant;

[0317] About 0.05% azelastine and about 0.5% decongestant;

[0318] About 0.1% azelastine and about 0.5% decongestant;

[0319] About 0.125% azelastine and about 0.5% decongestant;

[0320] About 0.15% azelastine and about 0.5% decongestant;

[0321] About 0.05% azelastine and about 1.0% decongestant;

[0322] About 0.1% azelastine and about 1.0% decongestant;

[0323] About 0.125% azelastine and about 1.0% decongestant;

[0324] About 0.15% azelastine and about 1.0% decongestant;

[0325] About 0.05% azelastine, about 0.1% decongestant and about 0.05% sucralose;

[0326] About 0.1% azelastine, about 0.1% decongestant and about 0.05% sucralose;

[0327] About 0.125% azelastine, about 0.1% decongestant and about 0.05% sucralose;

[0328] About 0.15% azelastine, about 0.1% decongestant and about 0.05% sucralose;

[0329] About 0.05% azelastine, about 0.1% decongestant and about 0.1% sucralose;

[0330] About 0.1% azelastine, about 0.1% decongestant and about 0.1% sucralose;

[0331] About 0.125% azelastine, about 0.1% decongestant and about 0.1% sucralose;

[0332] About 0.15% azelastine, about 0.1% decongestant and about 0.1% sucralose;

[0333] About 0.05% azelastine, about 0.1% decongestant and about 0.15% sucralose;

[0334] About 0.1% azelastine, about 0.1% decongestant and about 0.15% sucralose;

[0335] About 0.125% azelastine, about 0.1% decongestant and about 0.15% sucralose;

[0336] About 0.15% azelastine, about 0.1% decongestant and about 0.15% sucralose;

[0337] About 0.05% azelastine, about 0.5% decongestant and about 0.05% sucralose;

[0338] About 0.1% azelastine, about 0.5% decongestant and about 0.05% sucralose;

[0339] About 0.125% azelastine, about 0.5% decongestant and about 0.05% sucralose;

[0340] About 0.15% azelastine, about 0.5% decongestant and about 0.05% sucralose;

[0341] About 0.05% azelastine, about 0.5% decongestant and about 0.1% sucralose;

[0342] About 0.1% azelastine, about 0.5% decongestant and about 0.1% sucralose;

[0343] About 0.125% azelastine, about 0.5% decongestant and about 0.1% sucralose;

[0344] About 0.15% azelastine, about 0.5% decongestant and about 0.1% sucralose;

[0345] About 0.05% azelastine, about 0.5% decongestant and about 0.15% sucralose;

[0346] About 0.1% azelastine, about 0.5% decongestant and about 0.15% sucralose;

[0347] About 0.125% azelastine, about 0.5% decongestant and about 0.15% sucralose;

[0348] About 0.15% azelastine, about 0.5% decongestant and about 0.15% sucralose;

[0349] About 0.05% azelastine, about 1.0% decongestant and about 0.05% sucralose;

[0350] About 0.1% azelastine, about 1.0% decongestant and about 0.05% sucralose;

[0351] About 0.125% azelastine, about 1.0% decongestant and about 0.05% sucralose;

[0352] About 0.15% azelastine, about 1.0% decongestant and about 0.05% sucralose;

[0353] About 0.05% azelastine, about 1.0% decongestant and about 0.1% sucralose;

[0354] About 0.1% azelastine, about 1.0% decongestant and about 0.1% sucralose;

[0355] About 0.125% azelastine, about 1.0% decongestant and about 0.1% sucralose;

[0356] About 0.15% azelastine, about 1.0% decongestant and about 0.1% sucralose;

[0357] About 0.05% azelastine, about 1.0% decongestant and about 0.15% sucralose;

[0358] About 0.1% azelastine, about 1.0% decongestant and about 0.15% sucralose;

[0359] About 0.125% azelastine, about 1.0% decongestant and about 0.15% sucralose;

[0360] About 0.15% azelastine, about 1.0% decongestant and about 0.15% sucralose;

[0361] About 0.05% azelastine and about 0.1% pseudoephedrine or phenylephrine;

[0362] About 0.1% azelastine and about 0.1% pseudoephedrine or phenylephrine;

[0363] About 0.125% azelastine and about 0.1% pseudoephedrine or phenylephrine;

[0364] About 0.15% azelastine and about 0.1% pseudoephedrine or phenylephrine;

[0365] About 0.05% azelastine and about 0.5% pseudoephedrine or phenylephrine;

[0366] About 0.1% azelastine and about 0.5% pseudoephedrine or phenylephrine;

[0367] About 0.125% azelastine and about 0.5% pseudoephedrine or phenylephrine;

[0368] About 0.15% azelastine and about 0.5% pseudoephedrine or phenylephrine;

[0369] About 0.05% azelastine and about 1.0% pseudoephedrine or phenylephrine;

[0370] About 0.1% azelastine and about 1.0% pseudoephedrine or phenylephrine;

[0371] About 0.125% azelastine and about 1.0% pseudoephedrine or phenylephrine;

[0372] About 0.15% azelastine and about 1.0% pseudoephedrine or phenylephrine;

[0373] About 0.05% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0374] About 0.1% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0375] About 0.125% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0376] About 0.15% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0377] About 0.05% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0378] About 0.1% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0379] About 0.125% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0380] About 0.15% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0381] About 0.05% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0382] About 0.1% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0383] About 0.125% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0384] About 0.15% azelastine, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0385] About 0.05% azelastine, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0386] About 0.1% azelastine, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0387] About 0.125% azelastine, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0388] About 0.15% azelastine, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0389] About 0.05% azelastine, about 0.5% pseudoephedrine or phenylephrine or phenylephrine and about 0.1% sucralose;

[0390] About 0.1% azelastine, about 0.5% pseudoephedrine or phenylephrine or phenylephrine and about 0.1% sucralose;

[0391] About 0.125% azelastine, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0392] About 0.15% azelastine, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0393] About 0.05% azelastine, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0394] About 0.1% azelastine, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0395] About 0.125% azelastine, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0396] About 0.15% azelastine, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0397] About 0.05% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0398] About 0.1% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0399] About 0.125% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0400] About 0.15% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0401] About 0.05% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0402] About 0.1% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0403] About 0.125% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0404] About 0.15% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0405] About 0.05% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0406] About 0.1% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0407] About 0.125% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0408] About 0.15% azelastine, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0409] About 0.05% azelastine and about 0.1% NSAID;

[0410] About 0.1% azelastine and about 0.1% NSAID;

[0411] About 0.125% azelastine and about 0.1% NSAID;

[0412] About 0.15% azelastine and about 0.1% NSAID;

[0413] About 0.05% azelastine and about 0.5% NSAID;

[0414] About 0.1% azelastine and about 0.5% NSAID;

[0415] About 0.125% azelastine and about 0.5% NSAID;

[0416] About 0.15% azelastine and about 0.5% NSAID;

[0417] About 0.05% azelastine and about 10.0% NSAID;

[0418] About 0.1% azelastine and about 10.0% NSAID;

[0419] About 0.125% azelastine and about 10.0% NSAID;

[0420] About 0.15% azelastine and about 10.0% NSAID;

[0421] About 0.05% azelastine, about .1% NSAID and about 0.05% sucralose;

[0422] About 0.1% azelastine, about 0.1% NSAID and about 0.05% sucralose;

[0423] About 0.125% azelastine, about 0.1% NSAID and about 0.05% sucralose;

[0424] About 0.15% azelastine, about 0.1% NSAID and about 0.05% sucralose;

[0425] About 0.05% azelastine, about 0.1% NSAID and about 0.1% sucralose;

[0426] About 0.1% azelastine, about 0.1% NSAID and about 0.1% sucralose;

[0427] About 0.125% azelastine, about 0.1% NSAID and about 0.1% sucralose;

[0428] About 0.15% azelastine, about 0.1% NSAID and about 0.1% sucralose;

[0429] About 0.05% azelastine, about 0.1% NSAID and about 0.15% sucralose;

[0430] About 0.1% azelastine, about 0.1% NSAID and about 0.15% sucralose;

[0431] About 0.125% azelastine, about 0.1% NSAID and about 0.15% sucralose;

[0432] About 0.15% azelastine, about 0.1% NSAID and about 0.15% sucralose;

[0433] About 0.05% azelastine, about 0.5% NSAID and about 0.05% sucralose;

[0434] About 0.1% azelastine, about 0.5% NSAID and about 0.05% sucralose;

[0435] About 0.125% azelastine, about 0.5% NSAID and about 0.05% sucralose;

[0436] About 0.15% azelastine, about 0.5% NSAID and about 0.05% sucralose;

[0437] About 0.05% azelastine, about 0.5% NSAID and about 0.1% sucralose;

[0438] About 0.1% azelastine, about 0.5% NSAID and about 0.1% sucralose;

[0439] About 0.125% azelastine, about 0.5% NSAID and about 0.1% sucralose;

[0440] About 0.15% azelastine, about 0.5% NSAID and about 0.1% sucralose;

[0441] About 0.05% azelastine, about 0.5% NSAID and about 0.15% sucralose;

[0442] About 0.1% azelastine, about 0.5% NSAID and about 0.15% sucralose;

[0443] About 0.125% azelastine, about 0.5% NSAID and about 0.15% sucralose;

[0444] About 0.15% azelastine, about 0.5% NSAID and about 0.15% sucralose;

[0445] About 0.05% azelastine, about 10.0% NSAID and about 0.05% sucralose;

[0446] About 0.1% azelastine, about 10.0% NSAID and about 0.05% sucralose;

[0447] About 0.125% azelastine, about 10.0% NSAID and about 0.05% sucralose;

[0448] About 0.15% azelastine, about 1.0% NSAID and about 0.05% sucralose;

[0449] About 0.05% azelastine, about 10.0% NSAID and about 0.1% sucralose;

[0450] About 0.1% azelastine, about 10.0% NSAID and about 0.1% sucralose;

[0451] About 0.125% azelastine, about 10.0% NSAID and about 0.1% sucralose;

[0452] About 0.15% azelastine, about 10.0% NSAID and about 0.1% sucralose;

[0453] About 0.05% azelastine, about 10.0% NSAID and about 0.15% sucralose;

[0454] About 0.1% azelastine, about 10.0% NSAID and about 0.15% sucralose;

[0455] About 0.125% azelastine, about 10.0% NSAID and about 0.15% sucralose;

[0456] About 0.15% azelastine, about 10.0% NSAID and about 0.15% sucralose;

[0457] About 0.05% azelastine and about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen;

[0458] About 0.1% azelastine and about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen;

[0459] About 0.125% azelastine and about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen;

[0460] About 0.15% azelastine and about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen;

[0461] About 0.05% azelastine and about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen;

[0462] About 0.1% azelastine and about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen;

[0463] About 0.125% azelastine and about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen;

[0464] About 0.15% azelastine and about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen;

[0465] About 0.05% azelastine and about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen;

[0466] About 0.1% azelastine and about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen;

[0467] About 0.125% azelastine and about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen;

[0468] About 0.15% azelastine and about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen;

[0469] About 0.05% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0470] About 0.1% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0471] About 0.125% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0472] About 0.15% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0473] About 0.05% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0474] About 0.1% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0475] About 0.125% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0476] About 0.15% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0477] About 0.05% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0478] About 0.1% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0479] About 0.125% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0480] About 0.15% azelastine, about 0.1% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0481] About 0.05% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0482] About 0.1% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0483] About 0.125% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0484] About 0.15% azelastine, about 0.5% ibuprofen and about 0.05% sucralose;

[0485] About 0.05% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0486] About 0.1% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0487] About 0.125% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0488] About 0.15% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0489] About 0.05% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0490] About 0.1% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0491] About 0.125% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0492] About 0.15% azelastine, about 0.5% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0493] About 0.05% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0494] About 0.1% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0495] About 0.125% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0496] About 0.15% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.05% sucralose;

[0497] About 0.05% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0498] About 0.1% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0499] About 0.125% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0500] About 0.15% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.1% sucralose;

[0501] About 0.05% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0502] About 0.1% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0503] About 0.125% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0504] About 0.15% azelastine, about 10.0% ibuprofen, diclofenac, aceclofenac or naproxen and about 0.15% sucralose;

[0505] About 0.05% azelastine, about 0.01% steroid and about 0.1% decongestant;

[0506] About 0.1% azelastine, about 0.01% steroid and about 0.1% decongestant;

[0507] About 0.125% azelastine, about 0.01% steroid and about 0.1% decongestant;

[0508] About 0.15% azelastine, about 0.01% steroid and about 0.1% decongestant;

[0509] About 0.05% azelastine, about 0.05% steroid and about 0.1% decongestant;

[0510] About 0.1% azelastine, about 0.05% steroid and about 0.1% decongestant;

[0511] About 0.125% azelastine, about 0.05% steroid and about 0.1% decongestant;

[0512] About 0.15% azelastine, about 0.05% steroid and about 0.1% decongestant;

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[0514] About 0.1% azelastine, about 0.1% steroid and about 0.1% decongestant;

[0515] About 0.125% azelastine, about 0.1% steroid and about 0.1% decongestant;

[0516] About 0.15% azelastine, about 0.1% steroid and about 0.1% decongestant;

[0517] About 0.05% azelastine, about 0.01% steroid and about 0.5% decongestant;

[0518] About 0.1% azelastine, about 0.01% steroid and about 0.5% decongestant;

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[0526] About 0.1% azelastine, about 0.1% steroid and about 0.5% decongestant;

[0527] About 0.125% azelastine, about 0.1% steroid and about 0.5% decongestant;

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[0529] About 0.05% azelastine, about 0.01% steroid and about 1.0% decongestant;

[0530] About 0.1% azelastine, about 0.01% steroid and about 1.0% decongestant;

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[0534] About 0.1% azelastine, about 0.05% steroid and about 1.0% decongestant;

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[0539] About 0.125% azelastine, about 0.1% steroid and about 1.0% decongestant;

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[0541] About 0.05% azelastine, about 0.01% steroid, about 0.1% decongestant and about 0.05% sucralose;

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[0570] About 0.1% azelastine, about 0.05% steroid, about 1.0% decongestant and about 0.05% sucralose;

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[0604] About 0.15% azelastine, about 0.01% steroid, about 1.0% decongestant and about 0.1% sucralose;

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[0646] About 0.1% azelastine, about 0.1% steroid, about 1.0% decongestant and about 0.15% sucralose;

[0647] About 0.125% azelastine, about 0.1% steroid, about 1.0% decongestant and about 0.15% sucralose;

[0648] About 0.15% azelastine, about 0.1% steroid, about 1.0% decongestant and about 0.15% sucralose;

[0649] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0650] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0651] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0652] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0653] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0654] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0655] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0656] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0657] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0658] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0659] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0660] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% pseudoephedrine or phenylephrine;

[0661] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0662] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0663] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0664] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0665] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0666] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0667] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0668] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0669] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0670] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0671] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0672] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% pseudoephedrine or phenylephrine;

[0673] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0674] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0675] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0676] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0677] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0678] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0679] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0680] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0681] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0682] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0683] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0684] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 1.0% pseudoephedrine or phenylephrine;

[0685] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0686] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0687] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0688] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0689] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0690] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0691] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0692] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0693] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0694] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0695] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0696] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0697] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0698] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0699] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0700] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0701] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0702] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0703] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0704] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0705] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0706] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0707] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0708] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0709] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0710] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0711] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0712] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0713] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0714] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0715] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0716] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0717] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0718] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0719] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0720] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.05% sucralose;

[0721] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0722] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0723] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0724] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0725] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0726] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0727] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0728] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0729] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0730] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0731] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0732] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0733] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0734] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0735] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine or phenylephrine and about 0.1% sucralose;

[0736] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0737] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0738] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0739] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine or phenylephrine and about 0.1% sucralose;

[0740] About 0.15% azelastine, about 0.50% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0741] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0742] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0743] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine or phenylephrine and about 0.1% sucralose;

[0744] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0745] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0746] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0747] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0748] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0749] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0750] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0751] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0752] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0753] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0754] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0755] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0756] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.1% sucralose;

[0757] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0758] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0759] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0760] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0761] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0762] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0763] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0764] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0765] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0766] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0767] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0768] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0769] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0770] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0771] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0772] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0773] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0774] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0775] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0776] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0777] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0778] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0779] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0780] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0781] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0782] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0783] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0784] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0785] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0786] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0787] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0788] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0789] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0790] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0791] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0792] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 1.0% pseudoephedrine or phenylephrine and about 0.15% sucralose;

[0793] About 0.05% azelastine, about 0.01% steroid and about 0.1% leukotriene antagonist;

[0794] About 0.1% azelastine, about 0.01% steroid and about 0.1% leukotriene antagonist;

