Abstract: The present invention provides ophthalmic formulations of fluticasone that provide a comfortable formulation when instilled in the eye and is effective in the treatment of allergic conjunctivitis and/or allergic conjunctivitis. The invention further provides methods of treating allergic conjunctivitis and/or allergic conjunctivitis in a subject in need of such treatment by topical application of the fluticasone formulations of the invention directly to the eye.
Ophthalmic Formulations of Fluticasone and Methods of Use

REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 61/184,484, filed June 5, 2009, the contents of which are hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to compositions comprising fluticasone, alone or in combination with one or more additional active agents, and methods for using the same for treating allergic conjunctivitis and allergic rhinoconjunctivitis.

BACKGROUND OF THE INVENTION

There exists a need for topical ophthalmic pharmaceutical products to effectively treat allergic conjunctivitis, a disorder that presents with both acute allergic symptoms (i.e., seasonal allergy) and late phase inflammatory reactions (i.e., chronic, refractory or persistent allergy), as well as allergic rhinoconjunctivitis. It has been estimated that 46% (~70 million) of the adult allergy patients in the United States suffer from both the acute and late phase conditions of allergic conjunctivitis, whereas only 19% suffer from only acute or late phase allergy, respectively. It is estimated that allergic rhinoconjunctivitis (a combination of ocular and nasal symptoms) may occur in up to 90% of patients with allergies. The average age of allergy sufferers - between 20 and 40 years - coincides with the average age of the work force and the most productive period of an individual's life.

Both seasonal and perennial allergic conjunctivitis (ocular allergies) are characterized by itchy, red, swollen, and watery eyes. Allergic rhinitis (nasal allergies) manifests as a runny nose, sneezing, congestion, and similar symptoms. It can be difficult for a physician to distinguish allergic conjunctivitis from allergic rhinoconjunctivitis because both allergic reactions can occur simultaneously or be triggered by the same types of stimuli. It is further difficult to distinguish acute allergic symptoms from late phase symptoms of allergic conjunctivitis, as each of these
conditions can persist simultaneously or morph back and forth in any given individual. The signs and symptoms of allergic conjunctivitis and allergic rhinoconjunctivitis can significantly impact the quality of life of patients, from social interactions, productivity at work and school, to the ability to perform visual tasks such as working on a computer or reading.

Acute symptoms of allergic conjunctivitis are characterized by the clinical signs and symptoms of eye itching, redness, and swelling. Late phase or allergic inflammation reactions of allergic conjunctivitis include redness, lid swelling and tearing, and in some cases itching, as well as the predominance of congestion in the nose. Acute allergic symptoms are predominantly caused by the activation of mast cells, which when stimulated by an allergen (pollen, dust, dander) releases a host of substances that produce the signs and symptoms of allergic conjunctivitis (itching, redness, swelling, and tearing). Histamine is the primary mediator released and stimulates receptors on nerve endings and blood vessels to produce itching and redness. There are two histamine receptors that have been identified on the ocular surface. H1 receptors on nerve endings lead to itching, and H1 and H2 receptors on blood vessels lead to dilation of the blood vessels, leading to redness, and leakage of fluid from the vessels into the surrounding tissue producing swelling. Late phase inflammatory reactions are mediated by activation of inflammatory cells.

Like allergic conjunctivitis, allergic rhinoconjunctivitis is an allergen-induced, mast cell-mediated response. The reaction is triggered when airborne allergens bind to antibodies attached to the surface of mast cells in the eye and/or nose. Mast cells, in turn, release chemical mediators, which account for the immediate reaction in sensitized individuals exposed to allergen. Some of these mediators, such as histamine, directly affect blood vessels and nerves, leading to the signs and symptoms of allergic disease. Other released mediators cause the influx of white blood cells to the site, which leads to sustained symptoms in severe cases and particularly congestion in the nose.

Allergic conjunctivitis and rhinoconjunctivitis may also co-exist with other external ocular conditions and diseases, such as dry eye, or irritations caused by pollutants or other causes. This leads to a compromised tear film, which serves to protect the ocular surface from allergens.
Currently available treatments for eye allergy include: drops which can wash allergens off the ocular surface and act as a barrier for the eye (e.g. artificial tears), drugs which block histamine from binding to the histamine receptors (e.g. antihistamines), drugs that block the release of histamine and other substances from the mast cell (e.g. mast cell stabilizers), drugs with multiple modes of action (e.g. antihistamine/mast cell stabilizing agents), and drugs that can actively constrict blood vessels thus reducing redness and swelling (e.g. vasoconstrictors). The criteria which may be considered in evaluating the appropriateness of an agent for a patient include: efficacy at onset of action, duration of action, how well it controls the individual signs and symptoms of ocular allergy, and comfort of the drop when instilled in the eye. The comfort of an ophthalmic product depends on the active pharmaceutical ingredient itself, as well as the nature of the formulation and the vehicle that makes up the product. For example, oral antihistamines have been shown to induce decreased tear production and lead to dryness of the ocular surface, making the eye susceptible to irritation by an ophthalmic product.

The currently available treatments which contain an antihistamine or a mast cell stabilizer typically provide relief for only acute allergic conjunctivitis and don't address the signs and symptoms of the late phase inflammatory reactions (i.e., chronic, refractory, or persistent allergy).

Currently available treatments for allergic rhinoconjunctivitis include eyedrops, nasal sprays, and systemic oral agents. Currently approved anti-allergy eyedrops are indicated for ocular allergy and nasal sprays are targeted for nasal allergy. Systemic agents, while they have indications to treat both nasal and ocular symptoms, several well controlled clinical trials conducted to ophthalmic standards have shown that systemic antihistamines are inferior to eyedrops in treating the ocular signs and symptoms (Spangler et al., Clin. Ther. 25(8), 2245-2267 (2003), are not in fact clinically effective on eye allergy, and actually have been shown by objective measures to reduce tear production on the eye by 50%, causing ocular dryness (Ousler et al, Ann Allergy Asthma Immunol. Nov; 93(5):460-4 (2004)). Further studies have shown that the combination of an eyedrop and nasal steroid is more effective than a systemic agent in treating the ocular and nasal signs and symptoms of allergy (Lanier et al. Clin. Ther. 24(7), 1161-1174 (2002)).
Fluticasone propionate (S-(fluoromethyl)6. alpha., 9-difluro- 11.beta., 17-dihydroxy-
6.alpha.-methy- 1-3-oxoandrosta-1,4-diene-17.beta.-carbothioate,17-propionate) is an anti-
inflammatory corticosteroid described in U.S. Pat. No. 5,676,929, incorporated herein by
reference in its entirety. It is known within the art that the acute and chronic use of large doses
of corticosteroids, such as fluticasone propionate, may produce serious side effects. Such signs or
symptoms are generally dose dependent and may include musculoskeletal effects (including
osteooporosis, myopathy, aseptic necrosis of bone), ophthalmic effects (including posterior
subcapsular cataracts, increased intraocular pressure, and increased risk of infection),
gastrointestinal effects (including ulcers, pancreatitis, nausea, vomiting), cardiovascular effects
(hypertension, atherosclerosis), central nervous system effects (pseudotumor cerebri, psychiatric
reactions), dermatological effects (hirsutism, redistribution of subcutaneous fat, impaired wound
healing, thinning of the skin) and suppression of the hypothalamus-pituitary-adrenal axis.
Further, it is known in the art that chronic use of large doses of fluticasone propionate may result
in hypercorticism.

There thus exists a need to develop an effective, stable yet comfortable and safe
fluticasone formulation for ophthalmic administration for the treatment of allergic conjunctivitis
(i.e., the acute phase, the late inflammatory phase, or both) and allergic rhinoconjunctivitis. Such
formulations for administration directly to the eye would be advantageous over systemic oral
formulations and nasal sprays due to direct local effect, faster action and avoidance of the
systemic side effects associated with systemic administration.

SUMMARY OF THE INVENTION

The present invention provides comfortable topical ophthalmic formulations for the
treatment of both acute and late phase signs of allergic conjunctivitis as well as
rhinoconjunctivitis which contain fluticasone, alone or in combination with one or more
additional active agents (i.e., fluticasone alone or fluticasone combination formulations), to
relieve the signs and symptoms of allergic conjunctivitis and/or rhinoconjunctivitis, particularly
ocular itching and/or nasal symptoms (e.g., itchy, running nose, sneezing, nasal/sinus
congestion). Surprisingly, once a day dosing of the fluticasone formulations of the invention is
effective to mitigate the symptoms of allergic conjunctivitis and/or rhinoconjunctivitis,
particularly ocular itching and/or nasal symptoms (e.g., itchy, running nose, sneezing, nasal/sinus congestion). More surprisingly, the fluticasone formulations of the invention do not increase intraocular pressure in the eye after repeated use (e.g., after 14 days in a study population, described herein). As such the fluticasone formulations of the invention are safe for ocular use.

The ophthalmic administration of fluticasone using the formulations of the present invention may lower negative systemic side effects usually associated with nasal or systemic administration of the drug and may increase the efficacy of the drug in the eye. Accordingly, the present invention provides topical ophthalmic formulations of fluticasone that are comfortable when instilled in the eye and effective to mitigate the symptoms of ocular allergy such as ocular itching, redness, chemosis, lid swelling, and nasal symptoms associated with ocular allergy (e.g., stuffy, runny nose).

In a particular embodiment, the formulations described herein provide stable formulations comprising fluticasone as the only active agent, suitable for ophthalmic use in a comfortable ophthalmic formulation when instilled directly in the eye. The fluticasone alone formulations (i.e., fluticasone as the only active agent) of the invention, are surprisingly more effective in mitigating the signs and symptoms of ocular allergy such as ocular itching, redness, chemosis, lid swelling, and nasal symptoms associated with ocular allergy/rhinoconjunctivitis, than conventional antihistamine and/or mast cell stabilizer agents that are typically used to treat allergic conjunctivitis and/or rhinoconjunctivitis. Antihistamines and mast cell stabilizers do not effectively block all allergic and pro-inflammatory mediators from the mast cell. While antihistamines and mast cell stabilizers may effectively mask itching, they have minimal effects on redness, tearing, swelling and inflammation. Without intending to be bound by any theory, fluticasone can effectively halt the transcription and production of inflammatory mediators and down-regulate the production of anti-inflammatory mediators, thereby treating the signs and symptoms of both acute and late phase allergic conjunctivitis (i.e., the aggregate disease).

In one embodiment, the fluticasone formulation of the invention comprises a stable ophthalmic formulation of fluticasone as the only active ingredient at a concentration of 0.001% to 1.0% (w/v), or any specific value within said range. Preferably, fluticasone is present in the formulation at a concentration of 0.001% and 0.2% (w/v), or any specific value within said range. For example, fluticasone is formulated at a concentration of 0.001%, 0.005%, 0.01%,
0.015%, 0.025%, or 0.2% (w/v). In a particular embodiment, fluticasone is present in the formulation at a concentration of 0.005% (w/v). In another particular embodiment, fluticasone is present in the formulation at a concentration of 0.01% (w/v), and yet in another embodiment fluticasone is present in the formulation at a concentration of 0.001% (w/v).

The invention also provides ophthalmic formulations of fluticasone in combination with one or more active ingredients including but not limited to an antihistimine such as cetirizine, antazoline, astemizole, azelastine, bepotastine, bilastine, brompheniramine, chlorpheniramine, clemastine, desloratidine, dexamfetamine, diphenhydramine, doxylamine, ebastine, emedastine, epinastine, fexofenadine, hydroxyzine, ketotifen, levocabastine, levocetirizine, loratidine, mequitazine, mizolastine, norketotifen, olopatadine, oxatomide, phenindamine, pheniramine, pyrilamine, terfenadine, and triprolidine; a vasoconstrictor such as naphazoline, oxymetazoline, phenylephrine, or tetrahydrozoline; or any combination thereof.

The fluticasone combination formulations are effective in further mitigating the symptoms of ocular allergy such as ocular itching, redness, chemosis, lid swelling, and nasal symptoms associated with ocular allergy, as well as allergic rhinoconjunctivitis.

