Therapeutic Class Overview
Ophthalmic Antihistamines

Therapeutic Class

- **Overview/Summary:**
  All of the ophthalmic antihistamines listed in Table 1 are Food and Drug Administration (FDA)-approved for the prevention or treatment of the signs and symptoms of allergic conjunctivitis.[1-10] Ketotifen (Alaway®, Zaditor®) is also indicated for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander. Allergic conjunctivitis is the most common form of ocular allergy. Itching manifests as the primary symptom; however, other common symptoms include ocular burning, chemosis, conjunctival and eyelid edema, hyperemia, photophobia and tearing.[11,12] Symptoms usually occur in both eyes, yet one eye may be affected more than the other.[12] Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea.[13] None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis. Following topical administration to the conjunctiva, ophthalmic antihistamines competitively bind histamine receptor sites to reduce itching and vasodilation.[1] The ocular antihistamines are relatively selective for the histamine type 1 (H_1-antihistamine) receptor but may also inhibit the degranulation of mast cells, thereby limiting the release of inflammatory mediators such as histamine, eosinophil and neutrophil chemotactic factors.[2-4,6-9] Emedastine (Emadine®) has only H_1-antihistamine activity.[5] Ophthalmic antihistamines have demonstrated a faster onset of action compared to oral antihistamines and ophthalmic mast-cell stabilizers and they are all approved for use in children.[1-9,14] The most common adverse events associated with these agents are ocular burning, stinging and headache.[1-9] In general, drug interactions are limited due to low systemic bioavailability via the ocular route. The administration schedule for these products ranges from once daily to four times daily, with only alcaftadine (Lastacaft®) and olopatadine 0.2% (Pataday®) available for once daily use.[2,8] Azelastine (Optivar®), epinastine (Elestat®) and ketotifen are available generically. Ketotifen is also available over-the-counter.[15]

Table 1. Current Medications Available in the Therapeutic Class[1-9]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alcaftadine (Lastacaft®)	Allergic conjunctivitis†	Ophthalmic solution: 0.25% (5 mL)	-
Azelastine (Optivar®*)	Allergic conjunctivitis†	Ophthalmic solution: 0.05% (10 mL)	✔
Bepotastine (Bepreve®)	Allergic conjunctivitis†	Ophthalmic solution: 1.5% (5, 10 mL)	-
Emedastine (Emadine®)	Allergic conjunctivitis‡	Ophthalmic solution: 0.05% (5 mL)	-
Epinastine (Elestat®*)	Allergic conjunctivitis§	Ophthalmic solution: 0.05% (10 mL)	✔
Ketotifen (Alaway®, Zaditor®)	Allergic conjunctivitis§, ocular itching‖	Ophthalmic solution: 0.025% (OTC, RX) (5, 10 mL)	✔ #
Olopatadine (Pataday®, Patanol®)	Allergic conjunctivitis†‡	Ophthalmic solution: 0.1% (5 mL) 0.2% (4 mL)	-

OTC=over-the-count, RX=prescription
* Available generically in one dosage form or strength.
† For the treatment of ocular itching associated with allergic conjunctivitis.
‡ For the treatment of signs and symptoms of allergic conjunctivitis.
§ For the prevention of ocular itching associated with allergic conjunctivitis.
‖ For the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.
Product is also available over-the-counter in at least one dosage form or strength.

Evidence-based Medicine

- The ophthalmic antihistamines are significantly more effective compared to placebo for reducing the symptoms of allergic conjunctivitis including ocular itching and conjunctival redness.[16-20]
- Limited head-to-head trials comparing olopatadine, azelastine and ketotifen have failed to consistently show the "superiority" of one ophthalmic antihistamine over another for the management of allergic conjunctivitis.[21-26]
- A meta-analysis of four trials found that patients were 1.3 times more likely to perceive their treatment response as "good" with ophthalmic antihistamines compared to patients receiving pure ophthalmic mast-cell stabilizers; however, the difference was not statistically significant.[27]
- The ophthalmic antihistamines have consistently demonstrated a greater improvement in allergy symptoms and/or patient comfort scores compared to ophthalmic mast-cell stabilizers and ocular vasoconstrictors; however, many of these trials were conducted using single doses of study medication (conjunctival allergen challenge model) in a small number of patients.[28-38]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Ophthalmic formulations of agents from the following classes are useful in treating allergic conjunctivitis: corticosteroids, vasoconstrictor/antihistamine combinations, antihistamines, nonsteroidal anti-inflammatories (NSAIDs), mast-cell stabilizers, antihistamine/mast-cell stabilizers and immunosuppressants.[13]
    - An over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H_1-receptor antagonist is recommended for mild allergic conjunctivitis. No preference is given to any one OTC antihistamine/vasoconstrictor or antihistamine.[39]
    - If the condition is frequently recurrent or persistent, use mast-cell stabilizers. No single mast-cell stabilizer is preferred over another.[39]
    - Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. No one antihistamine/mast-cell stabilizer is preferred over another.[39]
    - If the symptoms are not adequately controlled, a brief course (one to two weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used because of the potential for adverse events with their protracted use (e.g., cataract formation and elevated intraocular pressure).[13,39]
    - Ketorolac, a NSAID, is also Food and Drug Administration-approved for the treatment of allergic conjunctivitis.[13,39]

- Other Key Facts:
    - Alcaftadine and emedastine are classified as pregnancy category B while the other agents in this class have a pregnancy category C rating.
    - Alcaftadine and olopatadine 0.2% are the only agents within the class that are approved for once daily use.
    - Ophthalmic formulations of azelastine, epinastine and ketotifen are available generically.
    - Ketotifen is also available over-the-counter.[15]

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Therapeutic Class Review
Ophthalmic Antihistamines

Overview/Summary

The ophthalmic antihistamines are Food and Drug Administration (FDA)-approved for the management of the signs and symptoms associated with allergic conjunctivitis and include alcaftadine (Lastacaft®), azelastine (Optivar®), bepotastine (Bepreve®), emedastine (Emadine®), epinastine (Elestat®), ketotifen (Alaway®, Zaditor®) and olopatadine (Pataday®, Patanol®).[1-11] Ketotifen is also approved for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander. Allergic conjunctivitis is the most common form of ocular allergy.[12] Based on clinical features, allergic conjunctivitis may be subdivided into acute, seasonal or perennial allergic conjunctivitis.[13] Ocular itching is the main symptom of allergic conjunctivitis while ocular burning, chemosis, conjunctival and eyelid edema, hyperemia, photophobia and tearing may also be reported.[12,13] Symptoms are usually present bilaterally; however, one eye may be more affected than the other.[13] Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea.[14] None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis. Allergic conjunctivitis results from a type I immunoglobulin E (IgE)-mediated hypersensitivity, where the immediate response to allergens is mediated predominantly by mast cells.[13] Mast cells are present in high concentrations in the conjunctiva and release chemical mediators when activated by allergen-IgE cross-linkage. Histamine, the primary mediator during the early response, causes itching, vasodilation and vasopermeability. During the late phase of the allergic reaction, mast cells release chemokines and cytokines, which results in the influx of other inflammatory cells and continued inflammation.[13]