[0795] About 0.125% azelastine, about 0.01% steroid and about 0.1% leukotriene antagonist;

[0796] About 0.15% azelastine, about 0.01% steroid and about 0.1% leukotriene antagonist;

[0797] About 0.05% azelastine, about 0.05% steroid and about 0.1% leukotriene antagonist;

[0798] About 0.1% azelastine, about 0.05% steroid and about 0.1% leukotriene antagonist;

[0799] About 0.125% azelastine, about 0.05% steroid and about 0.1% leukotriene antagonist;

[0800] About 0.15% azelastine, about 0.05% steroid and about 0.1% leukotriene antagonist;

[0801] About 0.05% azelastine, about 0.1% steroid and about 0.1% leukotriene antagonist;

[0802] About 0.1% azelastine, about 0.1% steroid and about 0.1% leukotriene antagonist;

[0803] About 0.125% azelastine, about 0.1% steroid and about 0.1% leukotriene antagonist;

[0804] About 0.15% azelastine, about 0.1% steroid and about 0.1% leukotriene antagonist;

[0805] About 0.05% azelastine, about 0.01% steroid and about 0.5% leukotriene antagonist;

[0806] About 0.1% azelastine, about 0.01% steroid and about 0.5% leukotriene antagonist;

[0807] About 0.125% azelastine, about 0.01% steroid and about 0.5% leukotriene antagonist;

[0808] About 0.15% azelastine, about 0.01% steroid and about 0.5% leukotriene antagonist;

[0809] About 0.05% azelastine, about 0.05% steroid and about 0.5% leukotriene antagonist;

[0810] About 0.1% azelastine, about 0.05% steroid and about 0.5% leukotriene antagonist;

[0811] About 0.125% azelastine, about 0.05% steroid and about 0.5% leukotriene antagonist;

[0812] About 0.15% azelastine, about 0.05% steroid and about 0.5% leukotriene antagonist;

[0813] About 0.05% azelastine, about 0.1% steroid and about 0.5% leukotriene antagonist;

[0814] About 0.1% azelastine, about 0.1% steroid and about 0.5% leukotriene antagonist;

[0815] About 0.125% azelastine, about 0.1% steroid and about 0.5% leukotriene antagonist;

[0816] About 0.15% azelastine, about 0.1% steroid and about 0.5% leukotriene antagonist;

[0817] About 0.05% azelastine, about 0.01% steroid and about 5.0% leukotriene antagonist;

[0818] About 0.1% azelastine, about 0.01% steroid and about 5.0% leukotriene antagonist;

[0819] About 0.125% azelastine, about 0.01% steroid and about 5.0% leukotriene antagonist;

[0820] About 0.15% azelastine, about 0.01% steroid and about 5.0% leukotriene antagonist;

[0821] About 0.05% azelastine, about 0.05% steroid and about 5.0% leukotriene antagonist;

[0822] About 0.1% azelastine, about 0.05% steroid and about 5.0% leukotriene antagonist;

[0823] About 0.125% azelastine, about 0.05% steroid and about 5.0% leukotriene antagonist;

[0824] About 0.15% azelastine, about 0.05% steroid and about 5.0% leukotriene antagonist;

[0825] About 0.05% azelastine, about 0.1% steroid and about 5.0% leukotriene antagonist;

[0826] About 0.1% azelastine, about 0.1% steroid and about 5.0% leukotriene antagonist;

[0827] About 0.125% azelastine, about 0.1% steroid and about 5.0% leukotriene antagonist;

[0828] About 0.15% azelastine, about 0.1% steroid and about 5.0% leukotriene antagonist;

[0829] About 0.05% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0830] About 0.1% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0831] About 0.125% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0832] About 0.15% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0833] About 0.05% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0834] About 0.1% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0835] About 0.125% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0836] About 0.15% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0837] About 0.05% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0838] About 0.1% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0839] About 0.125% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0840] About 0.15% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.05% sucralose;

[0841] About 0.05% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0842] About 0.1% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0843] About 0.125% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0844] About 0.15% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0845] About 0.05% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0846] About 0.1% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0847] About 0.125% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0848] About 0.15% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0849] About 0.05% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0850] About 0.1% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0851] About 0.125% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0852] About 0.15% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.05% sucralose;

[0853] About 0.05% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0854] About 0.1% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0855] About 0.125% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0856] About 0.15% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0857] About 0.05% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0858] About 0.1% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0859] About 0.125% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0860] About 0.15% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0861] About 0.05% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0862] About 0.1% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0863] About 0.125% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0864] About 0.15% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.05% sucralose;

[0865] About 0.05% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0866] About 0.1% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0867] About 0.125% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0868] About 0.15% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0869] About 0.05% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0870] About 0.1% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0871] About 0.125% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0872] About 0.15% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0873] About 0.05% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0874] About 0.1% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0875] About 0.125% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0876] About 0.15% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.1% sucralose;

[0877] About 0.05% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0878] About 0.1% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0879] About 0.125% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0880] About 0.15% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0881] About 0.05% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0882] About 0.1% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0883] About 0.125% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0884] About 0.15% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0885] About 0.05% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0886] About 0.1% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0887] About 0.125% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0888] About 0.15% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.1% sucralose;

[0889] About 0.05% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0890] About 0.1% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0891] About 0.125% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0892] About 0.15% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0893] About 0.05% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0894] About 0.1% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0895] About 0.125% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0896] About 0.15% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0897] About 0.05% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0898] About 0.1% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0899] About 0.125% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0900] About 0.15% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.1% sucralose;

[0901] About 0.05% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0902] About 0.1% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0903] About 0.125% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0904] About 0.15% azelastine, about 0.01% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0905] About 0.05% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0906] About 0.1% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0907] About 0.125% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0908] About 0.15% azelastine, about 0.05% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0909] About 0.05% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0910] About 0.1% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0911] About 0.125% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0912] About 0.15% azelastine, about 0.1% steroid, about 0.1% leukotriene antagonist and about 0.15% sucralose;

[0913] About 0.05% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0914] About 0.1% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0915] About 0.125% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0916] About 0.15% azelastine, about 0.01% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0917] About 0.05% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0918] About 0.1% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0919] About 0.125% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0920] About 0.15% azelastine, about 0.05% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0921] About 0.05% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0922] About 0.1% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0923] About 0.125% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0924] About 0.15% azelastine, about 0.1% steroid, about 0.5% leukotriene antagonist and about 0.15% sucralose;

[0925] About 0.05% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0926] About 0.1% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0927] About 0.125% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0928] About 0.15% azelastine, about 0.01% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0929] About 0.05% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0930] About 0.1% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0931] About 0.125% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0932] About 0.15% azelastine, about 0.05% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0933] About 0.05% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0934] About 0.1% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0935] About 0.125% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0936] About 0.15% azelastine, about 0.1% steroid, about 5.0% leukotriene antagonist and about 0.15% sucralose;

[0937] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0938] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0939] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0940] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0941] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0942] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0943] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0944] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0945] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0946] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0947] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0948] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.1% montelukast;

[0949] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0950] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0951] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0952] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0953] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0954] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0955] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0956] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0957] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0958] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0959] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0960] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 0.5% montelukast;

[0961] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0962] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0963] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0964] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0965] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0966] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0967] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0968] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0969] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0970] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0971] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0972] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone and about 5.0% montelukast;

[0973] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0974] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0975] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0976] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0977] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0978] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0979] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0980] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0981] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0982] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0983] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0984] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.05% sucralose;

[0985] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0986] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0987] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0988] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0989] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0990] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0991] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0992] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0993] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0994] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0995] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0996] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.05% sucralose;

[0997] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[0998] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[0999] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[1000] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[1001] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[1002] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[1003] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[1004] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[1005] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[1006] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[1007] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[1008] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.05% sucralose;

[1009] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1010] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1011] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1012] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1013] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1014] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1015] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1016] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1017] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1018] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1019] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1020] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.1% sucralose;

[1021] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1022] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1023] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1024] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1025] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1026] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1027] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1028] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1029] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1030] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1031] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1032] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.1% sucralose;

[1033] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1034] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1035] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1036] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1037] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1038] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1039] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1040] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1041] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1042] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1043] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1044] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.1% sucralose;

[1045] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1046] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1047] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1048] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1049] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1050] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1051] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1052] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1053] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1054] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1055] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1056] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.1% montelukast and about 0.15% sucralose;

[1057] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1058] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1059] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1060] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1061] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1062] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1063] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1064] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1065] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1066] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1067] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1068] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 0.5% montelukast and about 0.15% sucralose;

[1069] About 0.05% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1070] About 0.1% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1071] About 0.125% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1072] About 0.15% azelastine, about 0.01% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1073] About 0.05% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1074] About 0.1% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1075] About 0.125% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1076] About 0.15% azelastine, about 0.05% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1077] About 0.05% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1078] About 0.1% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1079] About 0.125% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

[1080] About 0.15% azelastine, about 0.1% fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone, about 5.0% montelukast and about 0.15% sucralose;

Chewable and/or Orally Dissolving Formulations

Chewable Formulations

[1081] In addition to the solid dosage forms disclosed throughout, the present invention also provides chewable oral formulations. In certain such embodiments, the formulations will comprise (or consist essentially of) an effective amount of azelastine (e.g., azelastine HCl) along with suitable excipients that allow the formulations to be chewed by the patient. In additional embodiments, the formulations can further comprise one or more taste-masking or sweetening agents, such as those described herein. In one embodiment, sucralose is used in the chewable formulations. Additional active agents, such as those described herein, can also optionally be added to the chewable formulations. The amounts of azelastine, other optional active agents (e.g., steroids, decongestants, leukotriene antagonists, and combinations thereof), and sweetening agents (e.g., sucralose) in the chewable formulations of the present invention are readily determinable by those of

ordinary skill in the art, and include those amounts and combinations described herein. For example, the chewable formulations of the present invention comprise (or consist essentially of) about 0.05% to about 5% azelastine, optionally about 0.01% to about 10% other active agent(s) (or more as required), and about 0.05% to about 0.15% sucralose. Such chewable formulations are especially useful in patient populations where compliance is an issue, such as children, the elderly, and patients who may have difficulty swallowing or using spray/inhalable formulations.

[1082] The formulations may also contain colorants to improve the appearance of the chewable formulations, especially since an attractive coloration imparted by a colorant may improve patient compliance. The relative amounts of the colorants selected will vary depending upon the particular hue of the individual colorants and the resultant color desired.

[1083] Any standard pharmaceutically acceptable excipient can be used in the chewable tablet formulations which provides adequate compression such as diluents (e.g., mannitol, xylitol, maltitol, lactitol, sorbitol, lactose, sucrose, and compressible sugars such as DiPac® (dextrinized sucrose), available from Austin Products Inc. (Holmdel, N.J.), binders, disintegrants, splitting or swelling agents (e.g., polyvinyl polypyrrolidone, croscarmellose sodium (e.g., Ac-Di-Sol available from FMC BioPolymer, Philadelphia, Pa.), starches and derivatives, cellulose and derivatives, microcrystalline celluloses, such as Avicel™ PH 101 or Avicel™ CE-15 (a microcrystalline modified with guar gum), both available from FMC BioPolymer, (Philadelphia, Pa.), lubricating agents (e.g., magnesium stearate), and flow agents (e.g., colloidal silicon dioxide, such as Cab-O-Sil M5® available from Cabot Corporation, Kokomo, Ind.).

[1084] Suitable amounts of sweetener (e.g., sucralose) used in the chewable formulations, will be familiar to, and can be readily determined by, those skilled in the art. In certain embodiments, the sweetener is present in an amount from about 0.05% to about 5.0% (e.g., about 0.05%, about 0.1%, about 0.125%, about 0.15%, about 0.2%, about 0.3%, about 0.4%, about 0.5%,

about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 1.25% about 1.5%, about 1.75%, about 2%, about 2.25%, about 2.5%, about 2.75%, about 3%, about 3.25%, about 3.5%, about 3.75%, about 4%, about 4.25%, about 4.5%, about 4.75% or about 5%). Those or ordinary skill in the art will appreciate that the amount of sweetener may vary depending on the strength of the particular sweetener used and the levels approved by the regulatory authorities for use in pharmaceutical products.

[1085] Suitable cyclodextrins for use in the chewable formulations of the present invention include α, β, or γ cyclodextrins, or an alkylated or hydroxyalkylated derivatives thereof, such as heptakis (2,6-di-o-methyl)-β-cyclodextrin (DIMEB), randomly methylated β-cyclodextrin (RAMEB), and hydroxypropyl β-cyclodextrin (HPβCD). A suitable cyclodextrin is β-cyclodextrin (available from Cerestar USA, Inc., Hammond, Ind. or from Roquette America, Inc., Keokuk. IA under the trade name Kleptose™). If desired, the complex of the active substance with cyclodextrin can be prepared in advance, for example, by malaxating or granulating the azelastine and any additional active substance(s) and the cyclodextrin in the presence of water, or by preparing an aqueous solution containing the azelastine and any additional active substance(s) and the cyclodextrin in the desired molar ratio. Alternatively, the azelastine and any additional active substance(s) and the cyclodextrin can be simply mixed with other excipients and adjuvants. The molar ratio of the azelastine and any additional active substance(s) to cyclodextrin is suitably from about 1.0:1.0 to about 4.0:1.0.

[1086] A typical manufacturing process for making either a single layer or bi-layer chewable tablet generally involves blending of the desired ingredients to form a uniform distribution of the azelastine (and any other active agent(s)), excipients (e.g., colorants and flavoring agents as well as others). If desired, an inclusion complex of the azelastine and any other active agent(s) and cyclodextrin (e.g., β-cyclodextrin) may be formed prior to blending into the mixture by malaxating the azelastine and any other active agent(s) and cyclodextrin in the presence of water in a planetary mixer for about 20

minutes. The mixture is then dried in a drying oven. After drying, the complex is mixed with any color/flavoring blend. The blend is then compressed into a single layer or bi-layer tablet using standard methods well-known to those skilled in the art (e.g., Kilian T-100 tablet press or Courtoy 292/43 rotary bi-layer press). The colorants and flavoring agents may be added to both layers to form a uniform presentation of the tablet. Methods for preparation of chewable tablets and various components for use in the tablets can be found throughout the detailed description section and the Examples of U.S. Patent Publication No. 2003/0215503, the disclosure of which is incorporated by reference herein for all purposes. Additional chewable/orally dissolving tablets, and methods for their manufacture, are disclosed in U.S. Patent Publication No. 2004/0265372 and U.S. Patent No. 6,270,790, the disclosures of each of which are incorporated by reference herein for all purposes.

Orally Disintegrating Tablets

[1087] In another embodiment, the present invention provides orally disintegrating/orodispersible tablets, such as those disclosed in U.S. Patent No. 6,723,348, the disclosure of which is incorporated herein by reference in its entirety for all purposes. The orally disintegrating/orodispersible tablets suitably disintegrate in the buccal cavity upon contact with saliva forming an easy-to-swallow suspension. Such tablets comprise (or consist essentially of) azelastine (e.g., azelastine HCl), and optionally, one or more additional active agents (such as those described herein), in the form of coated granules, and a mixture of excipients comprising at least one disintegrating agent, a soluble diluent agent, a lubricant and optionally a swelling agent, an antistatic (fluid flow) agent, a permeabilising agent, taste-masking agents/sweeteners, flavoring agents and colors. In certain such embodiments, the disintegrating/orodispersible tablets comprise the taste-masking agent sucralose. The amounts of azelastine, other optional active agents (e.g., steroids, decongestants, leukotriene antagonists, and combinations thereof),

and sweetening agents (e.g., sucralose) in the orally disintegrating tablet formulations of the present invention are readily determinable by those of ordinary skill in the art, and include those amounts and combinations described herein. For example, the orally disintegrating tablet formulations of the present invention comprise about 0.1% to about 0.15% azelastine, optionally about 0.01% to about 10% other active agent(s) (or more as required), and about 0.05% to about 0.15% sucralose.

[1088] In suitable embodiments, the particles/granules of azelastine (and any other optional active agents) have a particle size such that about 100% of the particles have an average size of less than about 50 μm. In suitable such embodiments, azelastine (and any other optional active agents) are present as coated granules.

[1089] In one embodiment, the disintegrating tablets according to the invention comprise coated granules of azelastine (and optionally, one or more additional active agents) or one of its pharmaceutically acceptable salts (such as azelastine HCl), a taste-masking agent such as sucralose, and a mixture of excipients, the ratio of the mixture of excipients to the coated granules suitably is about 0.4:1 to about 9:1, more suitable about 1.5:1 to about 5:1, or about 2 to 3 parts by weight, the mixture of excipients suitably comprising: at least one disintegrating agent, a soluble diluent agent, a lubricant, and optionally a permeabilising agent, a swelling agent, an antistatic agent, flavoring agents and one or more coloring agents.