More specifically, the fluticasone combination formulations of the invention (for example without limitation, fluticasone and cetirizine in combination) provide a comprehensive treatment benefit for both acute and late phase reactions of allergic conjunctivitis that cannot be achieved by the use of a single anti-allergic, or other active agent, alone. As previously stated, antihistamines and mast cell stabilizers do not effectively block all allergic and pro-inflammatory mediators from the mast cell. Antihistamines and mast cell stabilizers may effectively mask itching but they have minimal effects on redness, tearing, swelling and inflammation. However, when an antihistamine or mast cell stabilizer is combined with another active agent which can halt the transcription and production of inflammatory mediators and down-regulate the production of anti-inflammatory mediator, such as a steroid (e.g., fluticasone), treatment of the signs and symptoms of acute and late phase allergic conjunctivitis (i.e., the aggregate disease) is achieved. Likewise, such fluticasone combination formulations provide a comprehensive treatment benefit for rhinoconjunctivitis that cannot be achieved by the use of a single anti-allergic, or other active agent alone, for these same reasons.
In one embodiment, the fluticasone combination formulation of the invention comprises a stable ophthalmic formulation of fluticasone at a concentration of 0.001% to 1.0% (w/v), or any specific value within said range. Preferably, fluticasone is present in the combination formulation at a concentration of 0.001% and 0.2% (w/v), or any specific value within said range. For example, fluticasone is formulated at a concentration of 0.001%, 0.005%, 0.01%, 0.015%, 0.025%, or 0.2% (w/v). In a particular embodiment, fluticasone is present in the combination formulation at a concentration of 0.005% (w/v). In another particular embodiment, fluticasone is present in the combination formulation at a concentration of 0.01% (w/v).

In some embodiments, the fluticasone formulations of the invention comprise a tear substitute. In particular embodiments, the tear substitute is hydroxypropylmethyl cellulose (Hypromellose or HPMC). According to some embodiments, the concentration of HPMC ranges from about 0.1% to about 2% w/v, or any specific value within said range. According to some embodiments, the concentration of HPMC ranges from about 0.5% to about 1% w/v, or any specific value within said range. In a preferred embodiment, the concentration of HPMC ranges from about 0.1% to about 1.0% w/v, or any specific value within said range (e.g., 0.1-0.2%, 0.2-0.3%, 0.3-0.4%, 0.4-0.5%, 0.5-0.6%, 0.6-0.7%, 0.7-0.8%, 0.8-0.9%, 0.9-1.0%; about 0.2%, about 0.21%, about 0.22%, about 0.23%, about 0.24%, about 0.25%, about 0.26%, about 0.27%, about 0.28%, about 0.29%, about 0.30%, about 0.70%, about 0.71%, about 0.72%, about 0.73%, about 0.74%, about 0.75%, about 0.76%, about 0.77%, about 0.78%, about 0.79%, about 0.80%, about 0.81%, about 0.82%, about 0.83%, about 0.84%, about 0.85%, about 0.86%, about 0.87%, about 0.88%, about 0.89%, or about 0.90%).

In another particular embodiment the tear substitute is carboxymethyl cellulose (CMC). According to some embodiments, the concentration of CMC ranges from about 0.1% to about 2% w/v, or any specific value within said range. According to some embodiments, the concentration of CMC ranges from about 0.1% to about 1% w/v, or any specific value within said range. In a preferred embodiment, the concentration of CMC ranges from about 0.7% to about 0.9% w/v, or any specific value within said range (i.e., about 0.70%, about 0.71%, about 0.72%, about 0.73%, about 0.74%, about 0.75%, about 0.76%, about 0.77%, about 0.78%, about 0.79%, about 0.80%, about 0.81%, about 0.82%, about 0.83%, about 0.84%, about 0.85%, about 0.86%, about 0.87%, about 0.88%, about 0.89%, or about 0.90%).
In yet another particular embodiment, the fluticasone formulations of the invention comprise a polymeric, mucoadhesive vehicle. Examples of mucoadhesive vehicles suitable for use in the methods or formulations of the invention include but are not limited to aqueous polymeric suspensions comprising one or more polymeric suspending agents including without limitation dextran, polyethylene glycol, polyvinylpyrolidone, polysaccharide gels, Gelrite®, cellulosic polymers, and carboxy-containing polymer systems. In a particular embodiment, the polymeric suspending agent comprises a crosslinked carboxy-containing polymer (e.g., polyacrylate). In another particular embodiment, the polymeric suspending agent comprises a polyethylene glycol (PEG). Examples of cross-linked carboxy-containing polymer systems suitable for use in the topical stable ophthalmic fluticasone formulations of the invention include but are not limited to Noveon AA-I, Carbopol®, and/or DuraSite® (InSite Vision).

Optionally, the formulations of the invention contain a preservative. In particular embodiments the preservative is benzalkonium chloride or a derivative thereof (e.g., Polyquad®), or a stabilized oxychloro complex (e.g., Purite®), or sodium perborate, or sorbate.

In certain embodiments, the fluticasone alone and fluticasone combination formulations of the invention are formulated in a vehicle comprising 1% Polyethylene Glycol 400, NF; 0.2% Dibasic Sodium Phosphate, Anhydrous, USP; 0.25% Hypromellose, USP; 0.1% Polysorbate 80, NF; 1.2% to 1.8% Glycerin (or any specific value within said range), USP; 0.025% Edetate Disodium, USP; 0.01% Benzalkonium Chloride, NF (pH 7.0).

In one preferred embodiment, the fluticasone formulation comprises 0.005% fluticasone, 1% Polyethylene Glycol 400, NF, 0.2% Dibasic Sodium Phosphate, Anhydrous, USP, 0.25% Hypromellose, USP, 0.1% Polysorbate 80, NF, 1.8% Glycerin, USP, 0.025% Edetate Disodium, USP, and 0.01% Benzalkonium Chloride, NF (pH 7.0).

In another preferred embodiment, the fluticasone formulation comprises 0.01% fluticasone, 1% Polyethylene Glycol 400, NF, 0.2% Dibasic Sodium Phosphate, Anhydrous, USP, 0.25% Hypromellose, USP; 0.1% Polysorbate 80, NF, 1.2% Glycerin, USP, 0.025% Edetate Disodium, USP, and 0.01% Benzalkonium Chloride, NF (pH 7.0).

According to some embodiments, the ophthalmic formulations of the present invention has a viscosity that ranges from about 10 to about 150 centipoise (cpi), preferably about 15 to
about 120 cpi, even more preferably about 20 to about 90 cpi (or any specific value within said range). According to a preferred embodiment, the ophthalmic formulations of the present invention has a viscosity that ranges from about 15 cpi to about 30 cpi, or any specific value within said range (i.e., about 15 cpi, about 16 cpi, about 17 cpi, about 18 cpi, about 19 cpi, about 20 cpi, about 22 cpi, about 23 cpi, about 24 cpi, about 25 cpi, about 26 cpi, about 27 cpi, about 28 cpi, about 29 cpi, about 30 cpi). According to another preferred embodiment, the ophthalmic formulations of the present invention has a viscosity that ranges from about 70 cpi to about 90 cpi, or any specific value within said range (i.e., about 70 cpi, about 71 cpi, about 72 cpi, about 73 cpi, about 74 cpi, about 75 cpi, about 76 cpi, about 77 cpi, about 78 cpi, about 79 cpi, about 80 cpi, about 81 cpi, about 82 cpi, about 83 cpi, about 84 cpi, about 85 cpi, about 86 cpi, about 87 cpi, about 88 cpi, about 89 cpi or about 90 cpi).

The invention also provides methods for the treatment of allergic conjunctivitis in a subject in need of such treatment by administering a fluticasone formulation of the invention (i.e., alone or in combination with one or more active ingredients) directly to the eye of a subject in need of such treatment or prevention. Preferably, the formulation of the invention is administered once a day (q.d.). In certain embodiments, the methods of the invention (i.e., administration of a formulation of the invention directly to the eye) are also effective to treat nasal symptoms associated with allergic conjunctivitis. The invention also provides methods of treating and preventing the symptoms of allergic rhinoconjunctivitis by administering a fluticasone formulation of the invention (i.e., fluticasone alone or in combination with an additional active agent such as an antihistamine (e.g., without limitation cetirizine or ketotifen) or a vasoconstrictor (e.g. without limitation, naphazoline or oxymetazoline) directly to the eye of a subject in need of such treatment or prevention. By providing a treatment option in eye drop form, the present invention will improve quality of life in patients with allergic rhinoconjunctivitis/rhinitis (See e.g., Berger et al., Ann. Allergy Asthma Immunol. Oct 95(4), 361-71 (2005)).

The invention also provides kits comprising a pharmaceutical composition of fluticasone formulated for ophthalmic use and instructions for such use. Other features and advantages of the invention will become apparent from the following detailed description and claims.
BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B depict a study design (screening and evaluation) for testing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing ocular and nasal symptoms of ocular allergy in an allergic conjunctivitis model.

Figure 2 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing ocular itching assessed on a scale of 0 (no itching) to 4 (severe itching) over time.

Figure 3 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing conjunctival redness, assessed on a scale of 0 (no redness) to 4 (severe redness) over time.

Figure 4 is line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing lidswelling, assessed on a scale of 0 (no swelling) to 3 (severe swelling) over time.

Figure 5 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing nasal congestion, assessed on a scale of 0 (no congestion) to 4 (severe congestion) over time.

Figure 6 is a bar graph summarizing the results shown in Figures 1-5.

Figure 7 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing ciliary redness, assessed on a scale of 0 (no redness) to 4 (severe redness) over time.

Figure 8 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing episcleral redness, assessed on a scale of 0 (no redness) to 4 (severe redness) over time.

Figure 9 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing chemosis, assessed on a scale of 0 (none) to 4 (severe) over time.

Figure 10 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing watery eyes, assessed on a scale of 0 (none) to 4 (severe) over time.

Figure 11 is a bar graph summarizing the results shown in Figures 7-10.
Figure 12 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing rhinorrhea, assessed on a scale of 0 (none) to 4 (severe) over time.

Figure 13 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing ear or palate pruritis, assessed on a scale of 0 (none) to 4 (severe) over time.

Figure 14 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle in reducing nasal pruritis, assessed on a scale of 0 (none) to 4 (severe) over time.

Figure 15 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle on total nasal score, assessed on a scale of 0 (no nasal symptoms) to 16 (multiple nasal symptoms) over time.

Figure 16 is a bar graph summarizing the results shown in Figures 12-15.

Figure 17 is a line graph comparing the efficacy of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle on PNIF.

Figure 18 a line graph comparing the drop comfort of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle, assessed on a scale of 0 (extremely comfortable) to 10 (extremely uncomfortable) over time.

Figure 19 a line graph comparing the drop comfort of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle, assessed on a scale of 0 (extremely comfortable) to 10 (extremely uncomfortable) over time.

Figure 20 is a chart summarizing the incidence of adverse events associated with installation of Fluticasone 0.001%, 0.005% and 0.01% in the eye.

Figure 21 is a bar graph summarizing the effects of Fluticasone 0.001%, 0.005% and 0.01% as compared to vehicle on intraocular pressure.

**DETAILED DESCRIPTION**

The invention is based, in part, upon the surprising and uppredicatable discovery that stable topical ophthamic formulations of fluticasone alone (i.e., fluticasone as the only active agent in the formulation) are both comfortable when applied directly to the eye and effective to treat both the acute and late phase reactions of allergic conjunctivitis, as well as allergic
rhinoconjunctivitis. An even further unexpected finding was that the most efficacious dose was not the highest concentration tested. Preferably, fluticasone is in the form of fluticasone propionate or fluticasone dipropionate. Moreover, the stable topical fluticasone formulations of the invention do not increase intraocular pressure in the eye after repeated use and are therefore safe for short term ocular administration.