All of the ophthalmic antihistamines with the exception of emedastine have demonstrated both histamine type 1 (H_1-antihistamine) and mast cell stabilizing properties.[12] Following topical administration to the conjunctiva, ophthalmic antihistamines competitively bind to histamine receptor sites to reduce itching and vasodilation. They also inhibit the degranulation of mast cells, thereby limiting the release of inflammatory mediators such as histamine, eosinophil and neutrophil chemotactic factors and platelet-activating factor.[14] Ophthalmic antihistamines have demonstrated a faster onset of action compared to oral antihistamines and ophthalmic mast cell stabilizers.[12] All of the ophthalmic antihistamines are approved for use in children.[1-11] Alcaftadine and emedastine are classified as pregnancy category B, while the other agents in this class are pregnancy category C. The most common adverse events associated with the use of the ophthalmic antihistamines are ocular burning, stinging and headache.[1-11] The ophthalmic antihistamines are generally administered one to four times daily; however, alcaftadine and olopatadine 0.2% (Pataday®) approved for once daily use.[4,8] Ophthalmic formulations of azelastine and epinastine are available generically, and ketotifen is available over-the-counter (OTC).[15]

According to the American Academy of Ophthalmology, mild allergic conjunctivitis may be treated with an OTC antihistamine/vasoconstrictor or ophthalmic antihistamine.[16] Ophthalmic vasoconstrictors have a short duration of action and may cause rebound hyperemia and conjunctivitis medicamentosa; therefore, they should only be used short-term.[13] Ophthalmic mast cell stabilizers have a slower onset of action compared to ophthalmic antihistamines and may be used if the condition is recurrent or persistent.[13,16] Ophthalmic allergy preparations with dual H_1-antihistamine and mast cell stabilizing properties may be used for either acute or chronic disease, and no preference is given to one specific ophthalmic antihistamine vs another.[16] The results of some head-to-head studies have demonstrated small differences between agents; however, the clinical significance of these differences has not been established. Many of these studies were conducted using single doses of study medication (conjunctival allergen challenge model) and enrolled a small number of patients.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Alcaftadine ophthalmic (Lastacaft®)	Antihistamine/Mast cell stabilizer	-
Azelastine ophthalmic (Optivar®*)	Antihistamine/Mast cell stabilizer	✔

Generic Name (Trade Name)	Medication Class	Generic Availability
Bepotastine ophthalmic (Bepreve®)	Antihistamine/Mast cell stabilizer	-
Emedastine ophthalmic (Emadine®)	Antihistamine	-
Epinastine ophthalmic (Elestat®*)	Antihistamine/Mast cell stabilizer	✔
Ketotifen ophthalmic (Alaway®, Zaditor®)	Antihistamine/Mast cell stabilizer	✔ †
Olopatadine ophthalmic (Pataday®, Patanol®)	Antihistamine/Mast cell stabilizer	-

*Generic available in at least one dosage form and/or strength.
†Product is also available over-the-counter in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[4-11]

Generic Name	Allergic Conjunctivitis	Ocular Itching
Alcaftadine	✔ *	
Azelastine	✔ †	
Bepotastine	✔ †	
Emedastine	✔ ‡	
Epinastine	✔ *	
Ketotifen	✔ * (prescription)	✔ § (over-the-counter)
Olopatadine	✔ (0.2%†, 0.1%‡)	

* Prevention of ocular itching associated with allergic conjunctivitis.
†Treatment of ocular itching associated with allergic conjunctivitis.
‡Treatment of signs and symptoms of allergic conjunctivitis.
§Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.

Pharmacokinetics

Table 3. Pharmacokinetics[2-11]

Generic Name	Onset (minutes)	Duration (hours)	Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Alcaftadine	Not reported	Not reported	Not reported	Carboxylic acid metabolite	2*
Azelastine	3	8	Feces (75)	N-desmethyl-azelastine)	22
Bepotastine	<15 (1 to 2 hours peak)	8	Urine (75 to 90)	Minimal (not reported)	Not reported
Emedastine	Not reported	Not reported	Urine (44)	None	3 to 4
Epinastine	3 to 5	8	Feces (30); urine (55)	Not reported	12
Ketotifen	Minutes	8 to 12	Feces (30 to 40); urine (60 to 70)	Ketotifen N-glucuronide, nor-ketotifen	9 to 21
Olopatadine	<30	8	Urine (60 to 70)	None	3

*Half-life reported for the active metabolite.

Clinical Trials

Clinical trials evaluating the safety and efficacy of the ophthalmic antihistamines for their respective Food and Drug Administration (FDA)-approved indications are summarized in Table 4.[17-45]

Due to the rapid onset of action of the ophthalmic antihistamines, most trials used the conjunctival allergen challenge model to establish the relative efficacy of these formulations compared to placebo. The

results of most trials demonstrated improvements in symptoms, especially for itching, in those treated with ophthalmic antihistamines and antihistamines/mast cell stabilizers compared to placebo.

In one trial, ophthalmic alcaftadine significantly reduced conjunctival redness and most other allergic signs and symptoms at both 15 minutes and 16 hours following drug administration compared to placebo (*P*<0.05 for both comparisons).[17] In a second trial of patients with a history of ocular allergens (N=170), all treatment groups (ophthalmic alcaftadine 0.05%, 0.10%, 0.25% and ophthalmic olopatadine 0.1%) were associated with lower ocular itching scores compared to placebo (*P*<0.05 for all comparisons). Compared to placebo, all treatments significantly improved conjunctival redness scores at both 15 minutes and 16 hours following administration (*P*<0.05 for all comparisons). A clinically significant difference (≥1 unit difference from placebo) was only reported for the ophthalmic alcaftadine 0.25% treatment group. At 16 hours following administration, patients receiving ophthalmic alcaftadine 0.25% reported lower ocular itching scores following allergen challenge compared to patients receiving ophthalmic olopatadine (*P*=0.017).[18]

Using the conjunctival allergen challenge model for allergic conjunctivitis, ophthalmic bepotastine was shown to be more effective than placebo in relieving ocular itching after 15 minutes and eight hours in adults and children.[19,21] In a two-week trial comparing ophthalmic bepotastine to ophthalmic olopatadine 0.2%, there was a similar improvement in the relief of morning ocular itch between treatments (*P* value not reported). Patients treated with ophthalmic bepotastine reported a significantly greater relief in evening ocular itch compared to patients receiving ophthalmic olopatadine (*P*=0.011). With regard to patient preference, significantly more patients favored treatment with ophthalmic bepotastine compared to ophthalmic olopatadine for the all-day relief of ocular itching (63.3 vs 36.7%; *P*=0.04).[22]