[1090] In suitable embodiments, the disintegrating agent is selected from the group consisting of croscarmellose, available as e.g. Ac-di-sol™, crospovidone available as e.g. Kollidon CL™, sodium starch glycolate and mixtures thereof.

[1091] According to one embodiment of the invention, the soluble diluent is a polyol having less than 13 carbon atoms and being either in the form of a directly compressible product with an average particle size of about 100 to 500 μm, or in the form of a powder with an average particle size of less than about 100 μm, this polyol suitably being selected from the group consisting of

mannitol, xylitol, sorbitol and maltitol. The proportion of disintegrating agent suitably is from about 3 to about 15% by weight, e.g., about 5 to about 15% by weight, and in the case of a mixture, each disintegrating agent being present between about 1 and about 10% by weight, e.g., about 5 to about 10% by weight, and the proportion of soluble diluent agent being about 30 to about 90% by weight, e.g., about 40 to about 60% by weight, based in each case on the weight of the tablet.

[1092] Suitable lubricants for use in the disintegrating tablets include, but are not limited to, magnesium stearate, stearic acid, sodium stearyl fumarate, micronised polyoxyethyleneglycol (micronised Macrogol 6000), leukine, sodium benzoate and mixtures thereof. The amount of lubricant generally is from about 0 to about 3%, e.g., from about 1 to about 2% by weight, based on the weight of the tablet. The lubricant can be dispersed within the mixture of excipients, or according to one embodiment, sprayed over the outer surface of the tablet. Thus, according to one embodiment of the disintegrating tablets of the invention, the lubricant is in powder form and is, at least in part, disposed on the surface of the tablets.

[1093] The permeabilising agent allows the creation of a hydrophilic network which facilitates the penetration of saliva and hence assists the disintegration of the tablet. Suitable permeabilising agent include, but are not limited to, silica with a high affinity for aqueous solvents, such as colloidal silica (Aerosil™), precipitated silica (Syloid™ FP 244), maltodextrins, β-cyclodextrins and mixtures thereof. The amount of permeabilising agent suitably is between about 0 and about 5%, e.g., from about 0.5 to about 2% by weight, based on the weight of the tablet.

[1094] A swelling agent can be incorporated in the mixture of excipients. Suitable swelling agents include, but are not limited to, starch, modified starch or microcrystalline cellulose.

[1095] An antistatic agent can also be incorporated as a flow aid. Suitable antistatic agents include, but are not limited to, micronised or non-micronised

talc, fumed silica (Aerosil™ R972), colloidal silica (Aerosil™ 200), precipitated silica (Syloid™ FP 244), and mixtures thereof.

[1096] According to one such embodiment of the invention, the granules of azelastine or one of its pharmaceutically acceptable salts (and optionally, one or more additional active agents such as those described herein) are characterized in that the granules are coated and comprise microcrystals of azelastine or one of its pharmaceutically acceptable salts (e.g., azelastine HCl), sucralose, at least one binder, and optionally a diluent agent, an antistatic agent, and a coloring agent. Furthermore, the granulation excipients can also include disintegrating agents and/or surfactants.

[1097] Suitable binders include, but are not limited to, cellulosic polymers, such as ethylcellulose, hydroxypropylcellulose and hydroxypropylmethyl cellulose, acrylic polymers, such as insoluble acrylate ammoniomethacrylate copolymer, polyacrylate or polymethacrylic copolymer, povidones, copovidones, polyvinylalcohols, alginic acid, sodium alginate, starch, pregelatinized starch, sucrose and its derivatives, guar gum, polyethylene glycol, for example an acrylic polymer, such as Eudragit™ E100, and mixtures thereof.

[1098] Optionally, in order to enhance the granulation of the azelastine (and one or more additional active agents) or one of its pharmaceutically acceptable salts, a diluent agent can be used. Suitable diluent agents include, but are not limited to, microcrystalline cellulose, sucrose, dicalcium phosphate, starches, lactose and polyols of less than 13 carbon atoms, such as mannitol, xylitol, sorbitol, maltitol, pharmaceutically acceptable amino acids, such as glycin, and their mixtures.

[1099] In one embodiment, a granule of azelastine or one of its pharmaceutically acceptable salts (as well as any additional active agents, such as those described herein), can be in the form of a core of granulated microcrystals of azelastine, coated with at least one layer comprising azelastine. Such a coated core is characterized in that the core and the layer comprise each from 70% to 95%, preferably 80% to 95% by weight of

azelastine, or one of the pharmaceutically acceptable salts thereof, the balance to 100% being formed with at least one binder and optionally sucralose, and that the coated core is suitably a sphere. See e.g., French patent application FR 00 14803, the disclosure of which is incorporated by reference herein.

[1100] In one embodiment of the invention, the granules can comprise (or consist essentially of): from about 10% to about 95%, e.g., from about 50% to about 70% of azelastine or a pharmaceutically acceptable salt thereof (e.g., azelastine HCl) and optionally one or more additional active agents, such as those described herein, at most about 20% by weight of the binder, relative to the weight of azelastine, or one of the pharmaceutically acceptable salts thereof, at most about 5%, suitably about 2% by weight of the antistatic agent, relative to the weight of said granules, suitably about 0.05% to about 5% sucralose and optionally a diluent agent for the balance to 100%.

[1101] The granules can also be coated with a coating composition comprising at least one coating polymer selected from the group consisting of cellulosic polymers, acrylic polymers and their mixtures. Among the cellulosic polymers, ethylcellulose, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC), can be used. Among the acrylic polymers, insoluble acrylate ammonio-methacrylate copolymer (Eudragit™ RL100 or RS100 or Eudragit™ RL30D or RS30D), polyacrylate (Eudragit™NE30D), or methacrylic copolymers (e.g., Eudragit™ L100-55 Eudragit™ L30D, Eudragit™ E100 and Eudragit™ EPO) can be used, alone, in combination, or in admixture with pH-dependent polymers. Eudragit™ E100 or a mixture of Eudragit™ EPO and Eudragit™ NE30D are suitably used. In one embodiment, the binder and the coating polymer are the same polymer.

[1102] Optionally, permeabilising agents, plasticizers, soluble agents, disintegrating agents and surfactants, can be added as coating additives. Suitable plasticizers include, but are not limited to, triacetine, triethylacetate, triethylcitrate (Eudraflex™), ethylphthalate, or mixtures thereof. The plasticizer is used in proportions of at most about 30%, preferably 10% by

weight of the coating polymers. Suitable soluble agents include polyols having less than 13 carbon atoms. Surfactants may be an anionic, nonionic, cationic, zwitterionic or amphoteric surfactant. Suitable disintegrating agents include, but are not limited to, croscarmellose, available as e.g. Ac-di-sol™, crospovidone available as e.g. Kollidon CL™, and mixtures thereof.

[1103] Suitably, the coated granules according to the present invention have a particle size distribution between about 150 μm and about 500 μm, more suitably between about 150 μm and about 425 μm, such that at least 50%, more suitably at least 70% of the granules have a particle size ranging between about 150 and about 425 μm, and less than 15% of the granules have a particle size less than about 150 μm.

[1104] In one embodiment, the coated granules according to the invention comprise: from about 10% to about 95%, preferably about 40 to about 75% of granules of azelastine or one of its pharmaceutically acceptable salts, suitably azelastine HCl and optionally one or more optional additional active agents, such as those disclosed herein, sucralose from about 0.05% to about 5%, from about 5 to about 90%, suitably about 10 to about 70% and even more suitably from about 25 to about 55% of a coating polymer, such as Eudragit™ E100, the percentages being expressed by weight relative to the weight of the granules of azelastine, or one of its pharmaceutically acceptable salts, from about 0 to about 10% of a permeabilising agent, such as colloidal silica, the percentages being expressed by weight relative to the weight of the coating polymer.

Effervescent Formulations

[1105] In another embodiment, the present invention provides a solid, effervescent, rapidly dissolving dosage form of azelastine for oral administration, such as disclosed in U.S. Patent No. 6,245,353, the disclosure of which is incorporated by reference herein in its entirety. In such an embodiment, the effervescent formulation comprise (or consist essentially of) (a) azelastine or a pharmaceutically acceptable salt thereof (e.g., azelastine

HCl), and optionally one or more additional active agents such as those disclosed herein, (b) an effervescent base comprising at least one of (i) at least one of (1) an organic edible acid and (2) a salt thereof, (ii) at least one of an alkali metal and an alkaline earth metal carbonate and bicarbonate, and (c) optionally a pharmaceutically acceptable auxiliary ingredient. In certain suitable embodiments, the effervescent formulations further comprise one or more taste-masking agents, such as sucralose, and/or other taste-masking agents described herein. The amounts of azelastine, other optional active agents (e.g., steroids, decongestants, leukotriene antagonists, and combinations thereof), and sweetening agents (e.g., sucralose) in the effervescent formulations of the present invention are readily determinable by those of ordinary skill in the art, and include those amounts and combinations described herein. For example, the effervescent formulations of the present invention comprise about 0.1% to about 0.15% azelastine, optionally about 0.01% to about 10% other active agent(s) (or more if required), and about 0.05% to about 0.15% sucralose.

[1106] A solution or suspension of azelastine or salt thereof is formed by adding water to the soluble or dispersible effervescent tablets or soluble granules, with evolution of CO_2 gas. The resulting effervescent solution or suspension can be ingested very easily, even by patients who have difficulties swallowing. The rapidly disintegrating tablet can also be administered so that it directly disintegrates in the mouth. A rapid release of the active ingredient is of particular importance here, to ensure a rapid onset of action.

[1107] Effervescent agents capable of releasing CO_2, which can be used in the present invention, include alkali metal carbonates or alkali metal bicarbonates, such as sodium carbonate or sodium bicarbonate. Agents for inducing CO_2 release which are suitably employed are edible organic acids, or their acidic salts, which are present in solid form and which can be formulated with the azelastine active ingredient and the other auxiliary ingredients (as well as any other active agents) to provide granules or tablets, without premature evolution of CO_2. Edible organic acids which can be so used include for

example, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, ascorbic acid, maleic acid or citric acid. Pharmaceutically acceptable acidic salts include, for example, salts of polybasic acids which are present in solid form and in which at least one acid function is still present, such as sodium dihydrogen or disodium hydrogen phosphate or monosodium or disodium citrate.

[1108] In one embodiment, the present invention provides effervescent azelastine formulations including the formulations and compositions described herein, having an effervescent base comprising (a) a mixture of calcium carbonate with an organic edible acid; (b) a mixture of calcium carbonate, sodium carbonate, sodium bicarbonate and an organic edible acid; or (c) a mixture of sodium bicarbonates, sodium carbonate and an organic edible acid.

[1109] The soluble or dispersible effervescent azelastine tablets or the soluble granules suitably comprise (or consisting essentially of) from about 0.5 mg to about 10 mg azelastine (or salt thereof, e.g., azelastine HCl) and from about 50 mg to about 5000 mg, suitably from about 500 mg to about 3000 mg of an effervescent base, optionally, along with other active agents (such as those described herein) and excipients, including taste-masking agents such as sucralose, suitably at about 0.05% to about 5%.

[1110] The effervescent base suitably comprises from about 100 mg to about 500 mg calcium ions as, for example, calcium carbonate, and from about 20 mg to about 1500 mg citric acid and/or its salts. In another embodiment, the effervescent base comprises from about 50 mg to about 2000 mg sodium bicarbonate, from about 20 mg to about 200 mg of sodium carbonate and from about 20 mg to about 1500 mg citric acid and/or from about 20 mg to about 500 mg tartaric acid.

[1111] An additional suitable composition of the effervescent base comprises from about 50 mg to about 500 mg sodium bicarbonate, from about 20 mg to about 100 mg sodium carbonate, and from about 50 mg to about 750 mg calcium carbonate and from about 100 mg to about 1500 mg of citric acid.

[1112] The soluble/dispersible tablets can be prepared by known processes for preparing effervescent bases, such as those disclosed in U.S. Patent No. 6,245,353, the disclosure of which is incorporated herein by reference in its entirety.

Orally Dissolving/Consumable Films

[1113] Another embodiment of the present invention is directed to a physiologically acceptable film that is particularly well-adapted to dissolve in the oral cavity of a warm-blooded animal including humans, and adhere to the mucosa of the oral cavity, to allow delivery of azelastine or a salt thereof, e.g., azelastine HCl, and optionally one or more additional active agents such as those described herein. Such physiologically acceptable films suitable for use in accordance with this aspect of the present invention are disclosed in U.S. Patent Application No. 2004/0247648, the disclosure of which is incorporated herein by reference in its entirety.

[1114] In one such embodiment of the present invention, an orally dissolving/ consumable film comprises a modified starch, azelastine or a salt thereof, e.g., azelastine HCl, and optionally, one or more additional active agents such as those described herein, suitably, one or more taste-masking agents, such as sucralose, and optionally, at least one water soluble polymer. The amounts of azelastine, other optional active agents (e.g., steroids, decongestants, leukotriene antagonists, and combinations thereof), and sweetening agents (e.g., sucralose) in the orally dissolving/consumable film formulations of the present invention are readily determinable by those of ordinary skill in the art, and include those amounts and combinations described herein. For example, the orally dissolving/consumable film formulations of the present invention comprise about 0.5 mg to about 10 mg azelastine, optionally about 0.5 mg to about 10 mg other active agent(s), and about 0.05% to about 0.15% sucralose.

[1115] The consumable films of the present invention may comprise one or more of the following ingredients: water, antimicrobial agents, additional film forming agents or water soluble polymers, plasticizing agents, flavorings,

sulfur precipitating agents, saliva stimulating agents, cooling agents, surfactants, stabilizing agents, emulsifying agents, thickening agents, binding agents, coloring agents, triglycerides, polyethylene oxides, propylene glycols, additional taste-masking agents or sweeteners, fragrances, preservatives and the like, as described in US Patent No. 6,596,298, the disclosure of which is incorporated by reference herein in its entirety.

[1116] In one such embodiment, the consumable films of the present invention include a modified starch. The modified starches used in accordance with the present invention can be prepared by mechanically, chemically or thermally modifying unmodified starches. For example, modified starches may be prepared by chemically treating starches to produce, for example, acid treatment starches, enzyme treatment starches, oxidized starches, cross-bonding starches, and other starch derivatives. Starches suitable for modification to produce modified starches may be obtained from natural products such as corn, potatoes, tapioca as well as genetically modified forms of the same such as high amylose and waxy corn as well as sorghum varieties.

[1117] Examples of modified starches for use in the practice of the present invention include, but are not limited to, modified corn starches, modified tapioca starches, acid and enzyme hydrolyzed corn and/or potato starches, hypochlorite-oxidized starches, acid-thinned starches, ethylated starches, cross-bonded starches, hydroxypropylated tapioca starches, hydroxypropylated corn starches, pregelatinized modified starches, and the like. Preferred modified starches are selected from pregelatinized modified corn starches and pregelatinized modified tapioca starches.

[1118] Representative examples of commercially available modified starches useful in the present invention include PURE-COTE™ modified starches such as PURE-COTE™ B793 (a pregelatinized modified corn starch) and PURE-COTE™ B795 (a pregelatinized modified corn starch), for example, available from Grain Processing Corporation, 1600 Oregon Street, Muscatine, Iowa 52761-1494 USA.

[1119] In one such embodiment of the present invention, the modified starch is present in amounts ranging from about 1% to about 90% by weight, in another embodiment about 10% to about 90% by weight, and in yet another embodiment from about 35% to about 80% by weight of the film.

[1120] Modified starch may be included in the film alone or optionally in combination with an additional water soluble film forming polymers such as those selected from, for example, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymers, carboxyvinyl polymers, amylose, high amylose starch, hydroxypropylated high amylose starch, pectin, dextrin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and combinations thereof. A preferred water soluble polymer is pullulan. The amount of the water soluble polymer typically is up to about 99% by weight, suitably up to about 80% by weight, more suitably up to about 50% by weight, and most suitably up to about 40% by weight of the film.

Sustained Release Formulations

[1121] In another embodiment, the present invention provides sustained release azelastine formulations, such as the formulations and compositions described herein, which also comprise a taste-masking agent, such as sucralose. In additional embodiment, such sustained release formulations of the present invention can further comprise one or more additional active agents, such as those described herein.

[1122] Methods for preparing sustained release tablets, capsules, caplets, pellets and the like, as well as excipients for use in the sustained release formulations of the present invention, are well known in the art, and can be found, for example, throughout the detailed description section and the

Examples of U.S. Patent No. 5,271,946, the disclosure of which is incorporated herein by reference in its entirety for all purposes.