The invention also features ophthalmic formulations of fluticasone in combination with one or more additional active ingredients such as an antihistamine (e.g., without limitation, cetirizine or ketotifen) or a vasoconstrictor (e.g., without limitation, oxymetazoline or naphazoline). Such fluticasone combination formulations are effective in further mitigating the acute and late phase signs and symptoms of allergic conjunctivitis, such as ocular itching, redness, chemosis, lid swelling and nasal symptoms. Such formulations are also effective in mitigating the signs and symptoms of rhinoconjunctivitis, such as runny nose, sneezing, nasal/sinus congestion and red, watery and/or itchy eyes.

The comfort, safety, efficacy, solubility, and stability of the ophthalmic formulations of the invention could not have been predicted by one skilled in the art. Based on the known mechanism of action of steroids the skilled artisan would anticipate that the highest dose of steroid would offer the highest efficacy in reducing the signs and symptoms of allergic conjunctivitis and/or allergic rhinitis. Surprisingly, data presented herein demonstrates that a mid-range dose of fluticasone (0.005%) was consistently more effective than both a lower dose of fluticasone (0.001%) and a higher dose of fluticasone (0.01%) in reducing both ocular and nasal symptoms associated with allergic conjunctivitis (see Example 1). Even more surprisingly, the mid-range dose of fluticasone (0.005%) was more comfortable than the lower dose (0.001%) and the highest dose (0.01%), with no adverse effect on intraocular pressure. The data unexpectedly demonstrates that there is an optimal fluticasone concentration which is both comfortable and safe in the eye, as well as highly efficacious in reducing both ocular and nasal symptoms associated with allergic conjunctivitis and rhinitis. Such optimal concentration could not be arrived at by routine optimization.

In some embodiment, the fluticasone formulations of the invention comprise one or more tear substitute components. The fluticasone component provides relief of the symptoms of allergic conjunctivitis, and the one or more tear substitute component provides ocular surface protection via enhancement of the tear film (as evident by increased tear film break up time), and
can act to enhance dwell time on the ocular surface thus increasing duration of activity. An effective amount of such formulations may be used to treat and/or prevent signs and symptoms associated with acute and/or late phase allergic conjunctivitis and/or general eye irritation, and can also be used to treat another eye disorder if it contains a drug for that disorder. An effective amount of such formulations may also be used to treat and/or prevent signs and symptoms of allergic rhinoconjunctivitis. Such formulations provide a comfortable ophthalmic formulation when instilled in the eye and have enhanced efficacy and/or duration of action over formulations of fluticasone that are not combined with such other agents.

The superior efficacy of the fluticasone/tear substitute formulations is attributed to, among other things, the synergistic effect of the combination of ingredients in them. The combination of fluticasone and tear substitute, act synergistically to provide a longer dwell time of the fluticasone on the ocular surface, thus increasing duration and efficacy of action, and to prolong the integrity of the tear film thereby providing protection of the ocular surface (e.g., by increasing the tear film break up time and/or the Ocular Protection Index). As such, the compositions of the invention are comfortable upon instillation into the eye, and may be used for relief of acute or chronic allergic conjunctivitis and/or rhinoconjunctivitis, and are particularly suitable for both intermittent and long term use.

**Formulations**

Preferably, the ophthalmic compositions according to the present invention are formulated as solutions, suspensions, ointments, emulsions, gels and other dosage forms for topical administration (such as an eye drop, an ophthalmic ointment, an ophthalmic gel, and the like). For ophthalmic topical administration, the dosage form of the ophthalmic compositions includes solutions, ointments, ophthalmic inserting agents, gels, emulsions, suspensions and solid eye drops and the like, and may be properly selected therefrom. In addition, modifications such as sustained-releasing, stabilizing and easy-absorbing properties and the like may be further applied to such the preparations. These dosage forms are sterilized, for example, by filtration through a microorganism separating filter, heat sterilization or the like.

Aqueous solutions are generally preferred, based on ease of formulation, as well as a patient's ability to easily administer such compositions by means of instilling one to two drops of
the solutions in the affected eyes. However, the compositions may also be suspensions, viscous or semi-viscous gels, or other types of solid or semisolid compositions. In one embodiment, the fluticasone formulations of the invention are aqueous formulations. The aqueous formulations of the invention are typically more than 50%, preferably more than 75%, and most preferably more than 90% by weight water. In another embodiment, the fluticasone formulations are lyophilized formulations.

In a particular embodiment, the fluticasone formulations of the invention are formulated as a suspension. Such formulations generally have a particle size no greater than 30 μm. The skilled artisan would recognize that optimal particle size can be achieved by milling (jet, ball, or other mechanical sizing), or using techniques such as antisolvent crystallization. Additionally the suspension formulation of the invention may include suspending and dispersing agents to prevent agglomeration of the particles. For example, without limitation, a suspension formulation of the invention contains fluticasone propionate, a phosphate buffer system containing a combination of mono and dibasic phosphate to yield a pH of 7.0, propylene glycol, polysorbate 80, hypromellose, edetate disodium and benzalkonium chloride.

Active Agents

According to preferred embodiments, there is provided an ophthalmic composition comprising a therapeutically effective amount of fluticasone, or a pharmaceutically acceptable salt or ester thereof. As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids; and the salts prepared from organic acids such as acetic, fuoric, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, tolunesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic acids.
Fluticasone propionate is the preferred pharmaceutically acceptable salt. Fluticasone propionate, also known as S-fluoromethyl-6- α9-difluoro-1-β-hydroxy-16- α-methyl-3-oxoandrosta-1,4-diene-17-β-carbothioate, 17-propionate, is a synthetic, trifluorinated, corticosteroid having the chemical formula C25H31F3O5S. It is a white to off-white powder with a molecular weight of 500.6 g/mol. Fluticasone propionate is practically insoluble in water (0.14 µg/ml), freely soluble in dimethyl sulfoxide and dimethyl-formamide, and slightly soluble in methanol and 95% ethanol.

According to some embodiments, fluticasone is the primary active agent in the formulations of the present invention. According to some embodiments, the fluticasone formulations of the present invention comprise (or consist essentially of) fluticasone as the sole active agent. According to some embodiments, the fluticasone formulations of the present invention comprise (or consist essentially of) fluticasone as the sole anti-allergic agent. Preferably fluticasone is in the form of fluticasone propionate or fluticasone dipropionate. In certain embodiments of the invention, fluticasone is formulated at a concentration of 0.001% to 1.0% (w/v), or any specific value within said range. Preferably, fluticasone is present in the formulation at a concentration of 0.001% and 0.2% (w/v), or any specific value within said range. For example, fluticasone is formulated at a concentration of 0.001%, 0.005%, 0.01%, 0.015%, 0.025%, or 0.2% (w/v). In a particular embodiment, fluticasone is present in the formulation at a concentration of 0.005% (w/v). In another particular embodiment, fluticasone is present in the formulation at a concentration of 0.01% (w/v).

According to some embodiments, however, fluticasone may be formulated with other active agents as described herein. For example, fluticasone may be formulated with one or more additional anti-allergic agents. The term "anti-allergenic agent" refers to a molecule or composition that treats ocular allergy or reduces a symptom of ocular allergy. The term "ocular allergy" refers to any allergic disease of the eye, e.g., seasonal/perennial ocular allergy, vernal keratoconjunctivitis, giant papillary conjunctivitis, perennial ocular allergy and atopic keratoconjunctivitis. The signs and symptoms of ocular allergies include chemosis, eye itching, tearing, redness and swelling, and nasal symptoms associated with ocular allergy (e.g., stuffy, runny nose). Non-limiting examples of antiallergenic agents include "antihistamines" or drugs which block histamine from binding to the histamine receptors, "mast cell stabilizers" or drugs that block the release of histamine and other substances from the mast cell, "drugs with multiple
modes of action” or drugs that are antiallergenic agents having multiple modes of action (e.g. drugs that are antihistamines and mast cell stabilizers, drugs with antihistamine, mast cell stabilizing and anti-inflammatory activity, etc.), steroids, and nonsteroidal anti-inflammatory drugs or "NSAIDs."

In certain embodiments, fluticasone is formulated with one or more additional active agents selected from a mast cell stabilizer such as nedocromil, iodoxamide, cromolyn, or cromolyn sodium; a non-steroidal anti-inflammatory drug ("NSAID") such as diclofenac or ketorolac tromethamine, bromfenac, or nepafenac; a vasoconstrictor such as naphazoline, antolazine, tetrahydozoline or oxymetazoline; an antihistimine such as antazoline, astemizole, azelastine, bepotastine, bilastine, brompheniramine, chlorpheniramine, clemastine, desloratidine, dexampheniramine, diphenhydramine, doxylamine, ebastine, emedastine, epinastine, fexofenadine, hydroxyzine, ketotifen, levocabastine, levocetirizine, loratidine, mequitazine, mizolastine, norketotifen, olopatadine, oxatomide, phenindamine, pheniramine, pyrilamine, terfenidine, and triprolidine; or an alpha-adrenergic agonist such as epinephrine, fenoxazoline, indanazoline, naphazoline, oxedrine, phenylephrine, tefazoline, tetryzoline, tramazoline, tynamzoline, oxymetazoline, or xylometazoline.

**Excipients**

In some embodiments, the fluticasone formulations of the invention comprise one or more pharmaceutically acceptable excipients. The term excipient as used herein broadly refers to a biologically inactive substance used in combination with the active agents of the formulation. An excipient can be used, for example, as a solubilizing agent, a stabilizing agent, a surfactant, a demulcent, a viscosity agent, a diluent, an inert carrier, a preservative, a binder, a disintegrant, a coating agent, a flavoring agent, or a coloring agent. Preferably, at least one excipient is chosen to provide one or more beneficial physical properties to the formulation, such as increased stability and/or solubility of the active agent(s). A "pharmaceutically acceptable" excipient is one that has been approved by a state or federal regulatory agency for use in animals, and preferably for use in humans, or is listed in the U.S. Pharmacopia, the European Pharmacopia or another generally recognized pharmacopia for use in animals, and preferably for use in humans.
Examples of carriers that may be used in the formulations of the present invention include water, mixtures of water and water-miscible solvents, such as C1 to C7-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% non-toxic water-soluble polymers, natural products, such as gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar and acacia, starch derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products, such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably cross-linked polyacrylic acid, such as neutral Carbopol, or mixtures of those polymers. The concentration of the carrier is, typically, from 1 to 100000 times the concentration of the active ingredient.

Further examples of excipients include certain inert proteins such as albumins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as aspartic acid (which may alternatively be referred to as aspartate), glutamic acid (which may alternatively be referred to as glutamate), lysine, arginine, glycine, and histidine; fatty acids and phospholipids such as alkyl sulfonates and caprylate; surfactants such as sodium dodecyl sulphate and polysorbate; nonionic surfactants such as such as TWEEN®, PLURONICS®, or a polyethylene glycol (PEG) designated 200, 300, 400, or 600; a Carbowax designated 1000, 1500, 4000, 6000, and 10000; carbohydrates such as glucose, sucrose, mannose, maltose, trehalose, and dextrins, including cyclodextrins; polyols such as mannitol and sorbitol; chelating agents such as EDTA; and salt-forming counter-ions such as sodium.

In a particular embodiment, the carrier is a polymeric, mucoadhesive vehicle. Examples of mucoadhesive vehicles suitable for use in the methods or formulations of the invention include but are not limited to aqueous polymeric suspensions comprising one or more polymeric suspending agents including without limitation dextrans, polyethylene glycol, polyvinylpyrrolidone, polysaccharide gels, Gelrite®, cellulosic polymers, and carboxy-containing polymer systems. In a particular embodiment, the polymeric suspending agent comprises a crosslinked carboxy-containing polymer (e.g., polycarbophil). In another particular embodiment, the polymeric suspending agent comprises polyethylene glycol (PEG). Examples of cross-linked carboxy-containing polymer systems suitable for use in the topical stable ophthalmic fluticasone formulations of the invention include but are not limited to Noveon AA-I, Carbopol®, and/or DuraSite® (InSite Vision).
In other particular embodiments, the fluticasone formulations of the invention comprise one or more excipients selected from among the following: a tear substitute, a tonicity enhancer, a preservative, a solubilizer, a viscosity enhancing agent, a demulcent, an emulsifier, a wetting agent, a sequestering agent, and a filler. The amount and type of excipient added is in accordance with the particular requirements of the formulation and is generally in the range of from about 0.0001% to 90% by weight.