Using the conjunctival allergen challenge model, one dose of ophthalmic olopatadine 0.2% was comparable to two doses of ophthalmic olopatadine 0.1%, and both regimens were more effective than placebo in terms of mean itching scores.[23] Both strengths of ophthalmic olopatadine were found to be safe and well tolerated. Using the conjunctival allergen challenge model, ophthalmic olopatadine 0.1% was significantly more effective compared to ophthalmic azelastine in the management of itching associated with allergic conjunctivitis. Both agents were also more effective than placebo.[24] Clinical trials comparing ophthalmic olopatadine to ophthalmic ketotifen have produced mixed results. Using the conjunctival allergen challenge model, ophthalmic olopatadine 0.1% was more effective in reducing the itching associated with allergic conjunctivitis compared to ophthalmic ketotifen (N=32).[29] In this trial, olopatadine 0.1% caused less ocular discomfort than ophthalmic ketotifen and was preferred by 73% of patients compared to 27% with ophthalmic ketotifen. In an environmental study of patient preference, a significantly higher percentage of patients with active symptoms of seasonal or perennial allergic conjunctivitis selected ophthalmic olopatadine 0.1% over ophthalmic ketotifen primarily on the basis of efficacy and comfort (N=100).[30] In a three-week parallel-group trial in patients with seasonal allergic conjunctivitis (N=66), ophthalmic ketotifen was associated with higher global efficacy ratings compared to ophthalmic olopatadine 0.1% at day 21 (91 vs 55% and 94 vs 42% for patient and investigator assessment, respectively). Comfort ratings were comparable between the two agents.[31] In a similar 30-day trial in patients with seasonal allergic conjunctivitis, ophthalmic ketotifen and ophthalmic olopatadine 0.1% were comparable with regard to scores for tearing, itchiness, redness, chemosis and reduction in eyelid (*P* values not reported).[32]

Using the conjunctival allergen challenge model, ophthalmic emedastine and ophthalmic ketotifen significantly reduced the mean itching scores at all time points compared to placebo (*P*<0.05); however, there was no statistically significant difference between ophthalmic emedastine and ophthalmic ketotifen (*P* values not reported).[25] In a randomized controlled trial of patients with seasonal allergic conjunctivitis (N=100), no differences in efficacy were reported between ophthalmic formulations of emedastine, epinastine, ketotifen and olopatadine (*P* values not reported). All agents were more efficacious in preventing itching and redness compared to ophthalmic fluorometholone (*P*<0.001 for all).[33]

In a small trial (N=40) measuring ocular comfort, ophthalmic epinastine was rated as more comfortable compared to ophthalmic azelastine or ophthalmic ketotifen after administration of a single drop.

Ophthalmic ketotifen was reported to be more comfortable than ophthalmic azelastine.[26] Using the conjunctival allergen challenge model, ophthalmic olopatadine 0.1% was significantly more effective in controlling itching, redness and chemosis compared to ophthalmic epinastine.[27] Ophthalmic olopatadine 0.2% was also shown to be more effective in preventing ocular itching and redness compared to ophthalmic epinastine.[28] The ocular allergy preparations gave similar results in terms of reducing chemosis, eyelid swelling and tearing.

Using the conjunctival allergen challenge model, ophthalmic naphazoline/pheniramine and ophthalmic olopatadine were associated with significantly lower ocular allergy index scores (erythema, eyelid swelling, chemosis and itching) compared to placebo. Ophthalmic naphazoline/pheniramine was more effective than ophthalmic olopatadine in relieving redness and chemosis, while ophthalmic olopatadine was more effective than ophthalmic naphazoline/pheniramine for relieving itching.[34]

The efficacy of ophthalmic formulations of cromolyn, azelastine and placebo was evaluated in patients with seasonal allergic conjunctivitis or rhinoconjunctivitis (N=144).[36] Both active treatments demonstrated a marked effect on itching, tearing and conjunctival redness on day three with a sustained improvement on days seven and 14. Global assessment of efficacy was at least "satisfactory" for 90, 81 and 66% of patients receiving ophthalmic azelastine, cromolyn and placebo, respectively.

Using the conjunctival allergen challenge model, a single dose of ophthalmic ketotifen was shown to be more effective than a two-week regimen of ophthalmic cromolyn 4% in alleviating symptoms of allergic conjunctivitis (N=56).[37] In another conjunctival allergen challenge trial, ophthalmic ketotifen was significantly more effective than ophthalmic nedocromil for reducing ocular itching after both the five-minute and 12-hour allergen challenges (N=59).[41] Ophthalmic ketotifen-treated eyes were significantly more comfortable compared to ophthalmic nedocromil-treated eyes at one to 10 minutes after medication administration. While ophthalmic emedastine and ophthalmic nedocromil were both more effective than placebo in controlling ocular itching and redness after an allergen challenge, ophthalmic emedastine was more effective compared to ophthalmic nedocromil in alleviating redness and itching at three and 10 minutes after an allergen challenge (N=30).[40]

In a small trial, a single dose of ophthalmic olopatadine 0.1% was reported by patients to be more comfortable and efficacious in reducing the itching caused by an allergen challenge than a two-week course of ophthalmic nedocromil (N=52).[42] In a two-week crossover trial, physicians and patients judged ophthalmic nedocromil and ophthalmic olopatadine 0.1% to be similarly effective in preventing signs and symptoms of perennial allergic conjunctivitis.[43] Comparative studies have shown ophthalmic olopatadine and ophthalmic emedastine were more effective in reducing ocular itching than ophthalmic ketorolac, a nonsteroidal anti-inflammatory drug.[39,44]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Allergic Conjunctivitis				
Torkildsen et al[17] Alcaftadine 0.25% one drop in each eye once daily vs placebo one drop in each eye once daily	DB, MC, PC, RCT Patients >10 years of age with a history of allergic conjunctivitis and a reproducible, positive reaction to a CAC	N=58 4 visits (study duration not reported)	Primary: Ocular itching (assessed by subject at three, five and seven minutes following CAC) and conjunctival redness (assessed by investigator at seven, 15 and 20 minutes following CAC) Secondary: Other signs and symptoms of allergic conjunctivitis (assessed by investigator at seven, 15 and 20 minutes following CAC)	Primary: Alcaftadine was associated with a statistically significant reduction in conjunctival redness following the 16-hour (duration of action) and 15-minute (onset of action) CAC tests compared to placebo. The differences in mean ocular itching scores at the 16-hour CAC test were -1.731, -1.687 and -1.576 at three, five and seven minutes following CAC, respectively, compared to placebo (*P*<0.001 for all time points). The differences in mean ocular itching scores at the 15 minute CAC test were -1.500, -1.491 and -1.474 at three, five and seven minutes following CAC, respectively, compared to placebo (*P*<0.001 for all time points). Mean conjunctival redness scores were significantly improved for patients receiving alcaftadine compared to the placebo group at seven, 15 and 20 minutes following the 15 minute and 16 hour CAC tests (*P*<0.05 for all time points). The differences between groups were not clinically significant (>1 point difference in absolute mean scores groups). Secondary: Alcaftadine was associated with a statistically significant reduction in most secondary endpoints following the 16-hour and 15-minute CAC tests compared to placebo. Adverse events occurred more frequently in the placebo group compared to alcaftadine group (13.3 vs 6.7%; *P* value not reported).
Greiner et al[18] Alcaftadine 0.05% (dose and frequency not reported)	AC, DB, PC, PRO, RCT Patients ≥18 years of age with a	N=170 5 weeks	Primary: Ocular itching (at visit four, five minutes after an allergen	Primary: All active treatment groups exhibited greater clinically (≥1 unit difference) and statistically significant (*P*<0.001) reductions in itching scores at all time points following the 15 minute CAC test compared to placebo. At seven minutes following a CAC test, alcaftadine