[1123] As discussed in U.S. Patent No. 5,271,946, the sustained release formulations of the present invention can be obtained as follows:

[1124] 1. Through binding of azelastine or a pharmaceutically acceptable salt thereof (e.g., azelastine HCl), and optionally one or more additional active agents such as those described herein, to physiologically acceptable cation exchangers. The following may, for example, be used as such cation exchangers: acrylic and methacrylic resins with exchangeable protons, acid groups: COO^- e.g. Amberlite™ IRP-64 Polystyrene resins with exchangeable Na^+, acid groups: SO_3^-, e.g. Amberlite™ IRP-69.

[1125] 2. Coating of active ingredient particles, granulate or pellet grains or azelastine-containing tablets with coatings of the following substances, or mixtures of the following substances: hydroxypropylmethyl cellulose phthalate- or acetate succinate; cellulose-, starch-, as well as polyvinyl acetate phthalate; carboxymethyl cellulose; hypromellose; carbopol starch acetate; cellulose acetae; polyvinyl acetate; methylcellulose phthalate, methylcellulose succinate, methyl cellulose phthalate succinate as well as methyl cellulose phthalic acid half ester; zein; ethyl cellulose as well as ethyl cellulose succinate; shellac; gluten; ethylcarboxyethyl cellulose; ethacrylate- maleic acid anhydride copolymer; maleic acid anhydride vinyl methyl ether copolymer; sterol maleic acid copolymerizate; 2-ethylhexylacrylate maleic acid anhydride; crotonic acid vinyl acetate copolymer; glutaminic acid/glutaminic acid ester copolymer; carboxymethylethyl cellulose glycerin mono-octanoate; cellulose acetate succinate; polyarginin; fats, oils, waxes, fatty alcohols; anionic polymerizates of methacrylic acid and methacrylic acid esters (Eudragit™L, Eudragit™S); copolymerizates of acrylic and methacrylic acid esters with a low ammonium group (Eudragit™RS) content, as well as copolymers of acrylic and methacrylic acid esters and trimethyl ammonium methacrylate (Eudragit™RL), copolymerizates of acrylic acid ethyl- and methacrylic acid methyl esters 70:30 (Eudragit™NE 30 D), copolymerizates

of acrylic acid, methacrylic acid as well as their esters (ratio of the free carboxyl groups to the ester groups for example 1:1) (Eudragit™L 30 D).

[1126] Such sustained release formulations may also contain conventional softeners (e.g. dibutyl sebacate, citric and tartaric acid esters, glycerin and glycerin esters, phthalic acid esters and similar substances). It also is possible to add water-soluble substances such as polyethylene glycols, polyvinylpyrrolidone, copolymerizates of polyvinylpyrrolidone and polyvinyl acetate, hydroxypropyl cellulose, hydroxypropylmethyl cellulose. The addition of solids such as talcum and/or magnesium stearate to the coating is also possible.

[1127] Organic acids (such as for example citric acid, tartaric acid, maleic, fumaric, ascorbic acid) may also be incorporated into the pellet grains, granulate grains or tablets.

[1128] 3. Coating of pressed disks, tablets, granulates containing the azelastine or salt thereof, and optionally one or more additional active agents such as those described herein, and one or more osmotically active substances, (e.g. mannitol, sorbitol and the like) with a semi-permeable membrane, e.g. of 70 to 90 weight% of cellulose acetate and hydroxypropylmethyl cellulose or hypromellose (30 to 10 weight%).

[1129] Other osmotically active substances that can be used include organic and inorganic compounds or soluble substances which generate an osmotic pressure gradient as compared to the outer liquid via the semi-permeable wall. Osmotically active agents or osmotically active compounds include magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium hydrogen phosphate, urea, saccharose and the like. Other osmotically active agents are disclosed in U.S. Pat. Nos. 3,854,770, 4,077,407 and 4,235,236, the disclosures of each of which are incorporated herein by reference in their entireties.

[1130] Semi-permeable materials which can be used as polymers for osmosis and reverse osmosis are, for example: cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate,

β-glucan acetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, polyamide, polyurethane, sulphonated polystyrene, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylamino acetate, cellulose acetate chloracetate, cellulose dipalmitate, cellulose dioctanoate, cellulose dicaprylate, cellulose dipentanate, cellulose acetate valerate, cellulose acetate-p-toluene sulphonate, cellulose acetate butyrate, ethyl cellulose, selectively permeable polymers which are formed by joint precipitation of a polycation and a polyanion as disclosed in U.S. Pat. Nos. 3,173,876, 3,276,586, 3,541,005, 3,541,006 and 3,546,142, the disclosures of which are incorporated by reference herein in their entireties. Coatings of this type in semi-permeable membranes may for example also be effected according to U.S. Patent Nos. 4,455,143 and 4,449,983, the disclosures of which are incorporated by reference herein.

[1131] The proportion of osmotically active substance can be from about 10 to about 800 parts by weight, suitably about 20 to about 600, and more suitably about 50 to about 400 parts by weight, based on 1 part by weight of azelastine. The amount of coating substances applied is such that the semi-permeable membrane is about 50 to about 500 μm, suitably about 100 to about 300 μm thick.

[1132] 4. Embedding of or binding azelastine (or salt thereof) and/or any other optional additional active agent(s) to the following substances or mixtures of these substances:

[1133] Digestible fats, such as triglycerides of saturated fatty acids, $C_8H_{16}O_2$ to $C_{18}H_{36}O_2$, and mixtures thereof, peanut oil and hydrated peanut oil, castor oil and hydrated castor oil, olive oil, sesame oil, cottonseed oil and hydrogenated cottonseed oil, corn oil, wheat germ oil, sunflower seed oil, cod liver oil, mixtures of mono-, di- and triesters of palmitic and stearic acid with glycerine, glycerine trioleate, diglycol stearate, stearic acid.

[1134] Indigestible fats or fat-like substances, for example esters of aliphatic saturated or unsaturated fatty acids (2 to 22 carbon atoms, in particular 10 to

18 carbon atoms) with monovalent aliphatic alcohols (1 to 20 carbon atoms), carnauba wax, beeswax, fatty alcohols (straight chain or branched) of chain length $C_8H_{17}OH$ to $C_{30}H_{61}OH$, in particular $C_{12}H_{25}OH$ to $C_{24}H_{49}OH$.

[1135] Polymers such as polyvinyl alcohol, polyvinyl chloride, polyacrylic acid (Carbopol™); anionic polymerizates of methacrylic acid and methacrylic acid esters (Eudragit™L, Eudragit™S), acrylic and methacrylic acid ester copolymerizates with trimethyl ammonium methacrylate (Eudragit™RL, Eudragit™RS).

[1136] Copolymerizates of ethyl acrylates and methyl methacrylates (Eudragit™NE 30 D), as well as of acrylic acid, methacrylic acid as well as esters thereof (ratio of free carboxyl groups to ester groups 1:1) (Eudragit™L 30 D), polyethylene, polyglycolic acid, polyhydroxybutyric acid, polylactic acid, copolymers of lactic acid and glycolic acid (manufacturer: Boehringer Ingelheim), copolymers of lactic acid and ethylene oxide, copolymers of glycolic acid and ethylene oxide, copolymers of lactic acid and hydroxybutyric acid, hydroxypropylmethyl cellulose- phthalate or -acetate succinate; cellulose acetate phthalate, starch acetate phthalate as well as polyvinyl acetate phthalate; carboxymethyl cellulose; methylcellulose phthalate, -succinate, -phthalate succinate, methyl cellulose phthalic acid half ester; zein; ethyl cellulose; shellac, gluten; ethylcarboxyethyl cellulose; ethacrylate maleic acid anhydride copolymer; maleic acid anhydride vinyl methyl ether copolymer; styrene maleic acid copolymerizate; 2-ethylhexyl acrylate maleic acid anhydride; crotonic acid vinyl acetate copolymer; glutaminic acid/glutaminic acid ester copolymer; carboxymethyl cellulose glycerine mono-octanoate; cellulose acetate succinate; polyarginine; cross-linked alginate; cross-linked gelatin.

[1137] Swelling agents such as methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose (Pharmacoat, Methocel E (propylene glycol ether of methyl cellulose)), alginic acid and their salts (Na^-, Ca^- salt, also mixtures of sodium alginate and calcium salts such as $CaHPO_4$), starch, carboxymethyl starch, carboxymethyl cellulose and their salts (e.g. Na^- salts),

galacto mannan, gum arabic, karaya rubber, ghatti gum, agar-agar, carrageen, xanthan rubber, guar rubber and its derivatives, carob bean flour, propylene glycol alginate, pectin, tragacanth.

[1138] The amounts of azelastine or salt thereof, and optionally one or more additional active agents such as those described herein, in the formulations of the invention are about 0.1 mg to about 50 mg, suitably about 0.2 mg to about 30 mg, and more suitably about 0.5 mg to about 20 mg of azelastine.

[1139] Suitable exemplary sustained release components are:

[1140] a) Cation exchangers: Sodium poly(styrene, divinylbenzene)sulphonate (e.g. Amberlite™IRP 69). Suitably 3 to 10 parts of Amberlite™IRP 69 are for example used per 1 part of azelastine (base).

[1141] b) Coating substances: Hydroxypropylmethyl cellulose phthalate, suitably at 1.5 to 3 parts of hydroxypropyl methyl cellulose phthalate 55 are used per 1 part of azelastine. Ethyl cellulose, suitably 0.1 to 1 part of ethyl cellulose are used per 1 part of azelastine. Eudragit resins, for example Eudragit™RS 0.01 to 0.1 part of Eudragit™RS per 1 part of azelastine.

[1142] c) Semi-permeable layers with osmotically acting active substance containing core and outlet openings: Coating with 100 to 300 μm thick layer of 82% cellulose acetate and 18% hydroxypropyl methyl cellulose.

[1143] d) Embedding substances: Hydrocolloids e.g. hydroxypropyl methyl cellulose: 2 to 10 parts of hydrocolloid per 1 part of azelastine. Eudragit™RS: 10 to 15 parts of Eudragit™RS per 1 part of azelastine. Glycerineditripalmito stearate (e.g. Precirol Ato 5) 1 to 10 parts of Precirol Ato 5 per 1 part of azelastine.

[1144] The requisite release of azelastine (and optionally, any additional active agents) of 0.05 to 5 mg per hour suitably occurs within the desired range through the parameters described herein. Should it be desired to achieve a specific release rate within this range it is possible, for example, to proceed as follows:

[1145] 1. The preparation of the coating or embedding of the active substance in the described manner.

[1146] 2. Testing of the release of active substance from the dosage form using 0.1 N HCl (2 hours) and phosphate buffer pH 6.8 (subsequently) as release medium.

[1147] 3. a) Should too much substance be released: Increase of the proportion of the sustained release component and/or reduction of the proportion of water-soluble auxiliary substances. Reduction of the proportion of osmotically active substance.

[1148] b) Should too little substance be released: Reduction of the proportion of the sustained release component and/or increase of the proportion of water soluble auxiliary substances. Increase of the proportion of osmotically active substance.

[1149] In one embodiment, a release rate of about 0.05 mg of azelastine per hour can be achieved.

Liquid Dosage Forms Free of Preservatives

[1150] While preservatives are useful in limiting concerns related to chemical degradation or bacterial growth in the liquid formulations of the present invention, the presence of these preservatives can themselves cause stinging or irritation, especially when administered to the oral or nasal mucosa, or to ocular tissue or the conjunctival sac. Therefore, in order to reduce this irritation, in one embodiment, the liquid dosage forms disclosed herein, e.g., liquid dosage forms for nasal, ocular or oral administration, such as pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs, can be prepared free, or substantially free, of preservatives. As used herein the phrase "free, or substantially free, of preservatives" means that the liquid formulations contain less than about 0.0001% (weight/volume) of a preservative, more suitably less than about 0.00001% (weight/volume) of a preservative, and most suitably, no preservative.

[1151] In order to maintain the integrity of the liquid formulations, and specifically, to protect them from bacterial contamination transferred from the patient or external environment, the delivery systems useful for applying the

various liquid formulations can be appropriately engineered to limit bacteria from entering the solutions. For example, in order to limit the introduction of bacteria or particulates that may come from the user of a nasal spray (e.g. from the nasal passage), the spray bottle can be fitted with a filter or other device to limit or prevent the introduction of such bacteria into the bottle and/or formulation. This filter can form part of the spray or dropper nozzle, or can be located within the structure of the spray or dropper bottle itself. The filter allows the various liquid formulations of the present invention to pass through the filter to the patient, but limits bacteria or particulates from the patient or the external environment from entering the nozzle and bottle. Suitable filters are known in the art and are commercially available from well-known sources, and include microporous filtration membranes made from polymers, such as, but not limited to, poly(ethersulfone), poly(vinylidene fluoride), mixed cellulose esters, and poly(tetrafluoroethylene). In general, the pore size of such membranes are on the order of less than about 0.5 microns, more suitably less than about 0.3 microns and most suitably less than or equal to about 0.22 microns. Use of such membrane filters eliminate the need for preservatives in the various liquid formulations of the present invention when utilized in nasal spray or ocular drop delivery systems.

[1152] The preservative free liquid formulations and compositions of the present invention can also be provided in single unit-dose containers. Such containers are acceptable to deliver the therapeutic dose of azelastine (or salt or ester thereof, including azelastine hydrochloride) and optionally one or more additional active agents (such as those described herein) to the eyes, nose or mouth. In certain such embodiments of the invention, the compositions can be effectively contained in a package comprising a high density polyethylene (HDPE) container produced using a blow-fill-seal manufacturing technique with a volume capacity of about 1 mL.

[1153] The use of single unit-dose conatiners eliminates the concern of contamination for the user (or other outside sources), as once the unit-dose

container is opened and a single dose of the present formulations or compositions is delivered, the container is discarded.

[1154] The preservative-free formulations of the present invention can also be used with multi-dose containers, such as, high density polyethylene bottles with a volume capacity of about 10 mL fitted with a spray pump specifically designed for use with preservative free formulations.

Formulations For Pulmonary Delivery

[1155] In further embodiments, the present invention provides formulations and compositions for pulmonary delivery of azelastine or a salt thereof, and optionally, one or more additional active agents, such as those described herein. For example, inhalable preparations comprising azelastine or a salt thereof (e.g., azelastine HCl), and optionally, one or more additional active agents such as those described herein, can be produced.

[1156] Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable solutions. Inhalable powders according to the invention containing azelastine or a salt thereof, and optionally one or more additional active ingredients including those described herein, may comprise the active ingredients on their own, or a mixture of the active ingredients with physiologically acceptable excipients. In certain such embodiments, the inhalable formulas comprise the compositions of the present invention in an inhalable form. Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile inhalable solutions ready for use. The preparations according to the invention may comprise azelastine or a salt thereof and optionally one or more additional active ingredients including those described herein, in one formulation, or in two or more separate formulations.

[1157] Physiologically acceptable excipients that may be used to prepare the inhalable powders according to the present invention include, but are not limited to, monosaccharides (e.g., glucose or arabinose), disaccharides (e.g., lactose, saccharose, maltose), oligo- and polysaccharides (e.g., dextran),

polyalcohols (e.g., sorbitol, mannitol, xylitol), salts (e.g., sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Suitably, mono- or disaccharides are used, for example, lactose or glucose in the form of their hydrates. Lactose and lactose monohydrate represent exemplary excipients. Excipients for use in the inhalable preparations can have an average particle size of up to about 250 μm, suitably between about 10 μm and about 150 μm, most suitably between about 15 μm and about 80 μm. In certain such embodiments, finer excipient fractions can be added with an average particle size of about 1 μm to about 9 μm. These finer excipients are also selected from the group of possible excipients disclosed throughout. Finally, in order to prepare the inhalable powders according to the present invention, micronised active ingredients (e.g., azelastine and optionally one or more additional agents described throughout), suitably with an average particle size of about 0.5 μm to about 10 μm, more suitably from about 1 μm to about 5 μm, are added to the excipient mixture. Processes for producing the inhalable powders according to the present invention by grinding and micronizing and by finally mixing the ingredients together are routine and well known to those of ordinary skill in the art. The inhalable powders according to the present invention can be prepared and administered either in the form of a single powder mixture which contains azelastine or a salt thereof and optionally one or more additional active agents such as those described herein, or in the form of separate inhalable powders, in which one powder contains only azelastine or a salt thereof, and another powder contains one or more additional active agents such as those described herein. Methods for preparing the inhalable powders of the present invention, as well as devices for their delivery, are disclosed in U.S. Patent Nos. 6,696,042 and 6,620,438; U.S. Published Patent Application Nos. 2002/0009418, 2005/0121032, 2005/0121027 and 2005/0123486, the disclosures of each of which are incorporated herein by reference in their entireties.