According to preferred embodiments, the fluticasone formulations of the invention contain a viscosity enhancing agent or combination of viscosity enhancing agents, a tonicity agent or combination of tonicity agents, and a buffer or combination of buffers.

According to preferred embodiments, the fluticasone formulations of the invention contain a demulcent or combination of demulcents, a tonicity agent or combination of tonicity agents, and a buffer or combination of buffers.

According to preferred embodiments, the fluticasone formulations of the invention contain a demulcent or combination of demulcents

Tear substitutes

According to some embodiments, the fluticasone formulations may include an artificial tear substitute. The term "tear substitute" refers to molecules or compositions which lubricate, "wet," approximate the consistency of endogenous tears, aid in natural tear build-up, or otherwise provide temporary relief of dry eye signs or symptoms and conditions upon ocular administration. A variety of tear substitutes are known in the art and include, but are not limited to: monomeric polyols, such as, glycerol, propylene glycol, and ethylene glycol; polymeric polyols such as polyethylene glycol; cellulose esters such hydroxypropylmethyl cellulose, carboxymethyl cellulose sodium and hydroxy propylcellulose; dextrans such as dextran 70; water soluble proteins such as gelatin; vinyl polymers, such as polyvinyl alcohol, polyvinylpyrrolidone, and povidone; and caromers, such as caromer 934P, caromer 941, caromer 940 and caromer 974P. Many such tear substitutes are commercially available, which include, but are not limited to cellulose esters such as Bion Tears®, Celluvisc®, Genteal®, OccuCoat®, Refresh®, Systane®, Teargen II®, Tears Naturale®, Tears Natural II®, Tears Naturale Free®, and TheraTears®; and polyvinyl alcohols such as Akwa Tears®, HypoTears®, Moisture Eyes®, Murine Lubricating®, and Visine Tears®, Soothe®. Tear substitutes may also
be comprised of paraffins, such as the commercially available Lacri-Lube® ointments. Other commercially available ointments that are used as tear substitutes include Lubrifresh PM®, Moisture Eyes PM® and Refresh PM®.

In one preferred embodiment of the invention, the tear substitute comprises

- hydroxypropylmethyl cellulose (Hypromellose or HPMC). According to some embodiments, the concentration of HPMC ranges from about 0.1% to about 2% w/v, or any specific value within said range. According to some embodiments, the concentration of HPMC ranges from about 0.5% to about 1.5% w/v, or any specific value within said range. According to some embodiments, the concentration of HPMC ranges from about 0.1% to about 1% w/v, or any specific value within said range. According to some embodiments, the concentration of HPMC ranges from about 0.6% to about 1% w/v, or any specific value within said range. In a preferred embodiment, the concentration of HPMC ranges from about 0.1% to about 1.0% w/v, or any specific value within said range (i.e., 0.1-0.2%, 0.2-0.3%, 0.3-0.4%, 0.4-0.5%, 0.5-0.6%, 0.6-0.7%, 0.7-0.8%, 0.8-0.9%, 0.9-1.0%; about 0.2%, about 0.21%, about 0.22%, about 0.23%, about 0.24%, about 0.25%, about 0.26%, about 0.27%, about 0.28%, about 0.29%, about 0.30%, about 0.70%, about 0.71%, about 0.72%, about 0.73%, about 0.74%, about 0.75%, about 0.76%, about 0.77%, about 0.78%, about 0.79%, about 0.80%, about 0.81%, about 0.82%, about 0.83%, about 0.84%, about 0.85%, about 0.86%, about 0.87%, about 0.88%, about 0.89%, or about 0.90%).

For example, without limitation, a tear substitute which comprises hydroxypropyl methyl cellulose is GenTeal® lubricating eye drops. GenTeal® (CibaVision - Novartis) is a sterile lubricant eye drop containing hydroxypropylmethyl cellulose 3 mg/g and preserved with sodium perborate. Other examples of an HPMC-based tear are provided.

In another preferred embodiment, the tear substitute comprises carboxymethyl cellulose sodium. For example, without limitation, the tear substitute which comprises carboxymethyl cellulose sodium is Refresh® Tears. Refresh® Tears is a lubricating formulation similar to normal tears, containing a, mild non-sensitizing preservative, stabilised oxychloro complex (Purite™), that ultimately changes into components of natural tears when used.
In a preferred embodiment, the tear substitute, or one or more components thereof, is an aqueous solution having a viscosity in a range which optimizes efficacy of supporting the tear film while minimizing blurring, lid caking, etc. Preferably, the viscosity of the tear substitute, or one or more components thereof, ranges from about 10 to about 150 centipoise (cpi), preferably about 15 to about 120 cpi, even more preferably about 20 to about 90 cpi (or any specific value within said ranges). According to a preferred embodiment, the ophthalmic formulations of the present invention has a viscosity that ranges from about 15 cpi to about 30 cpi, or any specific value within said range (i.e., about 15 cpi, about 16 cpi, about 17 cpi, about 18 cpi, about 19 cpi, about 20 cpi, about 20 cpi, about 22 cpi, about 23 cpi, about 24 cpi, about 25 cpi, about 26 cpi, about 27 cpi, about 28 cpi, about 29 cpi, about 30 cpi). In a particular embodiment, the viscosity of the tear substitute, or one or more components thereof, is about 20 cpi. According to another preferred embodiment, the ophthalmic formulations of the present invention has a viscosity that ranges from about 70 cpi to about 90 cpi, or any specific value within said range (i.e., about 70 cpi, about 71 cpi, about 72 cpi, about 73 cpi, about 74 cpi, about 75 cpi, about 76 cpi, about 77 cpi, about 78 cpi, about 79 cpi, about 80 cpi, about 81 cpi, about 82 cpi, about 83 cpi, about 84 cpi, about 85 cpi, about 86 cpi, about 87 cpi, about 88 cpi, about 89 cpi or about 90 cpi).

Viscosity may be measured at a temperature of 20° C +/- 1° C using a Brookfield Cone and Plate Viscometer Model VDV-III Ultra+ with a CP40 or equivalent Spindle with a shear rate of approximately 22.50 +/- approximately 10 (1/sec), or a Brookfield Viscometer Model LVDV-E with a SC4-18 or equivalent Spindle with a shear rate of approximately 26 +/- approximately 10 (1/sec). Alternatively, viscosity may be measured at 25° C +/- 1° C using a Brookfield Cone and Plate Viscometer Model VDV-III Ultra+ with a CP40 or equivalent Spindle with a shear rate of approximately 22.50 +/- approximately 10 (1/sec), or a Brookfield Viscometer Model LVDV-E with a SC4-18 or equivalent Spindle with a shear rate of approximately 26 +/- approximately 10 (1/sec).

In some embodiments, the tear substitute, or one or more components thereof is buffered to a pH 5.0 to 9.0, preferably pH 5.5 to 7.5, more preferably pH 6.0 to 7.0 (or any specific value within said ranges), with a suitable salt (e.g., phosphate salts). In some embodiments, the tear substitute further comprises one or more ingredients, including without limitation, glycerol, propyleneglycerol, glycine, sodium borate, magnesium chloride, and zinc chloride.
Salts, buffers, and preservatives

The formulations of the present invention may also contain pharmaceutically acceptable salts, buffering agents, or preservatives. Examples of such salts include those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, boric, formic, malonic, succinic, and the like. Such salts can also be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts. Examples of buffering agents include phosphate, citrate, acetate, and 2-(N-morpholino)ethanesulfonic acid (MES).

The fluticasone formulations of the present invention may include a buffer system. As used in this application, the terms "buffer" or "buffer system" is meant a compound that, usually in combination with at least one other compound, provides a buffering system in solution that exhibits buffering capacity, that is, the capacity to neutralize, within limits, either acids or bases (alkali) with relatively little or no change in the original pH. According to some embodiments, the buffering components are present from 0.05% to 2.5% (w/v) or from 0.1% to 1.5% (w/v).

Preferred buffers include borate buffers, phosphate buffers, calcium buffers, and combinations and mixtures thereof. Borate buffers include, for example, boric acid and its salts, for example, sodium borate or potassium borate. Borate buffers also include compounds such as potassium tetraborate or potassium metaborate that produce borate acid or its salt in solutions.

A phosphate buffer system preferably includes one or more monobasic phosphates, dibasic phosphates and the like. Particularly useful phosphate buffers are those selected from phosphate salts of alkali and/or alkaline earth metals. Examples of suitable phosphate buffers include one or more of sodium dibasic phosphate (Na₂HPO₄), sodium monobasic phosphate (NaH₂PO₄) and potassium monobasic phosphate (KH₂PO₄). The phosphate buffer components frequently are used in amounts from 0.01% or to 0.5% (w/v), calculated as phosphate ion.

A preferred buffer system is based upon boric acid/borate, a mono and/or dibasic phosphate salt/phosphoric acid or a combined boric/phosphate buffer system. For example a combined boric/phosphate buffer system can be formulated from a mixture of sodium borate and phosphoric acid, or the combination of sodium borate and the monobasic phosphate.

In a combined boric/phosphate buffer system, the solution comprises about 0.05 to 2.5% (w/v) of a phosphoric acid or its salt and 0.1 to 5.0% (w/v) of boric acid or its salt. The
phosphate buffer is used (in total) at a concentration of 0.004 to 0.2 M (Molar), preferably 0.04 to 0.1 M. The borate buffer (in total) is used at a concentration of 0.02 to 0.8 M, preferably 0.07 to 0.2 M.

Other known buffer compounds can optionally be added to the lens care compositions, for example, citrates, sodium bicarbonate, TRIS, and the like. Other ingredients in the solution, while having other functions, may also affect the buffer capacity. For example, EDTA, often used as a complexing agent, can have a noticeable effect on the buffer capacity of a solution.

According to some embodiments, the pH of the aqueous ophthalmic solution is at or near physiological pH. Preferably, the pH of the aqueous ophthalmic solution is between about 5.5 to about 8.0, or any specific value within said range. According to some embodiments, the pH of the aqueous ophthalmic solution is between about 6.5 to 7.5, or any specific value within said range (e.g., 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5). According to some embodiments, the pH of the aqueous ophthalmic solution is about 7. The skilled artisan would recognize that the pH may be adjusted to a more optimal pH depending on the stability of the active ingredients included in the formulation. According to some embodiments, the pH is adjusted with base (e.g., IN sodium hydroxide) or acid (e.g., IN hydrochloric acid).

For the adjustment of the pH, preferably to a physiological pH, buffers may especially be useful. The pH of the present solutions should be maintained within the range of 5.5 to 8.0, more preferably about 6.0 to 7.5, more preferably about 6.5 to 7.0 (or any specific value within said ranges). Suitable buffers may be added, such as boric acid, sodium borate, potassium citrate, citric acid, sodium bicarbonate, TRIS, and various mixed phosphate buffers (including combinations of Na$_2$HPO$_4$, NaH$_2$PO$_4$ and KH$_2$PO$_4$) and mixtures thereof. Borate buffers are preferred. Generally, buffers will be used in amounts ranging from about 0.05 to 2.5 percent by weight, and preferably, from 0.1 to 1.5 percent.