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs alcaftadine 0.01% (dose and frequency not reported) vs alcaftadine 0.25% (dose and frequency not reported) vs olopatadine 0.1% (dose and frequency not reported) vs placebo (dose and frequency not reported)	history of ocular allergies and/or a positive skin test reaction to specified allergens within the last 24 months and best-corrected visual acuity of 0.6 log MAR or better in each eye		challenge), conjunctival redness (at visit four, 15 minutes after an allergen challenge) Secondary: Ciliary and episcleral redness, chemosis, lid swelling, tearing, ocular mucus discharge, nasal symptoms and adverse events	0.25% was significantly more effective at preventing ocular itching compared to olopatadine (*P*=0.017). At the 15-minute CAC test, mean conjunctival redness scores for all active treatments were significantly lower at every time point compared to placebo (*P*<0.05 for all). Mean reductions in scores for olopatadine (-1.27 units) and alcaftadine 0.25% (-1.35 units) achieved clinical significance compared to placebo at seven minutes following CAC test (*P* value not reported). At the 16-hour CAC test (duration of action), alcaftadine was associated with lower mean ocular itching scores compared to both placebo and olopatadine (*P* values not reported). At seven minutes following CAC test, ocular itching scores were significantly lower with alcaftadine 0.25% compared to olopatadine (*P*=0.017). At the 16-hour CAC test, alcaftadine 0.25% and olopatadine exhibited statistically significant reductions in mean conjunctival redness scores compared to placebo (*P*<0.05). Secondary: At both the 15-minute and 16-hour CAC tests, all treatment groups exhibited significantly greater improvements in all secondary endpoints compared to placebo (*P*<0.05). All ocular adverse events were self-limited and mild in severity. The most common non-ocular adverse event was nasopharyngitis. No ocular adverse events were reported in the olopatadine treatment group.
Abelson et al[19] Bepotastine 1% one drop in each eye once daily	DB, PC, PRO, RCT Patients ≥10 years of age with a	N=107 7 weeks (5 visits)	Primary: Ocular itching at three, five and seven minutes following CAC,	Primary: Bepotastine 1 and 1.5% were associated with clinically and statistically significant reductions in mean ocular itching scores compared to placebo in the 15-minute onset of action and eight-hour duration of action CAC tests (*P*<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs bepotastine 1.5% one drop in each eye once daily vs placebo one drop in each eye once daily	history of allergic conjunctivitis, study used CAC model		redness at seven, 15 and 20 minutes following CAC and safety Secondary: Not reported	Statistically significant reductions in conjunctival hyperemia were achieved with both bepotastine concentrations; however, these reductions were not considered clinically significant. Overall, 13 patients experienced a treatment-emergent adverse event considered related to the study drug, six whom received bepotastine 1%, four who received bepotastine 1.5% and three who received placebo). Secondary: Not reported
Williams et al[20] Bepotastine 1% one drop in each eye once vs bepotastine 1.5% one drop in each eye once vs placebo one drop in each eye once	DB, PC, RCT, SC Patients ≥10 years of age with a history of ocular allergies, positive skin test to cat hair, cat dander, grasses, ragweed, and/or trees within the past 24 months and positive bilateral CAC reaction within 10 minutes of allergen instillation	N=107 3 weeks (4 visits)	Primary: Patient-assessed ocular itching, physician-assessed conjunctival redness and safety Secondary: Patient-assessed tearing, ciliary and episcleral redness, eyelid swelling, chemosis and mucous discharge	Primary: The mean ocular itching scores in the PP population were significantly lower with bepotastine 1 and 1.5% compared to placebo (P<0.001 for both). There was a statistically significant reduction in CAC-induced ocular itching 16 hours following administration of bepotastine 1 and 1.5% compared to placebo in the ITT populations (P≤0.001 for both). In the PP population, 40.0% of patients receiving bepotastine 1.5% experienced a two-unit reduction in ocular itching at one or more CAC time points compared to 34.3% of those in the bepotastine 1% group and 5.9% in the placebo group (P<0.05 for both compared to placebo). Of patients with severe itching, a two-unit reduction in ocular itching score at one or more time points occurred in 8.7% of the placebo group compared to 37.5 and 43.5% of patients receiving bepotastine 1% (P=0.001) and 1.5% (P=0.008), respectively. Bepotastine 1% was significantly more effective compared to placebo for reducing mean conjunctival redness seven minutes following the 16-hour CAC test (P≤0.012). There were no clinically significant differences (one unit or more change) in conjunctival redness between bepotastine (1 or 1.5%) and placebo at any time