[1158] The inhalable powders according to the present invention may be administered using inhalers well known in the art. Inhalable powders

according to the present invention which contain a physiologically acceptable excipient in addition to the active agents may be administered, for example, by means of inhalers which deliver a single dose from a supply using a measuring chamber as described in U.S. Pat. No. 4,570,630, or by other means as described in U.S. Patent Nos. 5,035,237 and 4,811,731, the disclosures of which are incorporated by reference herein in their entireties. The inhalable powders of the present invention can also be administered by dry powder inhalers (DPIs) or pre-metered DPIs (*see e.g.*, U.S. Patent Nos. 6,779,520, 6,715,486 and 6,328,034, the disclosures of each of which are incorporated herein by reference in their entireties). Suitably, the inhalable powders according to the present invention which contain physiologically acceptable excipients in addition to the active agents are packed into capsules (to produce so-called inhalettes) which are used in inhalers as described, for example, in U.S. Patent No. 5,947,118, the disclosure of which is incorporated herein by reference in its entirety. An additional DPI that can be used with the powder formulations of the present invention is the Novalizer® by Sofotec (Bad Homburg, Germany). A description of this DPI, as well as methods to formulate powders for use in it, are disclosed in U.S. Patent Nos. 5,840,279; 5,881,719; 6,071,498; and 6,681,768, the disclosures of which are incorporated herein by reference in their entireties.

[1159] According to another embodiment of the present invention, inhalation aerosols containing propellant gas comprising (or consisting essentially of) azelastine or a salt thereof and optionally, one or more additional active ingredients such as those described herein, dissolved in a propellant gas or in dispersed form, can be produced. Azelastine or a salt thereof, and one or more optional active ingredients, such as those disclosed herein, may be present in separate formulations or in a single preparation, in which all active ingredients are each dissolved, each dispersed, or one or more active components are dissolved and any others are dispersed. The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known in the art. Suitable propellant gases include, but are not limited to, hydrocarbons

such as n-propane, n-butane or isobutane and halohydrocarbons such as fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases may be used on their own or in mixtures thereof. Particularly suitable propellant gases are halogenated alkane derivatives selected from TG134a and TG227.

[1160] The propellant-driven inhalation aerosols according to the present invention may also contain other ingredients such as co-solvents, stabilizers, surfactants, antioxidants, lubricants and pH adjusters. All of these ingredients, and suitable commercial sources thereof, are well known in the art.

[1161] The inhalation aerosols containing propellant gas according to the present invention may contain up to about 5 wt % of active substances (or more if required). Aerosols according to the invention contain, for example, about 0.002 wt. % to about 5 wt. %, about 0.01 wt. % to about 3 wt. %, about 0.015 wt. % to about 2 wt. %, about 0.1 wt. % to about 2 wt. %, about 0.5 wt. % to about 2 wt. %, or about 0.5 wt. % to about 1 wt. % of active substances (e.g., azelastine or a salt thereof and optionally one or more additional active agents such as those described herein).

[1162] In embodiments where the active substance(s) are present in dispersed form, the particles of active substance(s) suitably have an average particle size of up to about 10 μm, suitably from about 0.1 μm to about 5 μm, more suitably from about 1 μm to about 5 μm.

[1163] Propellant-driven inhalation aerosols according to certain such embodiments of the present invention may be administered using inhalers known in the art (e.g., MDIs: metered dose inhalers, *see e.g.*, U.S. Patent Nos. 6,380,046, 6,615,826 and 6,260,549, the disclosures of each of which are incorporated herein by reference in their entireties). Accordingly, in another aspect, the present invention provides pharmaceutical compositions in the form of propellant-driven aerosols combined with one or more inhalers suitable for administering these aerosols. In addition, the present invention provides inhalers which are characterized in that they contain the propellant gas-containing aerosols described throughout. The present invention also

provides cartridges which are fitted with a suitable valve and can be used in a suitable inhaler and which contain one or more of the propellant gas-containing inhalation aerosols described throughout. Suitable cartridges and methods of filling these cartridges with the inhalable aerosols containing propellant gas according to the invention are known in the art.

[1164] In another embodiment, the present invention provides propellant-free inhalable formulations, such as solutions and suspensions, comprising (or consisting essentially of) azelastine or a salt thereof and optionally one or more additional active agents such as those described herein. Suitable solvents for use in such embodiments include aqueous and alcoholic solvents, suitably an ethanolic solution. The solvents may be water on its own or a mixture of water and ethanol. The relative proportion of ethanol compared with water suitably is up to about 70 percent by volume, more suitably up to about 60 percent by volume, or up to about 30 percent by volume. The remainder of the volume is made up of water. The solutions or suspensions containing azelastine or a salt thereof and optionally one or more additional active agents, such as those described herein, separately or together, are adjusted to a pH of 2 to 7, using suitable acids or bases. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid. Examples of suitable organic acids include ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid, propionic acid, etc. Exemplary inorganic acids include hydrochloric and sulfuric acids. It is also possible to use the acids which have already formed an acid addition salt with one or more of the active substances. Exemplary organic acids include ascorbic acid, fumaric acid and citric acid. If desired, mixtures of the above acids may be used, particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g., as flavorings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. Hydrochloric acid can be used to adjust the pH.

[1165] Co-solvents and/or other excipients may be added to the propellant-free inhalable formulations of the present invention. Suitable co-solvents are those which contain hydroxyl groups or other polar groups, e.g., alcohols--such as isopropyl alcohol, glycols--such as propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Suitably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soy lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilizers, complexing agents, antioxidants and/or preservatives which prolong the shelf life of the finished pharmaceutical formulation, flavorings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents.

[1166] Exemplary excipients include antioxidants such as ascorbic acid, vitamin A, vitamin E, tocopherols and similar vitamins and provitamins occurring in the human body.

[1167] Preservatives may be used to protect the inhalable formulations disclosed herein from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. The preservatives mentioned above are suitably present in concentrations of up to about 50 mg/100 ml, more suitably between about 5 and about 20 mg/100 ml. Alternatively, the inhalable formulations can be prepared without preservatives, for example, in unit-dose forms, such as described herein.

[1168] The propellant-free inhalable formulations according to the present invention can be administered using inhalers of the kind which are capable of nebulizing a small amount of a liquid formulation in the therapeutic dose within a few seconds to produce an aerosol suitable for therapeutic inhalation. Suitable inhalers are those in which a quantity of less than about 100 μL, less than about 50 μL, or between about 10 μL and about 30 μL of active substance solution can be nebulized in one spray action to form an aerosol with an average particle size of less than about 20 μm, suitably less than about 10 μm, in such a way that the inhalable part of the aerosol corresponds to the therapeutically effective quantity.

[1169] Suitable apparatuses for propellant-free delivery of a metered quantity of a liquid pharmaceutical composition according to the present invention are described for example in U.S. Patent Nos. 5,497,944; 5,662,271; 5,964,416; 6,402,055; 6,497,373; 6,726,124; and 6,918,547, the disclosures of which are incorporated herein by reference in their entireties. In another embodiment, the present invention provides pharmaceutical formulations in the form of propellant-free inhalable formulations, such as solutions or suspensions, as described herein, combined with a device suitable for administering such formulations.

[1170] The propellant-free inhalable formulations, e.g., solutions or suspensions, according to the present invention may take the form of concentrates or sterile inhalable solutions or suspensions ready for use. Formulations ready for use may be produced from the concentrates, for example, by the addition of isotonic saline solutions. Sterile formulations ready for use may be administered using energy-operated fixed or portable nebulizers which produce inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other principles.

[1171] The present invention also provides fine particle dosages of azelastine or a salt thereof (e.g., azelastine HCl) and optionally one or more additional active agents such as those described herein. A delivered fine particle dose (FPD) of azelastine or a salt thereof (e.g., azelastine HCl) administered by

inhalation herein is not limited, and may generally be in a range from about 1 to about 50 μg, including about 5, 10, 15, 20, 30 and 40 μg. The correct metered dose loaded into an inhaler to be used for the purpose of administration can be adjusted for predicted losses such as retention and more or less efficient de-aggregation of the inhaled dose.

[1172] Excipient particles having a physical median particle size larger than about 25 μm and having a very narrow particle size distribution with generally less than 5% of the particles by mass being below 10 μm generally show good flow properties, and are suitable for use in mixtures together with azelastine or a salt thereof (e.g., azelastine HCl) and optionally one or more additional active agents, such as those described herein. For inhalation purposes, carrier particles having a mass median particle size in a range from about 10 to about 250 μm are typically selected, including about 30, 50, 70, 100, 130, 160, 190, and 220 μm. The median particle size chosen within this range depends on many factors, e.g. type of carrier substance, degree of powder flowability to be attained, type of inhaler and ease of de-aggregation during inhalation of the resulting medicament. Commercial grades of Respitos are available (lactose monohydrate from DMV of several defined particle size distributions up to 400 μm) suitable as particular excipients to be used in formulations containing azelastine, e.g. grade SV003. Uniform homogeneous azelastine powder formulations having a physical median particle size down to about 10 μm can also provide good flow properties when the particles have been modified to have a very smooth surface, thereby improving the flow properties of the formulation.

[1173] A practical lower limit for volumetric dose forming for such inhalable powder formulations is in a range of about 0.5 to 1 mg. Smaller doses can be difficult to produce and still maintain a low relative standard deviation between doses in the order of 10%. Typically, though, dose masses range from about 1 to 10 mg.

[1174] Suitable excipients for inclusion in the azelastine powder formulations include, but are not limited to, monosaccarides, disaccarides, polylactides, oligo- and polysaccarides, polyalcohols, polymers, salts or mixtures from these groups, e.g. glucose, arabinose, lactose, lactose monohydrate, lactose anhydrous (i.e., no crystalline water present in lactose molecule), saccharose, maltose, dextran, sorbitol, mannitol, xylitol, sodium chloride and calcium carbonate.

[1175] Excipients for use with azelastine or a salt thereof (e.g., azelastine HCl) and optionally one or more additional active agents, such as those described herein, generally are selected from among excipients which have good moisture qualities in the sense that the substance will not adversely affect the active agent fine particle dose (FPD) for the shelf life of the product regardless of normal changes in ambient conditions during storage. Suitable "dry" excipients are well known in the art and include those disclosed herein. For example, lactose can be selected as a dry excipient, or lactose monohydrate can be used in a formulation with azelastine or a salt thereof (and optionally one or more additional active agents, such as those described herein). Lactose has the inherent property of having a low and constant water sorption isotherm. Excipients having a similar or lower sorption isotherm can also be used.

[1176] As discussed throughout, and in a further aspect of the present invention, azelastine or a salt thereof (e.g., azelastine HCl) may be mixed or formulated with one or more additional active agents such as those described herein in the dry powder or other inhalable formulations. The present invention also encompasses the use of azelastine or a salt thereof where a combination of azelastine or a salt thereof with other agents, such as those described herein, constitute a formulation from which metered doses are then produced, filled and sealed into dry, moisture-tight, high barrier seal containers intended for insertion into a DPI to be administered according to a particular dosing regime or as needed by the user. Suitable additional active agents include those disclosed throughout, for example, inhaled steroids: e.g.,

budesonid, fluticasone, rofleponide, mometasone, and/or ciclesonide; NSAIDs, e.g., ibuprofen; leukotriene antagonists, e.g., montelukast; additional antihistamines, e.g., epinastine, cetirizine, fexofenadine, olopatadine, levocabastine, loratadine, mizolastine, ketotifene, emedastine, dirnetindene, clemastine, bamipine, cexchlorpheniramine, pheniramine, doxylamine, chlorphenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastine, desloratidine and/or meclozine; beta-mimetics: e.g., formoterol, salmeterol, salbutamol and/or terbutalinsulphate; PDE IV inhibitors: e.g., 3',5'-cyclic nucleotide phosphodiesterases and derivates; adenosine A2a receptor agonists: e.g., Ribofuranosylvanamide derivates, and/or substances described in U.S. Published Patent Application No. 2003/013675, the disclosure of which is incorporated by reference herein in its entirety.

[1177] A sealed, dry, high barrier container can be loaded with a powder form azelastine or a salt thereof (e.g., azelastine HCl) and optionally one or more additional active agents, such as those described herein, in the form of a blister and may comprise a flat dose bed or a formed cavity in aluminum foil or a molded cavity in a polymer material, using a high barrier seal foil against ingress of moisture, e.g. of aluminum or a combination of aluminum and polymer materials. The sealed, dry, high barrier container may form a part of an inhaler device or it may form a part of a separate item intended for insertion into an inhaler device for administration of pre-metered doses.

[1178] The inhalable pharmaceutical formulations of the present invention that comprise (or consist essentially of) azelastine or a salt thereof (e.g., azelastine HCl) and a suitable steroid (e.g., a safe steroid) are suitably formulated as azelastine:steroid in ratios by weight ranging from about 1:300 to about 50:1, and more suitably from about 1:250 to about 40:1. In exemplary formulations which contain azelastine or a salt thereof (e.g., azelastine HCl) and a steroid selected from among budesonide, fluticasone, mometasone, and ciclesonide, the weight ratio of azelastine (or salt thereof):steroid are suitably in the range of about 1:150 to about 30:1, and more suitably from about 1:50 to 20:1.

[1179] The inhalable formulations of the present invention are especially suitable for the treatment of inflammatory (including allergic) or obstructive diseases of the upper or lower respiratory tract, including asthma and chronic obstructive pulmonary disease (COPD), and complications thereof such as pulmonary hypertension, as well as allergic and non-allergic rhinitis. In addition, the inhalable formulations according to the present invention may be used to treat cystic fibrosis and allergic alveolitis (Farmer's Lung).

[1180] The present invention also provides inhalable spray pharmaceutical compositions comprising (or consisting essentially of), a suitable concentration to provide a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carrier, stabilizer or excipient, wherein the azelastine is in a solution form and wherein at least one of the pharmaceutically acceptable carriers or excipients is sucralose dissolved in the solution. Such inhalable spray pharmaceutical compositions when used with a suitable device provide a fine spray of the components (including active and non-active components) having an average particle size of about 1 μm to about 5 μm. Such inhalable spray pharmaceutical compositions of the present invention can be formulated for pulmonary delivery using, for example, a suitable device or inhaler. Suitably the amount of azelastine in such inhalable spray pharmaceutical compositions is about 0.1% to about 10% by weight and the amount of sucralose in such inhalable spray pharmaceutical compositions is about 0.05% to about 0.15% by weight, though other suitable amounts will readily be determined by the ordinarily skilled artisan..

Clinical Indications

[1181] The compositions provided by the present invention are useful in methods for the treatment of a variety of physical disorders in animals (particularly mammals including humans) that are predisposed to or suffering from a physical disorder that may be delayed, prevented, cured or otherwise

treated by the administration of azelastine or a pharmaceutically acceptable salt or ester thereof. Thus, in additional embodiments, the invention provides methods of treating or preventing such physical disorders, comprising administering an effective amount of one or more of the compositions of the invention to an animal (particularly a mammal, including a human) that is predisposed to or suffering from such a physical disorder. As used herein, an animal that is "predisposed to" a physical disorder is defined as an animal that does not exhibit a plurality of overt physical symptoms of the disorder but that is genetically, physiologically or otherwise at risk for developing the disorder. In such situations, the compositions of the present invention may thus be used prophylactically as chemopreventive agents for such disorders.

[1182] According to the invention, a mammal (preferably a human) that is predisposed to or suffering from a physical disorder may be treated by administering to the animal an effective dose of one or more of the pharmaceutical compositions of the present invention. Physical disorders treatable with the compositions and methods of the present invention include any physical disorder that is characterized by allergic rhinitis, vasomotor rhinitis, and/or allergic conjunctivitis, inflammatory or obstructive diseases of the upper or lower respiratory tract, including asthma and chronic obstructive pulmonary diseases (COPD), and complications thereof such as pulmonary hypertension, as well as allergic and non-allergic rhinitis, cystic fibrosis and allergic alveolitis (Farmer's Lung), reactions to plant or insect allergens, environmental allergens, allergic ocular conditions (e.g., hay fever conjunctivitis, perennial allergic conjunctivitis, giant papillary conjunctivitis, vernal keratoconjunctivitis or atopic keratoconjunctivitis) and irritant dermatitis, as well as other related or similar disorders. The compositions of the invention are also useful in treating or preventing the symptoms of such disorders, and thereby provide symptomatic relief to patients suffering from or predisposed to such disorders.