According to preferred embodiments, the formulations of the present invention do not contain a preservative. In certain embodiments, the ophthalmic formulations additionally comprise a preservative. A preservative may typically be selected from a quaternary ammonium compound such as benzalkonium chloride, benzoconnexion chloride or the like. Benzalkonium chloride is better described as: N-benzyl-N—(Cs-Cis alkyl)-N,N-dimethylammonium chloride. Further examples of preservatives include antioxidants such as vitamin A, vitamin E, vitamin C,
retinyl palmitate, and selenium; the amino acids cysteine and methionine; citric acid and sodium citrate; and synthetic preservatives such as thimerosal, and alkyl parabens, including for example, methyl paraben and propyl paraben. Other preservatives include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzethonium chloride, phenol, catechol, resorcinol, cyclohexanol, 3-pentanol, m-cresol, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate, sodium perborate, sodium chlorite, alcohols, such as chlorobutanol, butyl or benzyl alcohol or phenyl ethanol, guanidine derivatives, such as chlorohexidine or polyhexamethylene biguanide, sodium perborate, Germal®II, sorbic acid and stabilized oxychloro complexes (e.g., Purite®). Preferred preservatives are quaternary ammonium compounds, in particular benzalkonium chloride or its derivative such as Polyquad (see U.S. Pat. No. 4,407,791), alkyl-mercury salts, parabens and stabilized oxychloro complexes (e.g., Purite®). Where appropriate, a sufficient amount of preservative is added to the ophthalmic composition to ensure protection against secondary contaminations during use caused by bacteria and fungi.

In particular embodiments, the fluticasone formulations of the invention comprise a preservative selected from among the following: benzalkonium chloride, 0.001% to 0.05%; benzethonium chloride, up to 0.02%; sorbic acid, 0.01% to 0.5%; polyhexamethylene biguanide, 0.1 ppm to 300 ppm; polyquaternium-1 (Omamer M) - 0.1 ppm to 200 ppm; hypochlorite, perchlorite or chloride compounds, 500 ppm or less, preferably between 10 and 200 ppm); stabilized hydrogen peroxide solutions, a hydrogen peroxide source resulting in a weight % hydrogen peroxide of 0.0001 to 0.1% along with a suitable stabilizer; alkyl esters of p-hydroxybenzoic acid and mixtures thereof, preferably methyl paraben and propyl paraben, at 0.01% to 0.5%; chlorhexidine, 0.005% to 0.01%; chlorobutanol, up to 0.5%; and and stabilized oxychloro complex (Purite®) 0.001% to 0.5%.

In another embodiment, the ophthalmic formulations of this invention do not include a preservative. Such formulations would be useful for patients who wear contact lenses, or those who use several topical ophthalmic drops and/or those with an already compromised ocular surface (e.g. dry eye) wherein limiting exposure to a preservative may be more desirable.
Viscosity enhancing agents and demulcents

In certain embodiments, viscosity enhancing agents may be added to the fluticasone formulations of the invention. Examples of such agents include polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family, vinyl polymers, and acrylic acid polymers.

A variety of viscosity enhancing agents are known in the art and include, but are not limited to: polyols such as, glycerol, glycerin, polyethylene glycol 300, polyethylene glycol 400, polysorbate 80, propylene glycol, and ethylene glycol, polyvinyl alcohol, povidone, and polyvinylpyrrolidone; cellulose derivatives such hydroxypropyl methyl cellulose (also known as hypromellose and HPMC), carboxymethyl cellulose sodium, hydroxypropyl cellulose, hydroxyethyl cellulose, and methyl cellulose; dextrans such as dextran 70; water soluble proteins such as gelatin; carboxomers such as carbomer 934P, carbomer 941, carbomer 940 and carbomer 974P; and gums such as HP-guar, or combinations thereof. Other compounds may also be added to the formulations of the present invention to increase the viscosity of the carrier. Examples of viscosity enhancing agents include, but are not limited to: polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers. Combinations and mixtures of the above agents are also suitable.

According to some embodiments, the concentration of viscosity enhancing agent or combination of agents ranges from about 0.5% to about 2% w/v, or any specific value within said range. According to some embodiments, the concentration of viscosity enhancing agent or combination of agents ranges from about 0.5% to about 1.5% w/v, or any specific value within said range. According to some embodiments, the concentration of viscosity enhancing agent or combination of agents ranges from about 0.5% to about 1% w/v, or any specific value within said range. According to some embodiments, the concentration of viscosity enhancing agent or combination of agents ranges from about 0.6% to about 1% w/v, or any specific value within said range. According to some embodiments, the concentration of viscosity enhancing agent or combination of agents ranges from about 0.7% to about 0.9% w/v, or any specific value within said range (i.e., about 0.70%, about 0.71%, about 0.72%, about 0.73%, about 0.74%, about 0.75%, about 0.76%, about 0.77%, about 0.78%, about 0.79%, about 0.80%, about 0.81%,
0.82%, about 0.83%, about 0.84%, about 0.85%, about 0.86%, about 0.87%, about 0.88%, about 0.89%, or about 0.90%).

In certain embodiments, the fluticasone formulations of the invention comprise ophthalmic demulcents and/or viscosity enhancing polymers selected from one or more of the following: cellulose derivatives such as carboxymethylcellulose (0.01 to 5%) hydroxyethylcellulose (0.01% to 5%), hydroxypropyl methylcellulose or hypromellose (0.01% to 5%), and methylcellulose (0.02% to 5%); dextran 40/70 (0.01% to 1%); gelatin (0.01% to 0.1%); polyols such as glycerin (0.01% to 5%), polyethylene glycol 300 (0.02% to 5%), polyethylene glycol 400 (0.02% to 5%), polysorbate 80 (0.02% to 3%), propylene glycol (0.02% to 3%), polyvinyl alcohol (0.02% to 5%), and povidone (0.02% to 3%); hyaluronic acid (0.01% to 2%); and chondroitin sulfate (0.01% to 2%).

In one preferred embodiment of the invention, the viscosity enhancing component comprises hydroxypropylmethyl cellulose (Hypromellose or HPMC). HPMC functions to provide the desired level of viscosity and to provide demulcent activity. According to some embodiments, the concentration of HPMC ranges from about 0% to about 2% w/v, or any specific value within said range. According to some embodiments, the concentration of HPMC ranges from about 0% to about 1.5% w/v, or any specific value within said range. According to some embodiments, the concentration of HPMC ranges from about 0% to about 0.5% w/v, or any specific value within said range.

In another preferred embodiment, the viscosity enhancing component comprises carboxymethyl cellulose sodium.

The viscosity of the ophthalmic formulations of the invention may be measured according to standard methods known in the art, such as use of a viscometer or rheometer. One of ordinary skill in the art will recognize that factors such as temperature and shear rate may effect viscosity measurement. In a particular embodiment, viscosity of the ophthalmic formulations of the invention is measured at 20° C +/- 1° C using a Brookfield Cone and Plate Viscometer Model VDV-III Ultra® with a CP40 or equivalent Spindle with a shear rate of approximately approx. 22.50 +/- apprx 10 (1/sec), or a Brookfield Viscometer Model LVDV-E with a SC4-18 or equivalent Spindle with a shear rate of approximately 26 +/- apprx 10 (1/sec)).
Tonicity enhancers

Tonicity is adjusted if needed typically by tonicity enhancing agents. Such agents may, for example be of ionic and/or non-ionic type. Examples of ionic tonicity enhancers are alkali metal or earth metal halides, such as, for example, CaCl₂, KBr, KCl, LiCl, NaI, NaBr or NaCl, Na₂SO₄ or boric acid. Non-ionic tonicity enhancing agents are, for example, urea, glycerol, sorbitol, mannitol, propylene glycol, or dextrose. The aqueous solutions of the present invention are typically adjusted with tonicity agents to approximate the osmotic pressure of normal lachrymal fluids which is equivalent to a 0.9% solution of sodium chloride or a 2.5% solution of glycerol. An osmolality of about 200 to 1000 mθ sm/kg is preferred, more preferably 200 to 500 mθ sm/kg, or any specific value within said ranges (e.g., 200 mθ sm/kg, 210 mθ sm/kg, 220 mOsm/kg, 230 mOsm/kg, 240 mOsm/kg, 250 mOsm/kg, 260 mOsm/kg, 270 mOsm/kg, 280 mOsm/kg, 290 mOsm/kg, 300 mOsm/kg, 310 mOsm/kg, 320 mOsm/kg, 330 mOsm/kg, 340 mOsm/kg, 350 mOsm/kg, 360 mOsm/kg, 370 mOsm/kg, 380 mOsm/kg, 390 mOsm/kg or 400 mOsm/kg). In a particular embodiment, the ophthalmic formulations of the invention are adjusted with tonicity agents to an osmolality of ranging from about 240 to 360 mOsm/kg (e.g., 300 mOsm/kg).

The fluticasone formulations of the invention of the present invention may further comprise a tonicity agent or combination of tonicity agents. According to some embodiments, the fluticasone formulations of the invention may include an effective amount of a tonicity adjusting component. Among the suitable tonicity adjusting components that can be used are those conventionally used in contact lens care products such as various inorganic salts, polyols and polysaccharides can also be used to adjust tonicity. The amount of tonicity adjusting component is effective to provide an osmolality from 200 mθ smol/kg to 1000 mθ smol/kg, or any specific value within said range.

Preferably, the tonicity component comprises a physiologically balanced salt solution that mimics the mineral composition of tears. According to some embodiments, tonicity may be adjusted by tonicity enhancing agents that include, for example, agents that are of the ionic and/or non-ionic type. Examples of ionic tonicity enhancers are alkali metal or earth metal halides, such as, for example, CaCl₂, KBr, KCl, LiCl, NaI, NaBr or NaCl, Na₂SO₄ or boric acid.
Non-ionic tonicity enhancing agents are, for example, urea, glycerol, sorbitol, mannitol, propylene glycol, or dextrose.

According to some embodiments, the tonicity component comprises two or more of NaCl, KCl, ZnCl₂, CaCl₂, and MgCl₂ in a ratio that provides an osmolality range as above. According to some embodiments, the osmolality range of the formulations of the present invention is about 100 to about 1000 mΩ sm/kg, preferably about 500 to about 1000 mΩ sm/kg. According to some embodiments, the tonicity component comprises three or more of NaCl, KCl, ZnCl₂, CaCl₂, and MgCl₂ in a ratio that provides an osmolality range of about 100 to about 1000 mΩ sm/kg, preferably about 500 to about 1000 mΩ sm/kg. According to some embodiments, the tonicity component comprises four or more of NaCl, KCl, ZnCl₂, CaCl₂, and MgCl₂ in a ratio that provides an osmolality range of about 100 to about 1000 mΩ sm/kg, preferably about 500 to about 1000 mΩsm/kg. According to some embodiments, the tonicity component comprises NaCl, KCl, ZnCl₂, CaCl₂, and MgCl₂ in a ratio that provides an osmolality range of about 100 to about 1000 mΩ sm/kg, preferably about 500 to about 1000 mΩ sm/kg. According to some embodiments, NaCl ranges from about 0.1 to about 1% w/v, preferably from about 0.2 to about 0.8% w/v, more preferably about 0.39% w/v. According to some embodiments, KCl ranges from about 0.02 to about 0.5% w/v, preferably about 0.05 to about 0.3% w/v, more preferably about 0.14% w/v. According to some embodiments, CaCl₂ ranges from about 0.0005 to about 0.1% w/v, preferably about 0.005 to about 0.08% w/v, more preferably about 0.06% w/v.

According to some embodiments, MgCl₂ ranges from about 0.0005 to about 0.1% w/v, preferably about 0.005 to about 0.08% w/v, more preferably about 0.06% W/V. According to some embodiments, ZnCl₂ ranges from about 0.0005 to about 0.1% w/v, preferably about 0.005 to about 0.08% w/v, more preferably about 0.06% W/V.

According to some embodiments, the ophthalmic formulations of the present invention may be adjusted with tonicity agents to approximate the osmotic pressure of normal lachrymal fluids which is equivalent to a 0.9% solution of sodium chloride or a 2.5% solution of glycerol. An osmolality of about 225 to 400 mΩ sm/kg is preferred, more preferably 280 to 320 mΩsm.