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				point 16 hours after dosing. Secondary: Compared to placebo, bepotastine 1 and 1.5% were associated with statistically significant reductions in eyes with tearing (51.2 and 85.6 vs 27.5%, respectively; *P*<0.05 for both compared to placebo). Improvements in tearing were significantly greater in patients receiving bepotastine 1.5% compared to those treated with bepotastine 1% (*P*=0.0046).
Macejko et al[21] Bepotastine 1% one drop in each eye prior to CAC test vs bepotastine 1.5% one drop in each eye prior to CAC test vs placebo one drop in each eye prior to CAC test	DB, MC, PC, PRO, RCT Patients ≥10 years of age with a history of allergic conjunctivitis, a positive allergen skin test within the previous 24 months and CAC response on two separate occasions	N=130 7 weeks	Primary: Scores for ocular itching and conjunctival hyperemia Secondary: Not reported	Primary: Within three minutes following CAC test and at each other time point thereafter (performed 15 minutes or eight hours following drug administration), treatment with bepotastine 1 and 1.5% was associated with a significant reduction in ocular itching scores compared to placebo (*P*<0.0001 for both). Ocular itching improvements for bepotastine 1 and 1.5% were substantially less at the 16-hour CAC test compared to the 15- minute and eight-hour CAC tests. Conjunctival redness scores were significantly improved at most time points following the 15-minute CAC test for the 1 and 1.5% concentrations of bepotastine compared to placebo (*P*≤0.0125 for both). The most commonly reported adverse events included nasopharyngitis (8.5%), eye irritation (3.8%) and mild taste on instillation (3.1%). There were no reports of drowsiness or dry mouth. Dry eye was reported for a single subject in each of the placebo and bepotastine 1% treatment groups. Most events were reported as mild and transient. No patients discontinued therapy due to an adverse event. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
McCabe et al[22] Bepotastine 1.5% one drop in affected eye(s) twice daily vs olopatadine 0.2% one drop in affected eye(s) once daily	AC, RCT, SB, XO Patients ≥18 years of age with allergic conjunctivitis and no concurrent unrelated ocular diseases and no plans to undergo ocular surgery during the study period	N=30 2 weeks	Primary: Relief of ocular itch, itchy/runny nose, ocular allergy symptoms, eye drop comfort and patient preference Secondary: Not reported	Primary: There was a similar improvement in the relief of morning ocular itch between patients receiving bepotastine and olopatadine (*P* value not reported). Patients treated with bepotastine reported a significantly greater relief in evening ocular itch compared to patients receiving olopatadine (*P*=0.011). Olopatadine was significantly more effective at relieving ocular itching in the morning compared to the evening (*P*<0.0001), whereas bepotastine was equally effective at both time points. For the all-day relief of ocular itching, significantly more patients favored treatment with bepotastine compared to treatment with olopatadine (63.3 vs 36.7%; *P*=0.04). Bepotastine was significantly more effective at relieving morning and evening itchy/runny nose compared to olopatadine (*P*=0.0001). Bepotastine provided significantly more itchy/runny nose relief in the evening compared to the morning (*P*<0.035), whereas olopatadine provided a similar relief between morning and evening. A significantly greater proportion of patients preferred bepotastine compared to olopatadine for all-day relief of itchy/runny nose (66.7 vs 33.3%; *P*=0.01). A greater proportion of patients preferred bepotastine with regard to eye drop comfort compared to olopatadine (56.7 vs 43.3%; *P* value not reported). Treatment with bepotastine was significantly more effective for relief of morning and evening ocular allergy symptoms (*P*=0.032 and *P*<0.0001, respectively) compared to treatment with olopatadine. Bepotastine was equally efficacious for improving ocular allergy symptoms in the morning and evening, whereas olopatadine was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significantly more effective in the morning (*P*<0.001). Significantly more patients preferred bepotastine for the overall treatment of allergic conjunctivitis compared to olopatadine (66.7 vs 33.3%; *P*=0.01). Secondary: Not reported
Abelson et al[23] Olopatadine 0.1% one drop in one eye every eight hours for two doses vs olopatadine 0.2% one drop in one eye once vs placebo one drop in one eye every eight hours for two doses Study medications were administered contralaterally.	DB, PC, RCT Patients who responded to the ocular allergen challenge, study used CAC model	N=23 3 weeks (3 visits)	Primary: Ocular itching at three, five and seven minutes following CAC (allergen administered 24 hours after study drug instilled) and safety Secondary: Not reported	Primary: At the 24-hour CAC test, olopatadine 0.1 and 0.2% significantly reduced itching scores compared to placebo (*P*=0.002 and *P*=0.0007, respectively). There were no statistically significant differences between patients receiving olopatadine 0.1 and 0.2% (*P*=0.081). Olopatadine 0.1 and 0.2% were both found to be safe and well tolerated as used in this study. No adverse events were reported. Secondary: Not reported
Spangler et al[24] Azelastine 0.05% one drop in one eye once vs olopatadine 0.1% one drop in one eye once vs	AC, DB, MC, PRO, RCT Patients with a history of allergic conjunctivitis, study used CAC model	N=111 21 days (3 visits)	Primary: Ocular itching assessments every 30 seconds for a total period of 20 minutes following CAC and mean itching scores Secondary:	Primary: At visit three (evaluation visit), azelastine and olopatadine significantly improved ocular itching scores compared to placebo following a CAC test (*P*<0.05 for both). Olopatadine was significantly more effective compared to azelastine for preventing ocular itching at 3.5 minutes through 20 minutes following CAC test (*P*<0.05). No adverse events were reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo (artificial tears) one drop in one eye once Study medications were administered contralaterally.			Not reported	Secondary: Not reported
D'Arienzo et al[25] Emedastine 0.05% in one eye vs ketotifen 0.025% in one eye vs placebo in one eye Study medications were administered contralaterally.	AC, DB, PC, RCT, SC Patients with a history of allergic conjunctivitis, study used CAC model	N=45 3 weeks (3 visits)	Primary: Ocular itching at three, five and 10 minutes following CAC and safety Secondary: Not reported	Primary: Both emedastine and ketotifen significantly reduced mean itching scores at all time points following CAC test compared to placebo (*P*<0.05 for all). There were no statistically significant differences between emedastine and ketotifen in mean itching scores at any time points following CAC test (*P* values not reported). No adverse events were reported. Secondary: Not reported
Torkildsen et al[26] Epinastine 0.05% one drop in one eye at each visit vs ketotifen 0.025% or azelastine 0.05% one drop in other eye at each visit	AC, DB, RCT, SC, XO Patients with allergic conjunctivitis	N=40 4 weeks (4 visits)	Primary: Ocular comfort at zero, one, two and five minutes following administration (visit one), patient description of ocular sensation three minutes following administration, ocular drying (visits two to four) and safety	Primary: The mean ocular comfort score was significantly lower (indicating more comfort) with epinastine compared to azelastine at one, two and five minutes and compared to ketotifen at zero minutes (immediately) following instillation (*P*<0.05 for all). The mean ocular comfort score was significantly lower with ketotifen compared to azelastine at one and two minutes (*P*<0.05 for both). The proportion of patients who reported positive descriptors (e.g., refreshing, soothing) with epinastine, ketotifen and azelastine was 85, 55 and 41%, respectively (*P* values not reported). There were no significant differences between the treatments with regard to ocular drying (*P* values not reported). None of the 26 reported adverse events were considered to be