Dosing

[1183] As noted above, by the invention, a composition comprising an effective amount of azelastine or a pharmaceutically acceptable salt or ester thereof (e.g., azelastine HCl), and optionally, one or more additional active agents such as those described herein, can be administered to a patient to provide symptomatic relief from a variety of disorders, including allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, as well as the various other disorders disclosed throughout and known in the art. One of ordinary skill will appreciate that the amount or concentration of azelastine (or salt or ester thereof, including azelastine hydrochloride) that constitutes "an effective amount" of azelastine can be determined empirically. Non-limiting examples of effective amounts of azelastine (or salt or ester thereof, including azelastine hydrochloride) for use in the pharmaceutical compositions of the present invention include those described in detail herein. It also will be understood that, when administered to a human patient, the total daily usage of the compositions of the present invention will be decided or recommended by the attending physician, pharmacist or other medical practitioner within the scope of sound medical judgment.

[1184] The intranasal formulations of this invention are most effective when proper product design is utilized. The preferred product design includes a composition of the invention contained within a delivery system, such as a bottle and a pump, for nasal delivery of the formulation in a mist of spray droplets to coat the mucosa of the nasal cavity upon administration. Preferred pumps for use in such products of the invention are metered multi-dose pumps; however, single unit-dose containers are also acceptable to deliver the therapeutic dose of azelastine (or salt or ester thereof, including azelastine hydrochloride) to the nasal cavity. The selection of the pump is based on the desired dose/spray volume and spray pattern appropriate for local delivery to the nasal mucosa. In certain such embodiments of the invention, the compositions can be effectively contained in a package comprising a high density polyethylene bottle fitted with a screw cap, and are delivered by a

metered-dose spray pump designed for intranasal application in volumes of 0.07 to 0.15 ml such as the VP3/140 18/415 or the VP3/140F 18/415 Spigot 522 pumps designed by Valois Pharm, Marly le Roi, France. In addition, the intranasal formulations can be provided in a unit dose form, such as described herein.

[1185] The ocular formulations of this invention are also most effective when proper product design is utilized. The preferred product design includes a composition of the invention contained within a delivery system, such as a bottle and a dropper, for ocular delivery of the formulation to coat the conjunctival sac of the eyes upon administration. Preferred packages for use in such products of the invention are multi-dose; however, single unit-dose containers are also acceptable to deliver the therapeutic dose of azelastine (or salt or ester thereof, including azelastine hydrochloride) to the eyes. In certain such embodiments of the invention, the compositions can be effectively contained in a package comprising a high density polyethylene bottle (HDPE) in volume capacity of 10 mL fitted with a low density polyethylene dropper and secured with a HDPE cap closure. In addition, the ocular formulations can be provided in a unit dose form, such as described herein.

[1186] Suitable compositions of the present invention include about 0.1%, about 0.125% or about 0.15% azelastine, and about 0.05%-0.15% sucralose. Described below are non-limiting examples of the compositions of the present invention, comprising 0.05%, 0.1% or 0.15% azelastine hydrochloride, 0.1% to 0.3% of hypromellose as a thickener, 0.05% to 0.15% of sucralose as a sweetening and taste-masking agent, and/or 0.05% menthol as a taste-masking/flavoring agent. Suitable such compositions can also comprise one or more additional active agents such as those described herein at the various concentrations and amounts described herein. These compositions are well-tolerated despite the intense bitterness contributed by the presence of azelastine hydrochloride. Thus, use of such compositions of the invention provide symptomatic relief from allergic rhinitis, vasomotor rhinitis, or

allergic conjunctivitis, while significantly improving patient acceptability and compliance.

Treatment of Snoring

[1187] The present invention also provides a method for treating snoring that in some cases eliminates snoring entirely, and in other cases reduces the intensity and frequency of snoring. The treatment comprises administering a prescribed dosage in one or more doses per day of azelastine or a physiologically acceptable salt thereof along with a taste-masking agent. The azelastine is suitably topically applied to the nasal passage, generally in the form of a nasal spray or in other delivery forms described herein. Azelastine is administered in an amount effective to inhibit snoring and may be administered once or more than once a day. In a suitable embodiment, at least one dose is administered prior to bedtime. Published International Patent Application No. WO 02/056876, the disclosure of which is incorporated by reference herein in its entirety, describes compositions and methods for treatment of snoring that can be used in the practice of the present invention.

[1188] In one embodiment, the present invention provides a sterile and stable aqueous solution of azelastine or one or more of its salts (e.g., azelastine HCl), along with one or more taste-masking agents and optionally one or more additional active agents such as those described herein, which can be used in the form of drops, ointments, creams, gels, insufflatable powders or, in a suitable embodiment, in the form of a spray (preferably a nasal spray). The spray can be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. For example, 0.03 to 3 mg of azelastine base can be released per individual actuation.

[1189] In certain such embodiments, the formulations of the present invention for use in treating snoring comprise one or more taste-masking agents, one or more flavoring agents, and/or one or more sweetening agents, or a combination of such agents. Non-limiting examples of such substances

include those described herein. For example, sucralose is especially effective as a sweetening and taste-masking agent in the compositions of the present invention for use in treatment of snoring, particularly when used at concentrations of from about 0.001% to about 1%, suitably at concentrations of from about 0.01% to about 0.5%, and more suitably at concentrations of from about 0.02% to about 0.2%, and most suitably from about 0.05% to about 0.15%, of the total composition.

[1190] Solvents which may be used for such formulations include, but are not limited to, water, saturated aliphatic mono and polyvalent alcohols which contain 2-3 carbon atoms (for example ethanol. Isopropanol, 1,2-propylene glycol, glycerine), liquid polyglycols (molecular weight 200 to 600). The solvent used is suitably water or mixtures of water with other physiologically acceptable solvents (for example those mentioned above). Suitably, the amount of the latter solvent in the aqueous mixture should not exceed 15% by weight.

[1191] Such solutions or formulations suitably can contain preservatives and stabilizers, as well as other excipients disclosed herein. Suitable excipients include, for example: ethylene diamine tetra-acetic acid (eidetic acid) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Furthermore, it is possible, for example, to use sodium- (2-ethylmercurithio)-benzoate generally known as "thimerosal" which may be present in an amount of 0.001 to 0.05, preferably from 0.005 to 0.02, for example 0.01 % (weight/volume in liquid formulations, otherwise weight/weight). Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide," benzyldimethyl-[2- [2-[p-(1,1,3,3-tetramethyl-butyl)] phenoxy] ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-:-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to

0.05, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preservatives among the quaternary ammonium compounds are alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride."

[1192] Such formulations of the present invention for treatment of snoring (solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols) can contain about 0.0005 to about 2, preferably about 0.001 to about 1, or about 0.003 to about 0.5% (weight/weight) of azelastine (related to the free azelastine base). Should azelastine be present as a salt, the amounts should be recalculated as necessary to give the amounts of azelastine, in the free acid form shown above. In the case of powders, the concentration of azelastine base generally is about 0.0005 to about 2 percent by weight relative to the solid carrier substances.

[1193] In the case of solutions, the dosage per nostril is, for example, 0.01 to 0.2 ml, in particular 0.05 to 0.15 ml. Such a dosage should be applied once to several times, preferably 1 to 5 times daily (optionally also hourly).

[1194] Suitable acid components for azelastine salts are, for example, hydrophilic acids (HCl, HBr), sulfuric acid, phosphoric acids), nitric acid, organic mono-, di-or tricarboxylic acids of aliphatic, alicyclic, aromatic or heterocyclic organic acids (embonic acid, citric acid, tartaric acid), aliphatic and aromatic sulfonic acids (for example camphorsulfonic acid).

[1195] It is also suitable to add buffer substances such as citric acid/sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodiumhydrogenphosphate), tromethamol or equivalent conventional buffers in order, for example, to adjust the formulation to a pH value of 6 to 7.5, preferably 6.5 to 7.1.

[1196] In one embodiment, snoring is treated by use of a 0.1% or a 0.15% aqueous solution of azelastine hydrochloride, suitably as a nasal spray. The spray is metered to deliver about 137 μg of azelastine hydrochloride (equivalent to 125 μg of azelastine base).

[1197] In addition to azelastine, the compositions useful for treating snoring can also optionally contain one or more additional active agents such as those described herein. In addition, the compositions for treating snoring can also further comprise one more sedatives or sleeping aids to help assist the user in falling asleep. Suitable sedatives and sleep aids include, but are not limited to, melatonin (N-acetyl-5-methoxytryptamine), a melatonin agonist, GABA (gamma-amino-butyric acid), other antihistamines (for example, benocten and olopatadine), benzodiazepines (for example, midazolam, diazepam), diazepines, phenobarbiturates, diphenhydramines or methiazoles. Other suitable sleep aids include plant extracts such as: Valeriana officinalis, Lavandula angustifolia, Humulus lupulus, passiflora incarnate, Ocimum basilicum, Nardostachysjatamamsi, Hypericum perforatum, Corydalis cava, Daliva miltiorrhiza, Cyperipedium pubescens, Cymbopogon flexuosus, Melissa officinalis, Monarda didymia, Citrus aurantii, Psicidia piscioula, and the like.

[1198] It will be readily apparent to one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the methods and applications described herein may be made without departing from the scope of the invention or any embodiment thereof. It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the claims. Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the invention.

EXAMPLES

Example 1: **Azelastine Hydrochloride Nasal Solution**

[1199] In one exemplary composition of the invention, a nasal spray formulation containing azelastine hydrochloride was prepared using hypromellose as a thickener, sorbitol as an isotonicity agent and sweetener, and sucralose as both a sweetener and a taste-masking agent.

Ingredient	**%**
Azelastine Hydrochloride	0.150
Hypromellose 2900,USP 4000	0.100
Edetate Disodium, USP	0.050
Sorbitol 70%, USP	6.400
Sodium Citrate, USP, Dihydrate	0.068
Sucralose, NF	0.150
Benzalkonium Chloride 50% Solution, NF	0.025
Water Purified or Deionized	Q.S. to 100%

[1200] Following preparation, the composition was filtered, and was packaged into high density polyethylene bottles fitted with a screw cap and comprising a VP3 metered-dose spray pump designed for intranasal application in a volume of about 0.14 ml (Valois). For use, one or two sprays were administered to each nostril two times per day, or as prescribed.

Example 2: **Azelastine Hydrochloride Nasal Solution**

[1201] In another exemplary composition provided by the present invention, a nasal spray formulation containing azelastine hydrochloride was prepared using hypromellose as a thickener and sucralose and menthol as taste-masking agents:

Ingredient	%
Azelastine Hydrochloride	0.100
Hypromellose 2900,USP 4000	0.300
Edetate Disodium, USP	0.050
Sodium Citrate, USP, Dihydrate	0.068
Sucralose, NF	0.050
Propylene Glycol, USP	1.895
Menthol, USP	0.050
Benzalkonium Chloride 50%, NF	0.025
Water Purified or Deionized	Q.S. to 100%

[1202] Following preparation, the composition was filtered, and was packaged into high density polyethylene bottles fitted with a screw cap and comprising a VP3 metered-dose spray pump designed for intranasal application in a volume of about 0.14 ml (Valois). For use, one or two sprays were administered to each nostril two times per day, or as prescribed.

Example 3: **Azelastine Hydrochloride Nasal Solution**

[1203] In another exemplary composition of the invention, a nasal spray formulation containing azelastine hydrochloride was prepared using hypromellose as a thickener, sodium chloride as an isotonicity agent, and sucralose as both a sweetener and a taste-masking agent.

Ingredient	%
Azelastine Hydrochloride	0.100
Hypromellose 2900,USP 4000	0.100
Edetate Disodium, USP	0.050
Citric Acid Anhydrous, USP	0.044
Dibasic Sodium Phosphate Heptahydrate, USP	0.486
Sodium Chloride, USP	0.687
Sucralose, NF	0.150
Benzalkonium Chloride 50% Solution, NF	0.025
Water Purified or Deionized	Q.S. to 100%

[1204] Following preparation, the composition was filtered, and was packaged into high density polyethylene bottles fitted with a screw cap and comprising a VP3 metered-dose spray pump designed for intranasal application in a volume of about 0.14 ml (Valois). For use, one or two sprays were administered to each nostril about two times per day, or as prescribed.

Example 4: **Azelastine Hydrochloride Ocular Solution**

[1205] In another exemplary composition provided by the present invention, an ocular formulation containing azelastine hydrochloride was prepared using hypromellose as a thickener, sorbitol as an isotonicity agent, and sucralose as a taste-masking agent:

Ingredient	%
Azelastine Hydrochloride	0.050
Hypromellose 2900,USP 4000	0.100
Edetate Disodium, USP	0.050
Sucralose, NF	0.150
Sorbitol Solution 70%, USP	6.667
Benzalkonium Chloride 50%, NF	0.025
Water Purified or Deionized	Q.S. to 100%

[1206] Following preparation, the composition was aseptically filtered, and was packaged into high density polyethylene bottles fitted with low density polyethylene dropper tips and a high density polyethylene protective cap. The droppers were designed for delivery of approximately 0.03 mL per drop. For use, one drop was instilled into each affected eye twice a day, or as prescribed.

Example 5: **Sensory Descriptive Bitterness Taste Analysis of Astelin Nasal Spray**

[1207] To determine effectiveness of masking agents in improving the taste of Astelin® Nasal Spray, a sensory evaluation of various formulations was conducted. Testing was carried out via a randomized, double-blind, placebo-controlled trial to evaluate comparability between the currently FDA-approved Astelin® Nasal Spray formulation and various sweetened azelastine hydrochloride nasal spray formulations. The objective of the study was to determine if a sweetened formulation of azelastine hydrochloride (containing 137 μg azelastine HCl), that includes 0.15% sucralose as a taste masking agent, is equivalent in efficacy and safety to the currently approved formulation of Astelin® Nasal Spray (also containing 137 μg of azelastine HCl).

Methodology:

[1208] Panelists: Twelve highly trained descriptive panelists led by a panel leader.

[1209] Data Analysis: Data were entered into an Excel spreadsheet and proofed for accuracy. An analysis was conducted with the data using ANOVA and Duncan means separation at a confidence level of 95% using SPSS 13.0 for Windows.

[1210] Methodology: Panelists measured the bitterness, noted other flavors perceived as well as observed the length of time the bitterness lasted in the throat.

[1211] All solutions were prepared with Milli-Q Water

[1212] Standard Solutions

[1213] 0.05% caffeine, bitter 2

[1214] 0.08% caffeine, bitter 5

[1215] 0.11% caffeine, bitter 7.5

[1216] Test samples were coded with random three-digit numbers. Panelists scored samples on ballots individually. Samples were evaluated by panelists using a 15-point intensity scale divided into 0.1 point increments with zero indicating no measurable effect and 15 indicating an extremely strong effect.

Product Identification:

[1217] **(1)** Astelin Nasal Spray Batch #1326 (two sprays) (azelastine hydrochloride, 137 μg azelastine HCl per two sprays)

[1218] **(2)** Astelin Nasal Spray Batch #1326 (four sprays) (azelastine hydrochloride, 137 μg azelastine HCl per two sprays)

[1219] **(3)** Astelin Nasal Spray Batch #03-33-01c (two sprays) (azelastine hydrochloride solution 0.1% w/v Investigational Formulation with sorbitol and high concentration of sucralose, 137 μg azelastine HCl per two sprays)

[1220] **(4)** Astelin Nasal Spray Batch #03-33-01c (four sprays) (azelastine hydrochloride solution 0.1% w/v Investigational Formulation with sorbitol and high concentration of sucralose, 137 μg azelastine HCl per two sprays).

Results and Discussion

(A) Commercial Formulation (standard azelastine hydrochloride commercial formulation)

[1221] This sample and sample 1326 four sprays exhibited the most bitterness with nasal discomfort that fell between mild and moderate. The bitterness was more intense in those who experienced more drainage. However, the bitterness dissipated within 30 minutes for most panelists. A couple of panelists experienced some residual bitterness for 2 to 3 hours after testing. The nasal discomfort was predominately described as tingling, cooling or slight burning.

(B) Sample 1326 four sprays

[1222] This sample and the Commercial Formulation displayed the most bitterness with nasal discomfort that fell between mild and moderate. Several panelists described this sample as similar or identical to the Commercial Formulation. As with the Commercial Formulation, most panelists did not notice any bitterness after 30 minutes.

(C) Sample 1326 two sprays

[1223] This sample was significantly less bitter than the Commercial Formulation using four sprays. Additionally, the nasal discomfort was lessened and described as mild. For most, the bitterness lasted less than 30 minutes. Some panelists questioned the effectiveness of two sprays versus four sprays.