**Solubilizing agents**

The topical formulation may additionally require the presence of a solubilizer, in particular if one or more of the ingredients tend to form a suspension or an emulsion. Suitable
solubilizers include, for example, tyloxapol, fatty acid glycerol polyethylene glycol esters, fatty acid polyethylene glycol esters, polyethylene glycols, glycerol ethers, a cyclodextrin (for example alpha-, beta- or gamma-cyclodextrin, e.g. alkylated, hydroxyalkylated, carboxyalkylated or alkylxycarbonyl-alkylated derivatives, or mono- or diglycosyl-alpha-, beta- or gamma-cyclodextrin, mono- or dimaltosyl-alpha-, beta- or gamma-cyclodextrin or panosyl-cyclodextrin), polysorbate 20, polysorbate 80 or mixtures of those compounds. In a preferred embodiment, the solubilizer is a reaction product of castor oil and ethylene oxide, for example the commercial products Cremophor EL® or Cremophor RH40®. Reaction products of castor oil and ethylene oxide have proved to be particularly good solubilizers that are tolerated extremely well by the eye. In another embodiment, the solubilizer is tyloxapol or a cyclodextrin. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient. For example, the concentration of the solubilizer is from 0.1 to 5000 times the concentration of the active ingredient.

Demulcifing agents

The demulcents used in the present invention are used in effective amounts (i.e. “demulcifying amounts”) for providing a demulcifying effect, i.e. sufficient to lubricating mucous membrane surfaces and to relieve dryness and irritation. Examples of suitable demulcents may include polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, and other components such as polyethylene oxide and polyacrylic acid, are specifically excluded. In still other embodiments, other or additional demulcents may be used in combination with glycerin and propylene glycol. For example, polyvinyl pyrrolidone, polyvinyl alcohol, may also be used.

The specific quantities of demulcents used in the present invention will vary depending upon the application; however, typically ranges of several demulcents are provided: glycerin: from about 0.2 to about 1.5%, but preferably about 1% (w/w); propylene glycol: from about 0.2 to about 1.5%, but preferably about 1% (w/w); cellulose derivative: from about 0.2 to about 3%, but preferably about 0.5% (w/w). If additional demulcents are used, they are typically used in quantities specified in the over-the-counter monograph, cited above. A preferred cellulose derivative is pharmaceutical grade hydroxypropyl methylcellulose (HPMC).
**Stability**

The formulations of the present invention provide for the chemical stability of the formulated fluticasone and other optional active agents of the formulation. "Stability" and "stable" in this context refers to the resistance of the fluticasone and other optional active agents to chemical degradation and physical changes such as settling or precipitation under given manufacturing, preparation, transportation and storage conditions. The "stable" formulations of the invention also preferably retain at least 90%, 95%, 98%, 99%, or 99.5% of a starting or reference amount under given manufacturing, preparation, transportation, and/or storage conditions. The amount of fluticasone and other optional active agents can be determined using any art-recognized method, for example, as UV-Vis spectrophotometry and high pressure liquid chromatography (HPLC).

In certain embodiments, the fluticasone formulations are stable at temperatures ranging from about 20 to 30 °C for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, or at least 7 weeks. In other embodiments, the formulations are stable at temperatures ranging from about 20 to 30 °C for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, or at least 12 months. In one embodiment, the formulation is stable for at least 3 months at 20-25 °C.

In other embodiments, the fluticasone formulations are stable at temperatures ranging from about 2 to 8 °C for at least 1 month, at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 14 months, at least 16 months, at least 18 months, at least 20 months, at least 22 months, or at least 24 months. In one embodiment, the formulation is stable for at least 2 months at 2 to 8 °C.

In other embodiments, the fluticasone formulations are stable at temperatures of about -20 °C for at least 1 month, at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 14 months, at least 16 months, at least 18 months, at least 20 months, at least 22 months, or at least 24 months. In one embodiment, the formulation is stable for at least 6-12 months at -20 °C.
In a particular embodiment, a fluticasone formulation of the invention is stable at temperatures of about 20-30 °C at concentrations up to 0.10% for at least 3 months. In another embodiment, the formulation is stable at temperatures from about 2-8 °C at concentrations up to 0.10% for at least 6 months.

Examples of formulations

In a preferred embodiment, the fluticasone formulation comprises fluticasone as the only active agent in the formulation at 0.001% to 1.0% (w/v), or any specific value within said range. Preferably, fluticasone is present in the formulation at a concentration of 0.001% and 0.2% (w/v), or any specific value within said range. For example, fluticasone is formulated at a concentration of 0.001%, 0.005%, 0.01%, 0.015%, 0.025%, or 0.2% (w/v). In a particular embodiment, fluticasone is present in the formulation at a concentration of 0.005% (w/v). In another particular embodiment, fluticasone is present in the formulation at a concentration of 0.01% (w/v).

Optionally, the fluticasone formulation comprises one or more tear substitutes or a mucoadhesive, polymeric compound (e.g., Durasite®). Where the formulation comprises one or more tear substitutes, the tear substitute preferably contains hydroxypropylmethyl cellulose or carboxymethyl cellulose or both. In some embodiments, the hydroxypropylmethyl cellulose or carboxymethyl cellulose is present at a concentration of 0.5% to 1% (w/v) (or any specific value within said range) and the resulting viscosity of the solution is 60-80 cpi. In a particular embodiment, the hydroxypropylmethyl cellulose or carboxymethyl cellulose is present at a concentration of 0.7% to 0.9%. In another particular embodiment, the hydroxypropylmethyl cellulose or carboxymethyl cellulose is present at a concentration of 0.1% to 0.7% and the resulting viscosity of the solution is 10-30 cpi.

Optionally, the formulation also comprises a preservative, preferably benzalkonium chloride at a concentration of from 0.005% to 0.02% (w/v) (or any specific value within said range) or its derivative (e.g., Polysac®), or a stabilized oxychloro complex (e.g., Purite®). The pH of the formulation is between 5.0 and 7.5. For example, the pH of the formulation is 5, 5.5, 6.0, 6.5 or 7.0.

In one embodiment, the fluticasone formulation comprises fluticasone at 0.001% to 1.0% (w/v), glycerin at 0.1% to 5% (v/v) (e.g., 0.1% to 3% (v/v) or any specific value within said range.
range), and water. Optionally, the formulation also comprises benzalkonium chloride at 0.005% to 0.02% (w/v) or its derivative (e.g., Polyquad®), or a stabilized, oxychloro complex (e.g., Purite®). In a particular embodiment, the fluticasone formulation comprises fluticasone at 0.005%, glycerin at 1.2% to 3% (v/v), and water. In another particular embodiment, the fluticasone formulation comprises fluticasone at 0.01% (w/v), glycerin at 1.2% to 3% (v/v), and water. Optionally, the fluticasone formulations also comprise benzalkonium chloride at 0.01% (w/v) or a stabilized, oxychloro complex (e.g., Purite®). The pH of the formulation is between 5.0 and 7.5. For example, the pH of the formulation is 5, 5.5, 6.0, 6.5 or 7.0.

In yet another particular embodiment, the fluticasone formulation comprises fluticasone at 0.001% to 1.0% (w/v), preferably fluticasone 0.005%, and one or more tear substitutes or a mucoadhesive, polymeric compound (e.g., Durasite®). Preferably, the tear substitute preferably contains hydroxypropylmethyl cellulose or carboxymethyl cellulose or both. In some embodiments, the hydroxypropylmethyl cellulose or carboxymethyl cellulose is present at a concentration of 0.5% to 1% (w/v) (or any specific value within said range) and the resulting viscosity of the solution is 60-80 cpi. In a particular embodiment, the hydroxypropylmethyl cellulose or carboxymethyl cellulose is present at a concentration of 0.7% to 0.9%. Optionally, the formulation also comprises a preservative, preferably benzalkonium chloride at a concentration of from 0.005% to 0.02% (w/v) (or any specific value within said range) or stabilized oxychloro complex (Purite®). The pH of the formulation is between 5.0 and 7.5. For example, the pH of the formulation is 5, 5.5, 6.0, 6.5 or 7.0.

In still another particular embodiment, the fluticasone formulations of the invention are formulated in a vehicle comprising 1% Polyethylene Glycol 400, NF; 0.2% Dibasic Sodium Phosphate, Anhydrous, USP; 0.25% Hyromellose, USP; 0.1% Polysorbate 80, NF; 1.2% to 1.8% Glycerin (or any specific value within said range), USP; 0.025% Edetate Disodium, USP; 0.01% Benzalkonium Chloride, NF (pH 7.0).

In a certain embodiment, the fluticasone formulation comprises 0.005% fluticasone, 1% Polyethylene Glycol 400, NF, 0.2% Dibasic Sodium Phosphate, Anhydrous, USP, 0.25% Hyromellose, USP, 0.1% Polysorbate 80, NF, 1.8% Glycerin, USP, 0.025% Edetate Disodium, USP, and 0.01% Benzalkonium Chloride, NF (pH 7.0).
In yet another certain embodiment, the fluticasone formulation comprises 0.01% fluticasone, 1% Polyethylene Glycol 400, NF, 0.2% Dibasic Sodium Phosphate, Anhydrous, USP, 0.25% Hypromellose, USP; 0.1% Polysorbate 80, NF, 1.2% Glycerin, USP, 0.025% Edetate Disodium, USP, and 0.01% Benzalkonium Chloride, NF (pH 7.0).

Methods of Use

The fluticasone formulations of the invention are useful for the treatment and prevention of the signs and symptoms of both the acute phase (i.e., seasonal) and late phase inflammatory reactions (i.e., chronic, persistent or refractory) of allergic conjunctivitis, such as ocular itching, redness, and eyelid swelling, as well as associated nasal symptoms. The formulations of the invention are also useful for the treatment and prevention of the signs and symptoms of allergic rhinoconjunctivitis, such as itchy, running nose, sneezing, nasal/sinus congestion, and red, watery and/or itchy eyes.

The invention provides methods of treating or preventing allergic conjunctivitis and/or allergic rhinoconjunctivitis in a subject in need thereof comprising topically administering directly to the eye surface of the subject a an ophthalmic formulation comprising an effective amount of fluticasone. In certain embodiments, the administration of fluticasone directly to the eye of a subject in need of treatment or prevention of allergic conjunctivitis and/or rhinoconjunctivitis is also effective to mitigate or reduce one or more nasal symptoms associated with the either allergy (e.g., itchy, running nose, sneezing and/or nasal/sinus congestion).

Topical administration of the ophthalmic formulations directly to the eye of a subject will significantly reduce nasal signs and symptoms via drainage from the ocular surface into the nasal cavity through the nasolacrimal duct (See e.g., Abelson et al., Clin. Ther. 25(3), 931-947 (2003); Spangler et al., Clin. Ther. 25(8), 2245-2267 (2003); and Crampton et al., Clin Ther. Nov; 24(11): 1800-8 (2002)). Furthermore, significantly less active agent is required to treat the nasal symptoms when instilled through the eye of a subject as compared to administration through the nose of the subject. For example, each spray of Flonase® (commercially available nasal spray comprising fluticasone) delivers 50 micrograms of fluticasone to the nasal cavity to treat allergic rhinitis and allergic rhinoconjunctivitis. In contrast, one drop of a 0.005% fluticasone ophthalmic formulation (i.e., 2.5 micrograms in a 500 microliter drop) has been shown to significantly reduce nasal symptoms associated with ocular allergy when topically administered.
directly to the eye (see Example 1 herein). As such, the methods of the present invention are more optimal than the currently available treatment options for nasal symptoms of allergic conjunctivitis and allergic rhinoconjunctivitis.

The subject is preferably a human, but may be another mammal, for example a dog, a cat, a horse, a rabbit, a mouse, a rat, or a non-human primate.

The formulations of the present invention contain an amount of fluticasone, and optionally one or more additional active ingredients (for example without limitation a vasoconstrictor such as naphazoline or oxymetazoline, or an antihistamine such as cetirizine or ketotifen), in an amount that is effective for the intended use (i.e., to mitigate the signs and symptoms of allergic conjunctivitis and/or rhinoconjunctivitis). In certain embodiments, once a day administration of the formulations of the present invention is effective to mitigate the symptoms of allergic conjunctivitis and/or rhinoconjunctivitis. However, particular dosages are also selected based on a number of factors including the age, sex, species and condition of the subject. Effective amounts can also be extrapolated from dose-response curves derived from in vitro test systems or from animal models.