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	serious (six for epinastine, seven for ketotifen and 12 for azelastine; *P* values not reported). Secondary: Not reported
Lanier et al[27] Epinastine 0.05% one drop in one eye once vs olopatadine 0.1% one drop in one eye once vs placebo one drop in one eye once Study medications were administered contralaterally.	AC, DB, PC, PRO, RCT, SC Patients with a history of allergic conjunctivitis, study used CAC model	N=66 Duration not reported (3 visits)	Primary: Ocular itching at three, five and seven minutes following CAC, redness and chemosis at 10, 15 and 20 minutes following CAC Secondary: Not reported	Primary: Patients receiving olopatadine experienced significantly lower mean itching and conjunctival redness scores compared to patients receiving epinastine (*P*=0.003 and *P*<0.001, respectively). Olopatadine treatment was associated with significantly less chemosis, ciliary redness and episcleral redness compared to epinastine treatment (*P*≤0.001 for all). Comparisons to placebo were not reported. Secondary: Not reported
Mah et al[28] Epinastine 0.05% one drop in one eye once vs olopatadine 0.2% one drop in one eye once vs placebo one drop in one eye once Study medications were	AC, DB, PC, RCT Patients who responded to the ocular allergen challenge, study used CAC model	N=92 7 weeks (4 visits)	Primary: Ocular itching at three, five and seven minutes following CAC, redness at seven, 15 and 20 minutes following CAC, drop comfort at 30 seconds, one, two and five minutes following CAC and safety Secondary:	Primary: Patients treated with olopatadine experienced significantly lower mean ocular itching scores compared to those treated with epinastine at five (*P*=0.024) and seven minutes (*P*=0.003) following CAC test. Olopatadine treatment was associated with significantly lower mean ocular redness scores compared to epinastine treatment at all time points following CAC test (*P*<0.05). Olopatadine was rated as significantly more comfortable compared to epinastine at one minute following administration (*P*=0.003). Adverse events were not considered serious and were unrelated to study medication.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
administered contralaterally.			Not reported Secondary: Not reported	
Berdy et al[29] Ketotifen 0.025% one drop in one eye once vs olopatadine 0.1% one drop in one eye once Study medications were administered contralaterally.	AC, DB, PRO, RCT, SC Patients responding to a CAC	N=32 Duration not reported (3 visits)	Primary: Ocular itching at three, five and 10 minutes following CAC (12 hours after administration), ocular comfort and patient satisfaction Secondary: Not reported	Primary: Twelve hours following administration, efficacy scores for olopatadine were significantly higher at three and five minutes following CAC test compared to ketotifen (1.84 and 1.75 vs 1.25 and 1.34, respectively; *P*<0.05 for both). Olopatadine-treated eyes were rated as significantly more comfortable immediately following administration compared to eyes treated with ketotifen (*P*<0.05) and 12 hours later, as measured by patient ratings of ocular comfort. Of the 22 patients who had a preference, 16 (73%) were more satisfied with olopatadine than with ketotifen. Secondary: Not reported
Leonardi et al[30] Ketotifen 0.025% one to two drops in each eye daily as needed vs olopatadine 0.1% one to two drops in each eye daily as needed Patients were instructed to use both medications as needed over four weeks, but not to exceed two drops of medication per-eye per-day.	AC, DB, MC Patients with current symptoms of SAC or PAC	N=100 4 weeks (2 visits)	Primary: Patient rating of comfort, efficacy and preference Secondary: Not reported	Primary: A significantly greater percentage of patients (81%) preferred olopatadine compared to ketotifen with regard to comfort, efficacy, improvement in symptoms of allergy and which medication they would select if visiting the their physician (*P*<0.0001). Seventy-six percent of patients considered both efficacy and comfort when making their preference decisions (*P*<0.0001). No adverse events were reported. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ganz et al[31] Ketotifen 0.025% one drop in both eyes twice daily vs olopatadine 0.1% one drop in both eyes twice daily	AC, DB, PG, PRO, RCT Patients with SAC	N=66 3 weeks	Primary: Responder rate (patients with "excellent" or "good" global efficacy) on day five and 21, patient and investigator ratings of global efficacy, comfort and safety Secondary: Not reported	Primary: The responder rate was higher with ketotifen compared to olopatadine on day five (72 vs 54% for patient assessment and 88 vs 55% for investigator assessment, respectively) and day 21 (91 vs 55% and 94 vs 42%, respectively; *P* values not reported). Global efficacy ratings were higher with ketotifen, and severity scores for hyperemia and itching were significantly lower compared to olopatadine (*P* values not reported). Both drugs elicited comparable comfort ratings (*P* values not reported). The most common adverse events were burning/stinging and headache. Secondary: Not reported
Avunduk et al[32] Ketotifen 0.025% two drops in both eyes twice daily vs olopatadine 0.1% two drops in both eyes twice daily vs placebo (artificial tears) two drops in both eyes twice daily	AC, DB, PRO, RCT Patients with SAC	N=39 30 days	Primary: Scores for itching, tearing, redness, chemosis, eyelid swelling and safety Secondary: Not reported	Primary: Mean itching scores were significantly lower on days 15 and 30 in patients treated with ketotifen and olopatadine compared to placebo (*P*<0.05 for all). There were no statistically significant differences in mean itching scores between patients receiving ketotifen or olopatadine at any time point. Mean tearing scores were significantly lower on days 15 and 30 for patients receiving ketotifen compared to patients receiving placebo (*P*<0.05 for both). Mean tearing scores were significantly lower on day 15 (*P*<0.05) but not day 30 (*P* value not reported) for patients receiving olopatadine compared to patients receiving placebo. There were no statistically significant differences in mean tearing scores between ketotifen and olopatadine treatment groups. No statistically significant differences in mean scores for redness, chemosis or eyelid swelling were reported between patients receiving ketotifen, olopatadine or placebo. No adverse events were observed during the study.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Borazan et al[33] Ketotifen 0.025% one drop in one eye twice daily vs olopatadine 0.1% one drop in one eye twice daily vs emedastine 0.05% one drop in one eye twice daily vs epinastine 0.05% one drop in one eye twice daily vs fluorometholone 0.1% one drop in one eye twice daily vs placebo one drop in one eye twice daily One eye of each patient was treated with the study drug and the other eye was treated with placebo.	AC, DB, PC, PRO, RCT Patients with SAC	N=100 2 weeks	Primary: Scores for itching, redness, tearing, chemosis and eyelid swelling assessed after one and two weeks of treatment and conjunctival impression cytology at baseline and after treatment Secondary: Not reported	Primary: After one and two weeks of treatment, all agents were significantly more effective in alleviating itching, redness, tearing, chemosis and eyelid swelling compared to placebo (*P*<0.001 for all). Fluorometholone was significantly less effective in reducing itching and redness at all visits compared to the other agents (*P* values not reported). Although scores for tearing, chemosis and eyelid swelling showed a clinical improvement in all groups, there were no statistically significant differences between treatment groups (*P* values not reported). At the end of treatment, conjunctival impression cytology scores were significantly lower for all active treatments compared to placebo (*P*<0.01). There were no statistically significant differences between treatment groups (*P* values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Greiner et al[34] Olopatadine 0.1% 40 µL in one eye once vs naphazoline/pheniramine 0.025%/ 0.3% 40 µL one eye once vs placebo 40 µL in one eye once	AC, DB, PC, PRO, RCT Patients with allergic conjunctivitis, study used CAC model	N=83 Duration not reported (3 visits)	Primary: Ocular allergy index including erythema in three vessel beds, chemosis, eyelid swelling and itching at seven, 12 and 20 minutes following CAC Secondary: Not reported	Primary: At visit three (evaluation visit), both olopatadine and naphazoline/pheniramine treatments were associated with significantly lower ocular allergy index scores compared to placebo at all time points (*P*<0.001). Ocular allergy index scores were significantly lower with naphazoline/pheniramine treatment compared to olopatadine at 12 minutes and 20 minutes (*P*=0.005 and *P*=0.001, respectively). Olopatadine was associated with significantly lower itching scores compared to naphazoline/pheniramine at seven minutes following the CAC test (*P*=0.029). Secondary: Not reported