(D) Sample 03-33-01c four sprays

[1224] While this sample was also significantly less bitter than the Commercial Formulation using four sprays, the sweetness was notable. The nasal discomfort was described as mild and similar to Sample 1326 two sprays and 03-33-01c two sprays. Most panelists described this sample as more sweet than bitter. As they experienced drainage, the sweet flavor intensified overriding any bitterness. Both sweet and bitter flavors dissipated within an hour.

(E) Sample 03-33-01c two sprays

[1225] This sample exhibited the least bitterness. Although the panelists noted a slight sweetness in this sample, it was not nearly as strong as when using four sprays. The sweetness did not override the slight bitterness as it did when using four sprays. The nasal discomfort was described as mild. Most indicated no bitter or sweet taste after 30 minutes. The bitterness faded faster than the sweetness. As with Sample 1326 two sprays, some panelists questioned the effectiveness of two sprays versus four.

Panelists' Preferences

[1226] Of the four test samples, 4 of 11 panelists ranked 03-33-01c two sprays as their first choice. Four panelists ranked it as their second choice. They liked the slight sweetness that masked the bitterness; however, several did question whether two sprays were as effective as four.

[1227] Four of eleven panelists chose 03-33-01c four sprays as their first choice with four indicating it would be their second choice. Again, they preferred the sweet flavor that masked the bitterness and they felt it was effective.

[1228] Three of eleven panelist chose 1326 two sprays as their first choice, with one choosing it as a second choice. Some did not like the sweetness and preferred a slight bitterness. Some questioned the effectiveness of two sprays.

[1229] No panelists ranked 1326 four sprays as their first choice. One panelist chose it as her second choice because she did not like the sweet taste at all.

Conclusions

[1230] The panelists recognized the Commercial Formulation and sample 1326 four sprays as the same.

[1231] Using two sprays of sample 1326 helped significantly with the bitterness and nasal discomfort .

[1232] The 03-33-01c samples were significantly less bitter and gave less nasal discomfort than the Commercial Formulation.

[1233] The 03-33-01c samples were equally preferred due to the masking sweetness.

Example 6: **Preservative Free Ocular Solution for Unit Dose**

[1234] One exemplary composition provided by the present invention, is a liquid dosage formulation containing azelastine hydrochloride prepared using hypromellose as a thickener and sucralose and menthol as a taste-masking agent in the ranges provided below:

Ingredient	**%**
Azelastine Hydrochloride	0.0500-.150
Hypromellose 2900,USP 4000	0.300
Edetate Disodium, USP	0.050
Sodium Citrate, USP, Dihydrate	0.068
Sucralose, NF	0.050-0.150
Propylene Glycol, USP	1.895
Water Purified or Deionized	Q.S. to 100%

[1235] Following preparation, the solution is filtered, and packaged into high density polyethylene containers. An approximate unit dose volume of about 0.25 mL to 1 mL is filled in the container which has a capacity of about 1 mL. The use of a single unit-dose container eliminates the concerns of contamination and provides the convenience of portability.

Example 7: **Azelastine Hydrochloride Nasal Solution Comprising Steroid**

[1236] One exemplary composition of the invention is a nasal spray formulation containing azelastine hydrochloride prepared using hypromellose as a thickener, a steroid, and sucralose as both a sweetener and a taste-masking agent.

Ingredient	%
Azelastine Hydrochloride	0.05-0.150
Steroid (fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone)	0.01-2.0
Hypromellose 2900,USP 4000	0.100
Edetate Disodium, USP	0.050
Sorbitol 70%, USP	6.400
Sodium Citrate, USP, Dihydrate	0.068
Sucralose, NF	0.1-0.15
Benzalkonium Chloride 50% Solution, NF	0.025
Water Purified or Deionized	Q.S. to 100%

[1237] Following preparation, the solution is packaged into high density polyethylene bottles fitted with a screw cap and comprising a VP3 metered-dose spray pump designed for intranasal application of about 0.14 ml (Valois). For use, one or two sprays can be administered to each nostril two times per day, or as prescribed.

Example 8: **Azelastine Hydrochloride Nasal Solution Comprising Leukotriene Antagonist**

[1238] One exemplary composition of the invention is a nasal spray formulation containing azelastine hydrochloride prepared using hypromellose as a thickener, a leukotriene antagonist, and sucralose as both a sweetener and a taste-masking agent.

Ingredient	%
Azelastine Hydrochloride	0.05-0.150
Leukotriene antagonist (montelukast)	0.1-5.0
Hypromellose 2900,USP 4000	0.100
Edetate Disodium, USP	0.050
Sorbitol 70%, USP	6.400
Sodium Citrate, USP, Dihydrate	0.068
Sucralose, NF	0.1-0.15
Benzalkonium Chloride 50% Solution, NF	0.025
Water Purified or Deionized	Q.S. to 100%

[1239] Following preparation, the solution is packaged into high density polyethylene bottles fitted with a screw cap and comprising a VP3 metered-dose spray pump designed for intranasal application of about 0.14 ml (Valois). For use, one or two sprays can be administered to each nostril two times per day, or as prescribed.

Example 9: **Azelastine Hydrochloride Nasal Solution Comprising Decongestant**

[1240] One exemplary composition of the invention is a nasal spray formulation containing azelastine hydrochloride prepared using hypromellose as a thickener, a decongestant, and sucralose as both a sweetener and a taste-masking agent.

Ingredient	%
Azelastine Hydrochloride	0.05-0.150
Decongestant (pseudoephedrine or phenylephrine)	0.1-2.0
Hypromellose 2900,USP 4000	0.100
Edetate Disodium, USP	0.050
Sorbitol 70%, USP	6.400
Sodium Citrate, USP, Dihydrate	0.068
Optionally, Sucralose, NF	0.1-0.15
Benzalkonium Chloride 50% Solution, NF	0.025
Water Purified or Deionized	Q.S. to 100%

[1241] Following preparation, the solution is packaged into high density polyethylene bottles fitted with a screw cap and comprising a VP3 metered-dose spray pump designed for intranasal application of about 0.14 ml (Valois). For use, one or two sprays can be administered to each nostril two times per day, or as prescribed.

Example 10: **Azelastine Hydrochloride Nasal Solution Comprising NSAID**

[1242] One exemplary composition of the invention is a nasal spray formulation containing azelastine hydrochloride prepared using hypromellose as a thickener, an NSAID, and sucralose as both a sweetener and a taste-masking agent.

Ingredient	%
Azelastine Hydrochloride	0.05-0.150
NSAID (ibuprofen, diclofenac, aceclofenac or naproxen)	0.1-10.0
Hypromellose 2900,USP 4000	0.100
Edetate Disodium, USP	0.050
Sorbitol 70%, USP	6.400
Sodium Citrate, USP, Dihydrate	0.068
Optionally, Sucralose, NF	0.1-0.15
Benzalkonium Chloride 50% Solution, NF	0.025
Water Purified or Deionized	Q.S. to 100%

[1243] Following preparation, the solution is packaged into high density polyethylene bottles fitted with a screw cap and comprising a VP3 metered-dose spray pump designed for intranasal application of about 0.14 ml (Valois). For use, one or two sprays can be administered to each nostril two times per day, or as prescribed.

Example 11: **Azelastine Hydrochloride Nasal Solution Comprising Steroid and Decongestant**

[1244] One exemplary composition of the invention is a nasal spray formulation containing azelastine hydrochloride prepared using hypromellose as a thickener, a steroid, a decongestant, and sucralose as both a sweetener and a taste-masking agent.

Ingredient	%
Azelastine Hydrochloride	0.05-0.150
Steroid (fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone)	0.01-2.0
Decongestant (pseudoephedrine or phenylephrine)	0.1-1.0
Hypromellose 2900,USP 4000	0.100
Edetate Disodium, USP	0.050
Sorbitol 70%, USP	6.400
Sodium Citrate, USP, Dihydrate	0.068
Optionally, Sucralose, NF	0.1-0.15
Benzalkonium Chloride 50% Solution, NF	0.025
Water Purified or Deionized	Q.S. to 100%

[1245] Following preparation, the composition is packaged into high density polyethylene bottles fitted with a screw cap and comprising a VP3 metered-dose spray pump designed for intranasal application of about 0.14 ml (Valois). For use, one or two sprays can be administered to each nostril two times per day, or as prescribed.

Example 12: **Azelastine Hydrochloride Nasal Solution Comprising Steroid and Leukotriene antagonist**

[1246] One exemplary composition of the invention is a nasal spray formulation containing azelastine hydrochloride prepared using hypromellose as a thickener, steroid, a leukotriene antagonist, and sucralose as both a sweetener and a taste-masking agent.

Ingredient	%
Azelastine Hydrochloride	0.05-0.150
Steroid (fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, or triamcinolone)	0.01-2.0
Leukotriene antagonist (montelukast)	0.1-5.0
Hypromellose 2900,USP 4000	0.100
Edetate Disodium, USP	0.050
Sorbitol 70%, USP	6.400
Sodium Citrate, USP, Dihydrate	0.068
Optionally, Sucralose, NF	0.1-0.15
Benzalkonium Chloride 50% Solution, NF	0.025
Water Purified or Deionized	Q.S. to 100%

[1247] Following preparation, the solution was packaged into high density polyethylene bottles fitted with a screw cap and comprising a VP3 metered-dose spray pump designed for intranasal application of about 0.14 ml (Valois). For use, one or two sprays can be administered to each nostril two times per day, or as prescribed.

[1248] The present invention has been described with reference to certain embodiments thereof. However, the scope of the invention is not limited to the embodiments described or exemplified. Workers of ordinary skill in the relevant arts will readily appreciate that other embodiments and examples can be practiced without departing from the scope of the present invention. All such variations are considered to be part of, and therefore encompassed by, the present invention.

[1249] All publications, patents and patent applications mentioned or referenced in this specification are indicative of the level of skill of those skilled in the art to which the present invention pertains, and are herein incorporated by reference to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising azelastine, or a pharmaceutically acceptable salt or ester thereof, at a concentration of about 0.005% to about 5.0% by weight, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of said pharmaceutically acceptable carriers or excipients is a taste-masking agent that masks the taste of said azelastine or salt or ester thereof such that the sensation of a bitter taste by a patient caused by administration of said pharmaceutical composition to said patient is reduced or eliminated.

2. The pharmaceutical composition of claim 1, wherein said composition comprises azelastine hydrochloride.

3. The pharmaceutical composition of claim 1, wherein said taste-masking agent is selected from the group consisting of sucralose, sucrose, saccharin or a salt thereof, fructose, dextrose, corn syrup, aspartame, acesulfame-K, xylitol, sorbitol, erythritol, ammonium glycyrrhizinate, thaumatin, neotame, mannitol, menthol, eucalyptus oil, camphor, a natural flavoring agent, an artificial flavoring agent, and combinations thereof.

4. The pharmaceutical composition of claim 3, wherein said taste-masking agent is sucralose.

5. The pharmaceutical composition of claim 4, wherein sucralose is present in said composition at a concentration of from about 0.001% to about 1% (w/v).

6. The pharmaceutical compositions of claim 5, wherein said sucralose is present in said composition at a concentration of from about 0.01% to about 0.5%.

7. The pharmaceutical composition of claim 6, wherein said sucralose is present in said composition at a concentration of from about 0.02% to about 0.2%.

8. The pharmaceutical composition of claim 7, wherein said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15%.

9. The pharmaceutical composition of claim 4, further comprising one or more additional taste-masking agents.

10. The pharmaceutical composition of claim 9, wherein said additional taste-masking agent is menthol.

11. The pharmaceutical composition of claim 1, wherein said composition is formulated for intranasal administration.

12. The pharmaceutical composition of claim 1, wherein said composition is formulated for ocular administration.

13. The pharmaceutical composition of claim 11, wherein said composition comprises at least one viscosity-increasing agent that reduces or prevents postnasal drip of said composition into the pharynx upon intranasal administration of said composition.

14. The pharmaceutical composition of claim 13, wherein said viscosity-increasing agent is selected from the group consisting of a polyvinylpyrrolidone, a cellulose derivative, carrageenan, guar gum, an alginate, a carbomer, a polyethylene glycol, a polyvinyl alcohol and xanthan gum.

15. The pharmaceutical composition of claim 14, wherein said cellulose derivative is selected from the group consisting of hydroxyethyl cellulose, carboxymethyl cellulose and hypromellose.

16. The pharmaceutical composition of claim 15, wherein said viscosity-increasing agent is hypromellose.

17. The pharmaceutical composition of claim 16, wherein said hypromellose is hypromellose 2900 USP 4000 at a concentration of about 0.05% to about 0.5% (w/v).

18. The pharmaceutical composition of claim 12, wherein said composition comprises at least one viscosity-increasing agent that reduces or prevents postnasal drip of said composition into the pharynx upon intranasal administration of said composition.

19. The pharmaceutical composition of claim 18, wherein said viscosity-increasing agent is selected from the group consisting of a polyvinylpyrrolidone, a cellulose derivative, carrageenan, guar gum, an alginate, a carbomer, a polyethylene glycol, a polyvinyl alcohol and xanthan gum.

20. The pharmaceutical composition of claim 19, wherein said cellulose derivative is selected from the group consisting of hydroxyethyl cellulose, carboxymethyl cellulose and hypromellose.

21. The pharmaceutical composition of claim 20, wherein said viscosity-increasing agent is hypromellose.

22. The pharmaceutical composition of claim 21, wherein said hypromellose is hypromellose 2900 USP 4000 at a concentration of about 0.05% to about 0.5% (w/v).

23. The pharmaceutical composition of claim 1, further comprising one or more additional components selected from the group consisting of one or more solvents, one or more preservatives, one or more stabilizers, one or more solubility-improving agents, one or more isotonicity agents, and one or more buffers.

24. A pharmaceutical composition comprising:

about 0.005% to about 0.5% (w/v) azelastine hydrochloride;

about 0.001% to about 5.00% (w/v) of a water-soluble polymer;

about 0.01% to about 0.1% (w/v) disodium edetate;

about 0.001% to about 0.5% (w/v) benzalkonium chloride;

about 0.001% to about 1.0% sucralose;

a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4;

a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and

QS water.

25. The pharmaceutical composition of claim 24, wherein said composition comprises azelastine hydrochloride at a concentration of from about 0.05% to about 0.15% (w/v).

26. The pharmaceutical composition of claim 24, wherein said water soluble polymer is hypromellose.

27. The pharmaceutical composition of claim 26, wherein said hypromellose is present in said composition at a concentration sufficient to provide a viscosity of said solution of from about 2 centipoise to about 300 centipoise.

28. The pharmaceutical composition of claim 27, wherein said hypromellose is present in said composition at a concentration of from about 0.1% to about 0.3% (w/v).

29. The pharmaceutical composition of claim 24, wherein said composition comprises sucralose at a concentration of from about 0.05% to about 0.15% (w/v).

30. The pharmaceutical composition of claim 24, further comprising menthol at a concentration of from about 0.01% to about 1% (w/v).

31. The pharmaceutical composition of claim 30, wherein said menthol is present in said composition at a concentration of from about 0.05% to about 0.1%.

32. The pharmaceutical composition of claim 24, wherein the osmolality of said composition is from about 250 mosmol/kg to about 320 mosmol/kg.

33. A method of treating or preventing a physical disorder in an animal suffering from or predisposed thereto, comprising administering to said animal an effective amount of the pharmaceutical composition of any one of claims 1, 4, 9, 12, 18 and 24.

34. The method of claim 33, wherein said animal is a mammal.

35. The method of claim 34, wherein said mammal is a human.

36. The method of claim 33, wherein said physical disorder is selected from the group consisting of allergic rhinitis, non-allergic vasomotor rhinitis and allergic conjunctivitis.

37. An oral dosage pharmaceutical composition comprising a therapeutically effective dose of azelastine, or a pharmaceutically acceptable

salt or ester thereof, at a concentration of from about 0.05% to about 5.0% by weight, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of said pharmaceutically acceptable carriers or excipients is sucralose.

38. The oral dosage pharmaceutical composition of claim 37, wherein said azelastine is present in said composition at a concentration of about 0.125% to about 0.15%.

39. The oral dosage pharmaceutical composition of claim 37, wherein said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

40. The oral dosage pharmaceutical composition of claim 37, wherein said azelastine is present in said composition at a concentration of about 0.1% by weight and said sucralose is present in said composition at a concentration of about 0.15% by weight.

41. The oral dosage pharmaceutical composition of claim 37, wherein said azelastine is present in said composition at a concentration of from about 0.125% to about 0.15% by weight and said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

42. The oral dosage pharmaceutical composition of claim 37, wherein said azelastine is present in said composition at a concentration of about 0.15% by weight and said sucralose is present in said composition at a concentration of about 0.15% by weight.