The term "effective amount" means an amount of fluticasone that is sufficient to eliminate or reduce a symptom of allergic conjunctivitis and/or rhinoconjunctivitis. In certain embodiments, the effective amount is the amount sufficient for the treatment or prevention of allergic conjunctivitis and/or rhinoconjunctivitis. "Treatment" in this context refers to reducing or ameliorating at least one symptom of allergic conjunctivitis and/or rhinoconjunctivitis. "Prevention" in this context refers to a reduction in the frequency of, or a delay in the onset of, symptoms associated with allergic conjunctivitis and/or rhinoconjunctivitis, relative to a subject who does not receive the composition. The effective amount of fluticasone and other active agents in the formulation will depend on absorption, inactivation, and excretion rates of the drug as well as the delivery rate of the compound from the formulation. Particular dosages may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Typically, a dosing regimen will be determined using techniques known to one skilled in the art.
Examples of dosing regimens that can be used in the methods of the invention include, but are not limited to, once daily, twice daily, three times, and four times daily. In certain embodiments, the method comprises administering a fluticasone formulation of the invention directly to the eye of the subject once a day. In some embodiments, the administration is 2 to 4 times a day.

In certain embodiments, once a day administration (q.d.) is effective to mitigate the symptoms of ocular and/or nasal allergy. However, particular dosages may also be selected based on a number of factors including the age, sex, species and condition of the subject. Effective amounts can also be extrapolated from dose-response curves derived from in vitro test systems or from animal models.

The combined use of several active agents formulated into the compositions of the present invention may reduce the required dosage for any individual component because the onset and duration of effect of the different components may be complimentary. In such combined therapy, the different active agents may be delivered together or separately, and simultaneously or at different times within the day.

In a particular embodiment, a formulation comprising fluticasone as the only active agent in the formulation is administered to the eye of a subject in need of treatment or prevention of an allergic conjunctivitis and/or rhinoconjunctivitis once daily (q.d.). In certain embodiments, the fluticasone formulation is administered two to four times a day.

Surprisingly the fluticasone alone formulations as described herein were more effective at relieving ocular itching and associated nasal symptoms of allergic conjunctivitis than could be predicted. Even more surprising was the finding that a lower dose fluticasone was more effective at relieving ocular itching and associated nasal symptoms of allergic conjunctivitis than a higher dose of fluticasone, when administered directly to the eye. For example, as described in the Examples, the efficacy of 0.005% fluticasone was more efficacious than the higher dose 0.01% fluticasone.

In another particular embodiment, cetirizine is formulated with one or more of naphazoline, oxymetazoline cetirizine or ketotifen, and administered to the eye of a subject in need of treatment or prevention of allergic conjunctivitis and/or rhinoconjunctivitis once daily.
(q.d.). In certain embodiments, the combination formulation is administered two to four times a day.

Packaging

The formulations of the present invention may be packaged as either a single dose product or a multi-dose product. The single dose product is sterile prior to opening of the package and all of the composition in the package is intended to be consumed in a single application to one or both eyes of a patient. The use of an antimicrobial preservative to maintain the sterility of the composition after the package is opened is generally unnecessary.

Multi-dose products are also sterile prior to opening of the package. However, because the container for the composition may be opened many times before all of the composition in the container is consumed, the multi-dose products must have sufficient antimicrobial activity to ensure that the compositions will not become contaminated by microbes as a result of the repeated opening and handling of the container. The level of antimicrobial activity required for this purpose is well known to those skilled in the art, and is specified in official publications, such as the United States Pharmacopoeia ("USP") and corresponding publications in other countries. Detailed descriptions of the specifications for preservation of ophthalmic pharmaceutical products against microbial contamination and the procedures for evaluating the preservative efficacy of specific formulations are provided in those publications. In the United States, preservative efficacy standards are generally referred to as the "USP PET" requirements. (The acronym "PET" stands for "preservative efficacy testing.")

The use of a single dose packaging arrangement eliminates the need for an antimicrobial preservative in the compositions, which is a significant advantage from a medical perspective, because conventional antimicrobial agents utilized to preserve ophthalmic compositions (e.g., benzalkonium chloride) may cause ocular irritation, particularly in patients suffering from dry eye conditions or pre-existing ocular irritation. However, the single dose packaging arrangements currently available, such as small volume plastic vials prepared by means of a process known as "form, fill and seal", have several disadvantages for manufacturers and consumers. The principal disadvantages of the single dose packaging systems are the much larger quantities of packaging materials required, which is both wasteful and costly, and the inconvenience for the consumer. Also, there is a risk that consumers will not discard the single
dose containers following application of one or two drops to the eyes, as they are instructed to do, but instead will save the opened container and any composition remaining therein for later use. This improper use of single dose products creates a risk of microbial contamination of the single dose product and an associated risk of ocular infection if a contaminated composition is applied to the eyes.

While the formulations of this invention are preferably formulated as "ready for use" aqueous solutions, alternative formulations are contemplated within the scope of this invention. Thus, for example, the active ingredients, surfactants, salts, chelating agents, or other components of the ophthalmic solution, or mixtures thereof, can be lyophilized or otherwise provided as a dried powder or tablet ready for dissolution (e.g., in deionized, or distilled) water. Because of the self-preserving nature of the solution, sterile water is not required.

Sterility or adequate antimicrobial preservation may be provided as part of the present formulations. Since certain formulations of the present invention are intended to be administered ophthalmically, it is preferred that they be free of pathogenic organisms. A benefit of a sterile liquid suspension is that it reduces the possibility of introducing contaminants into the individual when the suspension formulation is administered to the eye, thereby reducing the chance of an opportunistic infection. Processes which may be considered for achieving sterility may include any appropriate sterilization steps known in the art. In one embodiment, the drug substance (e.g., fluticasone) is produced under sterile conditions, the micronization is performed in a sterile environment, and the mixing and packaging is conducted under sterile conditions. In alternative embodiment, the formulations of the present invention may be sterile filtered and filled in vials, including unit dose vials providing sterile unit dose formulations which are used in a nasal spray device for example. Each unit dose vial may be sterile and is suitably administered without contaminating other vials or the next dose. In one alternative embodiment, one or more ingredients in the present formulation may be sterilized by steam, gamma radiation or prepared using or mixing sterile steroidal powder and other sterile ingredients where appropriate. Also, the formulations may be prepared and handled under sterile conditions, or may be sterilized before or after packaging.
Kits

The present invention provides a pharmaceutical pack or kit comprising one or more containers filled with a liquid or lyophilized fluticasone formulation of the invention (i.e., a formulation comprising fluticasone alone or in combination with an additional active agent as described herein). In one embodiment, the formulation is an aqueous formulation of fluticasone. In one embodiment, the formulation is lyophilized. In preferred embodiments the liquid or lyophilized formulation is sterile. In one embodiment, the kit comprises a liquid or lyophilized formulation of the invention, in one or more containers, and one or more other prophylactic or therapeutic agents (e.g., fluticasone in combination with an additional active agent such as naphazoline, oxymetazoline, cetirizine or ketotifen) useful for the treatment of allergic conjunctivitis and/or allergic rhinoconjunctivitis. The one or more other prophylactic or therapeutic agents may be in the same container as the fluticasone or in one or more other containers. Preferably, the fluticasone is formulated at a concentration of from about 0.05% (w/v) to about 1.0% (w/v) and is suitable for topical ocular administration. In some embodiments, fluticasone is formulated with an additional active agent such as oxymetazoline, naphazoline, cetirizine or ketotifen, as described herein. In certain embodiments, the kit contains the fluticasone in unit dosage form.

In certain embodiments, the kit further comprises instructions for use in the treatment of allergic conjunctivitis and/or allergic rhinoconjunctivitis (e.g., using the fluticasone formulations of the invention alone or in combination with another prophylactic or therapeutic agent), as well as side effects and dosage information for one or more routes of administration. Optionally associated with such container(s) is a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. While the instructional materials typically comprise written or printed materials they are not limited to such. Any medium capable of storing such instructions and communicating them to an end user is contemplated by this invention. Such media include, but are not limited to electronic storage media (e.g., magnetic discs, tapes, cartridges, chips), optical media (e.g. CD ROM), and the like. Such media may include addresses to internet sites that provide such instructional materials.
In another embodiment, this invention provides kits for the packaging and/or storage and/or use of the formulations described herein, as well as kits for the practice of the methods described herein. The kits can be designed to facilitate one or more aspects of shipping, use, and storage.

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

**EXAMPLES**

The invention is further defined by reference to the following examples, which are not meant to limit the scope of the present invention. It will be apparent to those skilled in the art that many modifications, both to the materials and methods, may be practiced without departing from the purpose and interest of the invention.

**Example 1: Fluticasone Prevents Ocular and Nasal Symptoms Associated with Allergic Conjunctivitis**

A placebo controlled, double-blind study was conducted to evaluate the efficacy of Fluticasone 0.001% (N=16), Fluticasone 0.005% (N=16), Fluticasone 0.01% (N=15) compared to vehicle alone (N=15). Subjects underwent 2 screening visits (allergen titration and confirmation) followed by 2 drug evaluation visits, as indicated in the study design shown in Figures 1A and 1B. At the drug evaluation visits, one drop of masked study medication was instilled in each eye and ocular allergic assessments were taken. Eight hours later the subjects were challenged with allergen and primary and secondary ocular and nasal endpoints were assessed, as well as safety of the formulations. The results are presented in Figures 2-21.

**Primary Ocular Endpoints**

Ocular itching, conjunctival redness, lid swelling, and nasal congestion were assessed in each subject during visit 4B.
Ocular itching was subjectively assessed on a scale of 0 (no itching) to 4 (severe itching). As shown in Figure 2, Fluticasone 0.001%, 0.005% and 0.01% were about equally effective in reducing ocular itching over a 7 minute time period as compared to vehicle alone.

 Conjunctival redness was also subjectively assessed on a scale of 0 (no redness) to 4 (severe redness). As shown in Figure 3, Fluticasone 0.001%, 0.005% and 0.01% were about equally effective in reducing conjunctival redness over a 20 minute period as compared to vehicle alone.

 Lid swelling was subjectively assessed on a scale of 0 (no lid swelling) to 3 (severe lid swelling). As shown in Figure 4, Fluticasone 0.001% and 0.005% were each more effective than Fluticasone 0.01% at reducing lid swelling over a 20 minute period as compared to vehicle alone.

 Nasal Congestion was subjectively assessed on a scale of 0 (no congestion) to 4 (severe congestion). As shown in Figure 5, Fluticasone 0.001%, 0.005% and 0.01% were about equally effective in reducing nasal congestion over a 30 minute period as compared to vehicle alone.

 A summary of the results of the primary ocular endpoint assessments is shown in Figure 6. As shown in Figure 6, the reduction in conjunctival redness by Fluticasone 0.005% and 0.01% and the reduction in lid swelling by Fluticasone 0.001% were each statistically significant (p<0.05).

 Secondary Ocular Endpoints

 Ciliary Redness, episcleral redness, chemosis and watery eyes were assessed in each subject at visit 4B.

 Ciliary redness was assessed on a scale of 0 (no redness) to 4 (severe redness). As shown in Figure 7, Fluticasone 0.001%, 0.005% and 0.01% were each significantly effective in reducing ciliary redness over a 20 minute period as compared to vehicle alone (p<0.05 for each Fluticasone concentration).
Episcleral redness was assessed on a scale of 0 (no redness) to 4 (severe redness). As shown in Figure 8, Fluticasone 0.001%, 0.005% and 0.01% each reduce episcleral redness over a 20 minute period as compared to vehicle alone.

Chemosis was assessed on a scale of 0 (none) to 4 (extreme). As shown in Figure 9, Fluticasone 0.001%, 0.005% and 0.01% were each significantly effective in reducing chemosis over a 20 minute period.

Watery eyes were also subjectively assessed on a scale of 0 (not watery) to 4 (extremely watery). As shown in Figure 10, Fluticasone 0.001% and 0.05% were each more effective than Fluticasone 0.01% in reducing watery eyes over a 20 minute period, as compared to vehicle alone.