Owen et al[35] Ophthalmic antihistamines (antazoline* one trial, azelastine one trial, emedastine one trial, levocabastine* six trials) vs ophthalmic mast cell stabilizers (cromolyn 17 trials, lodoxamide one trial and nedocromil five trials) vs ophthalmic mast cell stabilizers (cromolyn five trials, lodoxamide one trial and nedocromil two trials) vs	MA of 40 DB, RCT Patients with SAC	N=not reported Duration varied	Primary: Subjective symptoms (e.g., ocular itching, burning, soreness and lacrimation) and patient's perception of improvement in subjective symptoms Secondary: Not reported	Primary: Most studies showed improvement in symptoms, especially for itching, in those treated with antihistamines compared to placebo. No antihistamine was more effective than another. Limited evidence suggests that antihistamines have a faster therapeutic effect compared to mast cell stabilizers; however, there was little difference in treatment efficacy after two weeks. Two short-term allergen provocation studies reported significantly less ocular itching and redness in patients treated with antihistamines compared to patients treated with mast cell stabilizers (*P*<0.05); however, no significant differences in subjective symptoms were noted in six long-term studies. Patients using antihistamines were 1.3 times (95% CI, 0.8 to 2.2) more likely to perceive a "good" treatment effect compared to patients using mast cell stabilizers; however, this was not statistically significant. Eight studies recorded subjective symptoms comparing cromolyn to placebo. An improvement in subjective symptoms was reported in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				five studies with no difference between treatments reported in three trials. A MA of six trials demonstrated that patients using cromolyn were 17 times (95% CI, 4 to 78) more likely to perceive benefit than those using placebo (of note, trials reporting marked and statistically significant benefits of cromolyn over placebo had small sample sizes.) No clinically relevant adverse events were reported with cromolyn treatment. In a small trial lasting four weeks, patients using lodoxamide reported significantly fewer symptoms of burning and itching, eyelid swelling, lacrimation and photophobia compared to those using placebo (*P* values not reported). Subjective symptoms were less pronounced in patients using nedocromil compared to patients using placebo with the differences reported as statistically significant in three studies. Patients using nedocromil were 1.8 times (95% CI, 1.3 to 2.6) more likely to report that their symptoms were "moderately" or "totally" controlled than those receiving placebo. Unpleasant taste following administration was the most reported adverse event. Patients using mast cell stabilizers were 4.9 times (95% CI, 2.5 to 9.6) more likely to perceive benefit from treatment compared to patients receiving placebo. No trials directly compared mast cell stabilizers with one another. Secondary: Not reported
James et al[36] Azelastine (strength not reported) in both eyes twice daily vs cromolyn (strength not reported) in	DB (azelastine vs placebo), MC, PG, OL (azelastine vs cromolyn) Patients with SAC or rhinoconjunctivitis	N=144 2 weeks	Primary: Ocular signs and symptoms, global assessment of efficacy and safety Secondary: Not reported	Primary: Both azelastine and cromolyn demonstrated an effect on itching, tearing and conjunctival redness on day three with a sustained improvement on days seven and 14 compared to placebo. A clear response to treatment occurred in 85.4% of azelastine patients and 83.0% of cromolyn patients compared to 56.3% of patients receiving placebo (*P*=0.005 and *P*=0.007, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
both eyes four times daily vs placebo in both eyes twice daily	and symptomatic at time of inclusion			Global assessment of efficacy was at least satisfactory for 90.0% of azelastine patients, 81.3% of cromolyn patients and 66.3% of placebo-treated patients (*P* values not reported). The most frequent adverse events were transient application site reactions, which tended to disappear with increasing duration of treatment, and, less frequently, taste perversion. Secondary: Not reported
Greiner et al[37] Cromolyn 4% in one eye four times daily for two weeks then one drop once at the final visit vs placebo other eye four times daily for two weeks then ketotifen 0.025% one drop once	AC, SB Patients who responded to the conjunctival provocation test, study used CAC model	N=56 2 weeks	Primary: Ocular itching, tearing and redness following CAC, comfort and safety Secondary: Not reported	Primary: At the 15-minute and four-hour CAC tests, ketotifen was significantly more effective than cromolyn in preventing itching (*P*<0.001) and redness (*P*≤0.001) at most assessments. Tearing scores were higher in patients receiving cromolyn compared to patients receiving ketotifen. Patients reported greater comfort in the eyes treated with ketotifen compared to cromolyn; however, the difference was not statistically significant (*P*=0.066). The most common adverse event associated with cromolyn was burning/stinging. A single dose of ketotifen was more effective than a two-week regimen of cromolyn in alleviating symptoms of allergic conjunctivitis in the CAC model. Secondary: Not reported
Katelaris et al[38] Cromolyn 2%* one drop in both eyes four times daily vs olopatadine 0.1% one drop in both	AC, DB, MC, PG, RCT Patients ≥4 years of age with SAC	N=185 6 weeks	Primary: Scores for ocular itching and conjunctival redness Secondary: Physicians'	Primary: After the first administration of cromolyn and olopatadine, self-rated ocular itching and redness scores decreased significantly from baseline (*P*<0.05 both). At 30 minutes after the first administration, self-rated ocular itching and redness decreased by 30 and 20% in each group, respectively. By four hours, itching had decreased by 38% in both groups, and redness had decreased by 26% with cromolyn and 38% with olopatadine. Differences between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
eyes twice daily and placebo one drop both eyes twice daily			impression of overall improvement and safety	treatments were not statistically significant. The reductions in ocular itching were significantly greater with olopatadine compared to cromolyn from days three to 42 (*P*<0.05). Improvements in ocular redness scores were significantly greater with olopatadine compared to cromolyn at day 42 (*P*<0.05). Secondary: The difference in physicians' impression of overall improvement on days 30 and 42 significantly favored olopatadine over cromolyn (*P*<0.05 on both days). Both treatments were well tolerated by patients in all age groups; however, olopatadine appeared to have better local tolerability in children <11 years of age compared to cromolyn.