43. The oral dosage pharmaceutical composition of claim 37, wherein said composition is in the form of a liquid solution or suspension.

44. The oral dosage pharmaceutical composition of claim 37, wherein said composition is in the form of a tablet or capsule.

45. The oral dosage pharmaceutical composition of claim 37, wherein said composition is a chewable tablet.

46. The oral dosage pharmaceutical composition of claim 37, wherein said composition is an orally disintegrating tablet.

47. The oral dosage pharmaceutical composition of claim 37, wherein said composition is an effervescent composition.

48. The oral dosage pharmaceutical composition of claim 37, wherein said composition is an orally dissolving/consumable film.

49. A pharmaceutical composition comprising a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, at a concentration of from about 0.05% to about 5% by weight, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of said pharmaceutically acceptable carriers or excipients is sucralose, and wherein said pharmaceutical composition further comprises one or more additional active agents.

50. The pharmaceutical composition of claim 49, wherein said one or more additional active agents are selected from the group consisting of:

(a) one or more antihistamines;

(b) one or more steroids;

(c) one or more leukotriene antagonists;

(d) one or more decongestants; and

(e) one or more non-steroidal anti-inflammatory agents.

51. The pharmaceutical composition of claim 50, wherein said one or more antihistamines are selected from the group consisting of cetirizine, olopatadine, fexofenadine, terfenadine and loratadine.

52. The pharmaceutical composition of claim 50, wherein said one or more steroids are selected from the group consisting of fluoromethalone, fluticasone, mometasone, triamcinolone, betamethasone, flunisolide, budesonide, beclomethasone, budesonide, rimexolone, loteprednol, beloxil, prednisone, loteprednol and dexamethasone.

53. The pharmaceutical composition of claim 50, wherein said one or more leukotriene antagonists are selected from the group consisting of montelukast, zafirlukast and zanamivir

54. The pharmaceutical composition of claim 50, wherein said one or more decongestants are selected from the group consisting of pseudoephedrine, phenylephedrine, phenylephrine, phenylpropanolamine, oxymetazoline, propylhexedrine, xylometazoline, epinephrine, ephedrine, desoxyephedrine, naphazoline, naphazoline, and tetrahydrozoline.

55. The pharmaceutical composition of claim 50, wherein said non-steroidal anti-inflammatory agents are selected from the group consisting of ibuprofen, diclofenac, naproxen, etodolac, flurbiprofen, fenoprofen, ketoprofen, suprofen, fenbufen, fluprofen, tolmetin sodium, oxaprozin, zomepirac, sulindac indomethacin, piroxicam, mefenamic acid, nabumetone, meclofenamate sodium, diflunisal, flufenisal, piroxicam, ketorolac, sudoxicam and isoxicam.

56. The pharmaceutical composition of claim 50, wherein said azelastine is present in said composition at a concentration of from about 0.125% to about 0.15% by weight.

57. The pharmaceutical composition of claim 50, wherein said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

58. The pharmaceutical composition of claim 50, wherein said composition comprises azelastine, or a pharmaceutically acceptable salt or ester thereof, sucralose and one or more steroids.

59. The pharmaceutical composition of claim 50, wherein said composition comprises azelastine, or a pharmaceutically acceptable salt or ester thereof, sucralose and one or more decongestants.

60. The pharmaceutical composition of claim 50, wherein said composition comprises azelastine, or a pharmaceutically acceptable salt or ester thereof, sucralose, one or more steroids and one or more decongestants.

61. The oral dosage pharmaceutical composition of claim 50, wherein said composition comprises azelastine, or a pharmaceutically acceptable salt or ester thereof at a concentration of about 0.05% to about 0.15% by weight, sucralose at a concentration of about 0.05% to about 0.15% by weight, and one or more steroids at a concentration of about 0.01% to about 0.1%.

62. The pharmaceutical composition of claim 50, wherein said composition comprises azelastine, or a pharmaceutically acceptable salt or ester thereof at a concentration of about 0.05% to about 0.15% by weight,

sucralose at a concentration of about 0.05% to about 0.15% by weight, and one or more decongestants at a concentration of about 0.1% to about 1.0%.

63. The pharmaceutical composition of claim 50, wherein said composition comprises azelastine, or a pharmaceutically acceptable salt or ester thereof at a concentration of about 0.05% to about 0.15% by weight, sucralose at a concentration of about 0.05% to about 0.15% by weight, one or more steroids at a concentration of about 0.01% to about 0.1%, and one or more decongestants at a concentration of about 0.1% to about 1.0%.

64. The pharmaceutical composition of claim 50, wherein said composition is formulated for intranasal administration.

65. The pharmaceutical composition of claim 50, wherein said composition is formulated for ocular administration.

66. A sustained release pharmaceutical composition, comprising a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of said pharmaceutically acceptable carriers or excipients is sucralose, and wherein said azelastine, or said pharmaceutically acceptable salt or ester thereof, is:

(a) coated with one or more sustained release components;

(b) bound to a cation exchanger;

(c) reacted with one or more osmotically active substances and coated with a semi-permeable membrane and a hole is bored into the membrane; or

(d) embedded in, or is bound to, one or more substances selected from of the group consisting of digestible fats, indigestible fats, polymers and swelling agents.

67. The sustained release pharmaceutical composition of claim 66, wherein said azelastine is present in said composition at a concentration of from about 0.5% to about 5.0% by weight.

68. The sustained release pharmaceutical composition of claim 66, wherein said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

69. The sustained release pharmaceutical composition of claim 66, wherein said azelastine is present in said composition at a concentration of about 0.1% by weight and said sucralose is present in said composition at a concentration of about 0.15% by weight.

70. The sustained release pharmaceutical composition of claim 66, wherein said azelastine is present in said composition at a concentration of from about 0.125% to about 0.15% by weight and said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

71. The sustained release pharmaceutical composition of claim 66, wherein said azelastine is present in said composition at a concentration of about 0.15% by weight and said sucralose is present in said composition at a concentration of about 0.15% by weight.

72. A liquid, unit-dose pharmaceutical composition, comprising a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of said pharmaceutically acceptable carriers or excipients is sucralose, wherein said composition is free, or substantially free of preservatives, and wherein said composition is provided in a single unit-dose container.

73. The liquid, unit-dose pharmaceutical composition of claim 72, wherein said azelastine is present in said composition at a concentration of from about 0.05% to about 5.0% by weight.

74. The liquid, unit-dose pharmaceutical composition of claim 72, wherein said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

75. The liquid, unit-dose pharmaceutical composition of claim 72, wherein said azelastine is present in said composition at a concentration of about 0.1% by weight and said sucralose is present in said composition at a concentration of about 0.15% by weight.

76. The liquid, unit-dose pharmaceutical composition of claim 72, wherein said azelastine is present in said composition at a concentration of from about 0.125% to about 0.15% by weight and said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

77. The liquid, unit-dose pharmaceutical composition of claim 72, wherein said azelastine is present in said composition at a concentration of about 0.15% by weight and said sucralose is present in said composition at a concentration of about 0.15% by weight.

78. The liquid, unit-dose pharmaceutical composition of claim 72, wherein said single unit-dose container comprises high density polyethylene.

79. The liquid, unit-dose pharmaceutical composition of claim 72, wherein said single unit-dose container is a blow-fill-seal high density polyethylene container with a volume capacity of about 1.0 mL.

80. An inhalable powder pharmaceutical composition comprising, a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers or excipients, wherein said azelastine is in the form of micronized particles and wherein at least one of said pharmaceutically acceptable carriers or excipients is micronized particles of sucralose.

81. The inhalable powder pharmaceutical composition of claim 80, wherein said micronized particles of azelastine have an average particle size of about 1 μm to about 5 μm.

82. The inhalable powder pharmaceutical composition of claim 80, wherein said micronized particles of sucralose have an average particle size of about 15 μm to about 80 μm.

83. The inhalable powder pharmaceutical composition of claim 80, wherein said composition is formulated for delivery using a dry powder inhaler.

84. The inhalable powder pharmaceutical composition of claim 80, wherein said azelastine is present in said composition at a concentration of from about 0.1% to about 0.15% by weight.

85. The inhalable powder pharmaceutical composition of claim 80, wherein said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

86. The inhalable powder pharmaceutical composition of claim 80, wherein said azelastine is present in said composition at a concentration of about 0.1% by weight and said sucralose is present in said composition at a concentration of about 0.15% by weight.

87. The inhalable powder pharmaceutical composition of claim 80, wherein said azelastine is present in said composition at a concentration of from about 0.125% to about 0.15% by weight and said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

88. The inhalable powder pharmaceutical composition of claim 80, wherein said azelastine is present in said composition at a concentration of about 0.15% by weight and said sucralose is present in said composition at a concentration of about 0.15% by weight.

89. A method of treating snoring in an animal, comprising administering to the animal a therapeutically effective dose of azelastine, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers or excipients, wherein at least one of the pharmaceutically acceptable carriers or excipients is sucralose.

90. The method of claim 89, wherein said azelastine is present in said composition at a concentration of from about 0.1% to about 0.15% by weight.

91. The method of claim 89, wherein said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

92. The method of claim 89, wherein said azelastine is present in said composition at a concentration of about 0.1% by weight and said sucralose is present in said composition at a concentration of about 0.15% by weight.

93. The method of claim 89, wherein said azelastine is present in said composition at a concentration of from about 0.125% to about 0.15% by weight and said sucralose is present in said composition at a concentration of from about 0.05% to about 0.15% by weight.

94. The method of claim 89, wherein said azelastine is present in said composition at a concentration of about 0.15% by weight and said sucralose is present in said composition at a concentration of about 0.15% by weight.

95. The method of claim 89, wherein said composition is administered in a nasal spray.

96. The method of claim 89, wherein said animal is a human.

97. A method of treating or preventing allergic rhinitis, non-allergic vasomotor rhinitis or allergic conjunctivitis in an animal suffering from or predisposed thereto, comprising administering to said animal a pharmaceutical composition comprising an effective amount azelastine and taste-masking amount of sucralose, thereby avoiding the bitter taste associated with the azelastine.

98. The method of claim 97, wherein said animal is a mammal.

99. The method of claim 98, wherein said mammal is a human.

100. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride; and

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone.

101. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; and

about 0.1% to about 0.15% (w/v) sucralose.

102. A pharmaceutical composition comprising:

about 0.1% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; and

about 0.1% (w/v) sucralose.

103. A pharmaceutical composition comprising:

about 0.1% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; and

about 0.15% (w/v) sucralose.

104. A pharmaceutical composition comprising:

about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone; and

about 0.15% (w/v) sucralose.

105. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride; and

about 0.1% to about 5.0% (w/v) montelukast.

106. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.1% to about 5.0% (w/v) montelukast; and

about 0.1% to about 0.15% (w/v) sucralose.

107. A pharmaceutical composition comprising:

about 0.1% (w/v) azelastine hydrochloride;

about 0.1% to about 5.0% (w/v) montelukast; and

about 0.1% (w/v) sucralose.

108. A pharmaceutical composition comprising:

about 0.1% (w/v) azelastine hydrochloride;

about 0.1% to about 5.0% (w/v) montelukast; and

about 0.15% (w/v) sucralose.

109. A pharmaceutical composition comprising:

about 0.15% (w/v) azelastine hydrochloride;

about 0.1% to about 5.0% (w/v) montelukast; and

about 0.15% (w/v) sucralose.

110. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride; and

about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine.

111. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and

about 0.1% to about 0.15% (w/v) sucralose.

112. A pharmaceutical composition comprising:

about 0.1% (w/v) azelastine hydrochloride;

about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and

about 0.1% (w/v) sucralose.

113. A pharmaceutical composition comprising:

about 0.1% (w/v) azelastine hydrochloride;

about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and

about 0.15% (w/v) sucralose.

114. A pharmaceutical composition comprising:

about 0.15% (w/v) azelastine hydrochloride;

about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and

about 0.15% (w/v) sucralose.

115. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride; and

about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen.

116. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen; and

about 0.1% to about 0.15% (w/v) sucralose.

117. A pharmaceutical composition comprising:

about 0.05% (w/v) azelastine hydrochloride;

about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen; and

about 0.1% (w/v) sucralose.

118. A pharmaceutical composition comprising:

about 0.05% (w/v) azelastine hydrochloride;

about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen; and

about 0.15% (w/v) sucralose.

119. A pharmaceutical composition comprising:

about 0.15% (w/v) azelastine hydrochloride;

about 0.1% to about 10.0% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen; and

about 0.15% (w/v) sucralose.

120. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; and

about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine.

121. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone;

about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and

about 0.1% to about 0.15% (w/v) sucralose.

122. A pharmaceutical composition comprising:

about 0.1% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone;

about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and

about 0.1% (w/v) sucralose.

123. A pharmaceutical composition comprising:

about 0.1% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone;

about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and

about 0.15% (w/v) sucralose.

124. A pharmaceutical composition comprising:

about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone;

about 0.1% to about 1.0% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine; and

about 0.15% (w/v) sucralose.

125. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone; and

about 0.1% to about 5.0% (w/v) montelukast.

126. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone;

about 0.1% to about 5.0% (w/v) montelukast; and

about 0.1% to about 0.15% (w/v) sucralose.

127. A pharmaceutical composition comprising:

about 0.1% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone;

about 0.1% to about 5.0% (w/v) montelukast; and

about 0.1% (w/v) sucralose.

128. A pharmaceutical composition comprising:

about 0.1% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone;

about 0.1% to about 5.0% (w/v) montelukast; and

about 0.15% (w/v) sucralose.

129. A pharmaceutical composition comprising:

about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone;

about 0.1% to about 5.0% (w/v) montelukast; and

about 0.15% (w/v) sucralose.

130. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide, and triamcinolone;

about 0.001% to about 5.00% (w/v) of a water-soluble polymer;

about 0.01% to about 0.1% (w/v) disodium edetate;

about 0.001% to about 0.5% (w/v) benzalkonium chloride;

about 0.1% to about 0.15% sucralose;

a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4;

a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and

QS water.

131. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.1% to about 5% (w/v) montelukast;

about 0.001% to about 5.00% (w/v) of a water-soluble polymer;

about 0.01% to about 0.1% (w/v) disodium edetate;

about 0.001% to about 0.5% (w/v) benzalkonium chloride;

about 0.1% to about 0.15% sucralose;

a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4;

a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and

QS water.

132. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.1% to about 1% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine;

about 0.001% to about 5.00% (w/v) of a water-soluble polymer;

about 0.01% to about 0.1% (w/v) disodium edetate;

about 0.001% to about 0.5% (w/v) benzalkonium chloride;

about 0.1% to about 0.15% sucralose;

a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4;

a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and

QS water.

133. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.1% to about 10% (w/v) NSAID selected from the group consisting of ibuprofen, diclofenac, aceclofenac and naproxen;

about 0.001% to about 5.00% (w/v) of a water-soluble polymer;

about 0.01% to about 0.1% (w/v) disodium edetate;

about 0.001% to about 0.5% (w/v) benzalkonium chloride;

about 0.1% to about 0.15% sucralose;

a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4;

a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and

QS water.

134. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone;

about 0.1% to about 1% (w/v) decongestant selected from the group consisting of pseudoephedrine and phenylephrine;

about 0.001% to about 5.00% (w/v) of a water-soluble polymer;

about 0.01% to about 0.1% (w/v) disodium edetate;

about 0.001% to about 0.5% (w/v) benzalkonium chloride;

about 0.1% to about 0.15% sucralose;

a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4;

a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and

QS water.

135. A pharmaceutical composition comprising:

about 0.05% to about 0.15% (w/v) azelastine hydrochloride;

about 0.01% to about 0.1% (w/v) steroid selected from the group consisting of fluticasone, mometasone, dexamethasone beloxil, loteprednol, budesonide and triamcinolone;

about 0.1% to about 5% (w/v) montelukast;

about 0.001% to about 5.00% (w/v) of a water-soluble polymer;

about 0.01% to about 0.1% (w/v) disodium edetate;

about 0.001% to about 0.5% (w/v) benzalkonium chloride;

about 0.1% to about 0.15% sucralose;

a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within a range of from about 4.5 to about 7.4;

a sufficient amount of an isotonicity agent to yield an osmolality of about 220 mosmol/kg to about 350 msomol/kg; and

QS water.

136. A method of treating or preventing a physical disorder in an animal suffering from or predisposed thereto, comprising administering to said animal an effective amount of the pharmaceutical composition of any one of claims 100-135.

137. The method of claim 136, wherein said animal is a mammal.

138. The method of claim 137, wherein said mammal is a human.

139. The method of claim 136, wherein said physical disorder is selected from the group consisting of allergic rhinitis, non-allergic vasomotor rhinitis and allergic conjunctivitis.