A summary of the secondary ocular endpoints assessed is shown in Figure 11. As shown in Figure 10, the reduction in ciliary redness by all three concentrations of Fluticasone, the reduction in episcleral redness by Fluticasone 0.005%, and the reduction of watery eyes by Fluticasone 0.05% were each statistically significant (p<0.05).

Secondary Nasal Endpoints

Rhinorrhea, ear or palate pruritis, nasal pruritis were assessed in each subject at visit 4B using a scale of 0 (none) to 4 (extreme) for each endpoint.

As shown in Figures 12 and 14, Fluticasone 0.001%, 0.005% and 0.01% each had a clinically significant effect in reducing rhinorrhea and nasal pruritis, respectively, over a 20 minute period as compared to vehicle alone. Shown in Figure 13, Fluticasone 0.001%, 0.005% and 0.01% were each had an effect in reducing ear and palate pruritis as compared to vehicle alone.

Total nasal scores were assessed on a scale of 0-16. As shown in Figure 15, Fluticasone 0.001%, 0.005% and 0.01%, each surprisingly had a clinically significant effect on total nasal score when administered directly to the eye of each subject. A summary of the nasal endpoints assessed is shown in Figures 16 and 17.
Safety

Intraocular pressure, drop comfort and adverse events such as blurry vision, conjunctival hemorrhage, dry eye, site pain and/or irritation and headache, were assessed for each subject.

Drop comfort was subjectively assessed on a scale of 0 (extremely comfortable) to 10 (extremely uncomfortable) during visit 2 and visit 3. As shown in Figures 18 and 19, Fluticasone 0.01 was highly uncomfortable upon instillation as compared to Fluticasone 0.001% and 0.005%, and as compared to vehicle alone. The comfort of Fluticasone 0.001% and 0.005% were comparable to the comfort of the vehicle control.

A summary of the total percentage of subjects who experienced adverse events such as blurry vision, conjunctival hemorrhage, dry eye, site pain and/or irritation, and headache, is shown in Figure 20.

The effect of each concentration of Fluticasone on intraocular pressure (IOP) as compared to vehicle alone is shown in Figure 21.

The results demonstrate that a single drop of either Fluticasone 0.001%, 0.005% or 0.01% was effective to prevent both ocular and nasal symptoms associated with allergic conjunctivitis. However, when taking all primary and secondary endpoints into consideration, the mid-strength Fluticasone 0.005% was the most efficacious in relieving both ocular and nasal symptoms, and was shown to be more comfortable than Fluticasone 0.001% and Fluticasone 0.01%, with no adverse effect on intraocular pressure.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.
What is claimed is:

1. A topical ophthalmic formulation comprising:
   fluticasone, or a pharmaceutically acceptable salt or ester thereof, wherein the fluticasone is present at a concentration of between 0.001% and 1.0% (w/v), wherein fluticasone is the sole antiallergic agent in the composition;
   a demulcifying agent at a concentration of between 0.2% and 5.0% (w/v);
   glycerin; and
   a buffer system comprising one or more of a borate buffer, phosphate buffer, or calcium buffer.

2. The ophthalmic formulation of claim 1, wherein fluticasone and is present in the formulation at a concentration of 0.001% to 0.2% (w/v).

3. The ophthalmic formulation of claim 2, wherein the concentration of fluticasone is 0.005% (w/v).

4. The ophthalmic composition of claim 1, wherein the demulcifying agent contains hydroxypropylmethylcellulose.

5. The ophthalmic composition of claim 1, wherein the composition comprises a preservative.

6. The ophthalmic formulation of claim 5, wherein the preservative is benzalkonium chloride or a derivative thereof, or a stabilized, oxychloro complex.

7. The ophthalmic composition of claim 1, wherein the composition does not comprise a preservative.

8. The ophthalmic formulation of claim 1, wherein the pH of the composition is 5 to 7.0.
9. The ophthalmic formulation of claim 1, wherein the formulation is an aqueous formulation, an ointment, an oil, a suspension, an emulsion, or incorporated in a drug delivery device.

10. The ophthalmic formulation of claim 9, wherein the formulation is in an aqueous formulation.

11. A topical ophthalmic formulation comprising 0.005% fluticasone, 1% Polyethylene Glycol 400, NF, 0.2% Dibasic Sodium Phosphate, Anhydrous, USP, 0.25% Hypromellose, USP, 0.1% Polysorbate 80, NF, 1.8% Glycerin, USP, 0.025% Edetate Disodium, USP, and 0.01% Benzalkonium Chloride, wherein the formulation has a pH 7.0.

12. A method for treating allergic conjunctivitis by topically administering to the eye of a subject in need of such treatment an ophthalmic formulation comprising the ophthalmic formulation of claim 1.

13. A method for treating allergic rhinoconjunctivitis by topically administering to the eye of a subject in need of such treatment an ophthalmic formulation comprising the ophthalmic formulation of claim 1.
Figure 1A: Study Design: Screening

Visit 1 (Day -1)
CAC Titration

Visit 2 A (Day 0)
Confirmation CAC

Visit 2 B (Day 0)
Confirmation CAC

Ocular allergic assessments: Itching: 3, 5, and 7 minutes post-CAC
Redness, Chemosis, Lid Swelling, Watery Eyes, Rhinorrhea, Nasal Pruritis, & Ear or palate
Pruritis: 7, 15, and 20 minutes post-CAC
Peak Nasal Inspiratory Flow: 9 and 30 minutes post-CAC

Only subjects who experienced a score of $\geq 2$ for ocular itching, conjunctival redness and nasal congestion at Visit 1 and a score of $\geq 2$ for ocular itching and conjunctival redness in 2 our of 3 time point and $\geq 2$ for nasal congestion in at least 2 out of 4 time points at Visit 2B were scheduled for Visit 3
Figure 1B: Study Design: Efficacy Evaluation

Visit 3 (Day 6)  Visit 4 A (Day 7)  Visit 4 B (Day 7)

Study Medication  Study Medication  CAC
CAC  CAC  CAC

\( t = -15 \text{ min} \)  \( t = 0 \)  \( t = 8 \text{ hours} \) (from V 4A Study Medication)

Ocular allergic assessments: Itching: 3, 5, and 7 minutes post-CAC
Redness, Chemosis, Lid Swelling, Watery Eyes, Rhinorrhea, Nasal Pruritis, & Ear or palate Pruritis: 7, 15, and 20 minutes post-CAC
Peak Nasal Inspiratory Flow: 9 and 30 minutes post-CAC
Figure 2: Primary: Ocular Itching (Visit 4B)
Figure 3: Primary: Conjunctival Redness (Visit 4B)

- Fl 0.001% (N=16)
- Fl 0.005% (N=16)
- Fl 0.01% (N=15)
- Vehicle (N=15)

* P<0.05 Fluticasone 0.005% vs. Vehicle
** P<0.05 Fluticasone 0.005% vs. Vehicle; Fluticasone 0.01% vs. Vehicle
Figure 4: Primary: Lid Swelling (Visit 4B)
Figure 5: Primary: Nasal Congestion (Visit 4B)

- Fl 0.001% (N=16)
- Fl 0.005% (N=16)
- Fl 0.01% (N=15)
- Vehicle (N=15)
Figure 6: ANCOVA: Primary Endpoints
Figure 7: Secondary: Ciliary Redness (Visit 4B)

** P<0.05 Fluticasone 0.005% vs. Vehicle; Fluticasone 0.01% vs. Vehicle
*** P<0.05 Fluticasone 0.001% vs. Vehicle; Fluticasone 0.005% vs Vehicle
Figure 8: Secondary: Episcleral Redness (Visit 4B)

* P<0.05 Fluticasone 0.01% vs. Vehicle
** P<0.05 Fluticasone 0.005% vs Vehicle
Figure 9: Secondary: Chemosis (Visit 4B)

- FL 0.001% (N=16)
- FL 0.005% (N=16)
- FL 0.01% (N=15)
- Vehicle (N=15)

*P < 0.05: All 3 concentrations vs. vehicle
Figure 10: Secondary: Watery Eyes (Visit 4B)

*P<0.05: Fluticasone 0.001% vs. Vehicle
Figure 11: ANCOVA Secondary Ocular Endpoints

- Vehicle
- FI 0.001%
- FI 0.005%
- FI 0.01%

* P<0.05

LS Means

- Ciliary Redness
- Episcleral Redness
- Chemosis
- Watery Eyes
Figure 12: Rhinorrhea (Visit 4B)

* P<0.05 Fluticasone 0.005% vs. Vehicle
** P<0.05 Fluticasone 0.001% vs. Vehicle; Fluticasone 0.005% vs. Vehicle

Mean Rhinorrhea (0-4) scale

CLINICALLY SIGNIFICANT DIFFERENCES
Figure 13: Ear or Palate Pruritis (Visit 4B)
Figure 14: Nasal Pruritis (Visit 4B)

* P<0.05 Fluticasone 0.005% vs. Vehicle
** P<0.05 Fluticasone 0.001% vs. Vehicle; Fluticasone 0.005% vs. Vehicle

CLINICALLY SIGNIFICANT DIFFERENCES
Figure 15: Total Nasal Score (Visit 4B)

* P<0.05 Fluticasone 0.005% vs. Vehicle
** P<0.05 Fluticasone 0.001% vs. Vehicle; Fluticasone 0.005% vs. Vehicle

Mean Total Nasal Composite (0-16) Scale
Figure 16: ANCOVA Nasal

- Vehicle (N=15)
- Fl 0.001% (N=16)
- Fl 0.005% (N=16)
- Fl 0.01% (N=15)

Legend:
- Rhinorrhea
- Ear or Palate Pruritis
- Nasal Pruritis
- Total Nasal Score

Bars indicate the mean values for each category, with asterisks possibly indicating statistical significance.
Figure 17: Secondary: PNIF Visit 4B

Mean % of Baseline PNIF
Figure 18: Visit 2 Drop Comfort Score

- FI 0.001% (N=16)
- FI 0.005% (N=16)
- FI 0.01% (N=16)

Vehicle (N=16)

Mean Comfort Score (0-10 scale)

Time (min) Post Instillation

Upon Installation
Figure 19: Visit 3 Drop Comfort Score

Time (min) Post Drop Instillation

Upper Instillation

Mean Comfort Score (0-10 scale)

Vehicle (N=16)

F1 0.005% (N=16)

F1 0.01% (N=16)

F1 0.001% (N=16)
Figure 20: SAFETY- ADVERSE EVENTS

- Fluticasone 0.001% - 1 Event - 6.3% of Subjects
  - Vision blurred

- Fluticasone 0.005% - 2 Events - 12.5% of Subjects
  - Conjunctival hemorrhage
  - Dry eye

- Fluticasone 0.01% - 5 Events - 18.8% of Subjects
  - 3 Instillation site pain
  - 1 Instillation site irritation
  - 1 Headache

- Vehicle - 1 Event - 6.3% of Subjects
  - 1 Gastroenteritis Viral
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/40 (2010 01)
USPC - 424/427

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC 424/427

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,EPAB,JPAB),Google Scholar
ophthalmic, ocular, eye, formulation, composition, drops, solution, allergic conjunctivitis, allergic rhinoconjunctivitis, fluticasone, hypromellose, hydroxypropyl methyl cellulose, hydroxypropyl methylcellulose, glycerin, glycerol, disodium edate, sodium, EDTA buffer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 2007/0178051 A1 (PRIUITT et al) 02 August 2007 (02 08 2007) para [0001], [0047]-[0048], [0071]-[0074], [0136], [0144] [0171]</td>
<td>1-13</td>
</tr>
<tr>
<td>Y</td>
<td>US 5,800,807 A (HU et al) 01 September 1998 (01 09 1998) col 1, ln 6-1 1, col 2, ln 51 56, col 3, ln 34-55</td>
<td>1-13</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C

*A* special categories of cited documents

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

-E* earlier application or patent but published on or after the international filing date

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

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

-T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

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

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INTERNATIONAL SEARCH REPORT

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