Discepola et al[39] Emedastine 0.05% in one eye and placebo in other eye once vs ketorolac 0.5% in one eye and placebo in the other eye once Patients received the alternate treatment in one eye and placebo in the contralateral eye at day 14.	AC, DB, PC, RCT, SC, XO Patients with a history of allergic conjunctivitis, study used CAC model	N=36 4 weeks	Primary: Ocular itching and redness at three, 10 and 20 minutes following CAC and ocular discomfort Secondary: Not reported	Primary: Emedastine significantly inhibited ocular itching and redness in vascular beds compared to placebo (*P*<0.05). Ketorolac failed to significantly inhibit ocular itching or redness compared to placebo (*P* value not reported). Patient assessment of comfort indicated emedastine was significantly more comfortable compared to ketorolac upon topical ocular administration (*P*<0.05). Secondary: Not reported
Orfeo et al[40] Emedastine 0.05% in one eye once and placebo other eye once vs nedocromil 2% in one eye once	AC, DB, PC, RCT, XO Patients with a history of allergic conjunctivitis, study used CAC model	N=30 Duration not reported (3 visits)	Primary: Ocular itching and redness at three, 10 and 20 minutes following CAC Secondary: Not reported	Primary: Emedastine and nedocromil were significantly more effective compared to placebo in controlling ocular itching and redness following CAC test (*P*<0.01). Emedastine was significantly more effective in alleviating redness and itching at three and 10 minutes after the allergen CAC test compared to nedocromil (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and placebo other eye once Each patient received both study drugs on two different visits.				Secondary: Not reported
Greiner et al[41] Ketotifen 0.025% one drop in one eye once vs nedocromil 2% one drop in one eye once vs placebo (artificial tears) one drop in one eye once Study medications were administered contralaterally.	AC, DB, PC, RCT, SC Patients >10 years with a history of allergic hypersensitivity to animal dander or grass, tree or ragweed pollens, study used CAC model	N=59 35 days (4 visits)	Primary: Ocular itching every 30 seconds for 20 minutes following CAC (five minutes and 12 hours after medication administration); medication comfort at zero, one, two, five and 10 minutes after administration, terms used to describe comfort, patient preference based on comfort and perceived efficacy and safety Secondary: Not reported	Primary: Eyes treated with ketotifen experienced significantly less ocular itching compared to eyes treated with nedocromil and placebo after both the five-minute and 12-hour CAC tests (P<0.05 for both). Eyes treated with nedocromil did not experience improvements in ocular itching compared to eyes treated with placebo at any time point. Ketotifen-treated eyes were not significantly more comfortable compared to placebo-treated eyes; however, ketotifen was significantly more comfortable than nedocromil at one, two, five and 10 minutes following administration (P<0.05 for all). Five minutes after administration, “comfortable” was the most common descriptive term for ketotifen and placebo (72 and 49%, respectively, compared to 27% for nedocromil). “Stinging” was the most common descriptive term for nedocromil (31%). The proportion of unfavorable descriptive terms (burning, stinging or irritation) was 6% for ketotifen, 12% for placebo and 55% for nedocromil (P values were not reported). Based on comfort and subjective efficacy, 60% of patients preferred ketotifen, 21% preferred nedocromil and 19% preferred placebo. No serious adverse events were reported. Mild burning was reported by two patients for nedocromil-treated eyes. Secondary: Not reported
Butrus et al[42] Nedocromil 2% one drop in one eye twice daily for two weeks then	AC, DB, PC, RCT, SC Patients with	N=52 21 days (3 visits)	Primary: Ocular itching at three, five and 10 minutes following	Primary: Olopatadine was significantly more effective in reducing itching following at all time points compared to nedocromil (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
one drop once vs placebo one drop in one eye twice daily for two weeks then olopatadine 0.1% one drop in one eye once vs placebo one drop in one eye twice daily Study medications were administered contralaterally.	allergic conjunctivitis, study used CAC model		CAC and patient preference based on comfort and efficacy Secondary: Not reported	Eyes treated with olopatadine were rated as being significantly more comfortable compared to eyes treated with nedocromil (*P*=0.034). Of the 14 patients treated with olopatadine and nedocromil, 10 patients (71%) were more satisfied with olopatadine than nedocromil, and four patients (29%) had no preference. Secondary: Not reported
Alexander et al[43] Olopatadine 0.1% twice daily vs nedocromil 2% twice daily After one week, patients XO to the other treatment for one week.	AC, RCT, XO Patients with PAC and previous olopatadine experience	N=28 2 weeks	Primary: Patient satisfaction, severity of ocular symptoms (daily diary scores), physician's assessment of clinical signs and global assessments of effectiveness Secondary: Not reported	Primary: Of the 28 patients, 16 (57.1%) would request a nedocromil prescription and 10 (35.7%) would request an olopatadine prescription (*P*=0.157). Twenty-two patients (78.6%) would recommend nedocromil to other allergy sufferers, while 18 patients (64.3%) would recommend olopatadine (*P*=0.480). Both drugs significantly (*P*<0.01) decreased erythema, conjunctival injection and overall conjunctival signs from baseline. Light sensitivity scores were significantly lower with nedocromil (*P*=0.0125). Other symptom scores were comparable between medications. Both physicians and patients judged nedocromil and olopatadine to be similarly effective in preventing signs and symptoms of allergic conjunctivitis. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Yaylali et al[44] Olopatadine 0.1% in one eye twice daily and placebo in the other eye twice daily vs ketorolac 0.5% in one eye four times daily and placebo in the other eye four times daily	AC, PC, PG, RCT, SC Patients with SAC	N=40 15 days	Primary: Hyperemia and itching at 30 minutes then at two, seven and 15 days Secondary: Not reported	Primary: Hyperemia and itching were significantly improved in eyes treated with olopatadine and ketorolac compared to eyes treated with placebo at all time points (*P*<0.05 for all). The mean hyperemia score was lower in the olopatadine group compared to the ketorolac group; however, the difference was not statistically significant. The mean itching score was significantly lower in the olopatadine group compared to the ketorolac group from day two through to the end of the study (*P*<0.05). Secondary: Not reported
Berdy et al[45] Olopatadine 0.1% one drop in both eyes four times daily for 14 days, then one drop in both eyes at evaluation visit vs loteprednol 0.2% one drop in both eyes four times daily for 14 days, then one drop in both eyes at evaluation visit vs placebo one drop in both eyes four times daily for 14 days, then one drop in both eyes at evaluation visit	AC, DB, PG, RCT, SC Patients >18 years of age with a history of SAC or PAC with no severe atopic, vernal or giant papillary conjunctivitis	N=50 21 days	Primary: Scores for itching and redness and IOP Secondary: Not reported	Primary: Greater itching relief was achieved following treatment with olopatadine compared to loteprednol at three, five and 10 minutes following CAC test (*P*=0.001, *P*<0.001 and *P*<0.001, respectively). Treatment with loteprednol significantly decreased itching scores compared to treatment with placebo at three and five minutes following CAC test (*P*<0.05 for both). No statistically significant difference between these two groups was reported at 10 minutes (*P* value not reported). Olopatadine provided a significant improvement in itching relief compared to placebo (*P*<0.001 at three, five and 10 minutes). Olopatadine was significantly more effective for the prevention of ocular redness compared to loteprednol at minutes 10, 15 and 20 (*P*=0.003, *P*=0.011 and *P*=0.034, respectively). No statistically significant difference in the prevention of ocular redness was reported at minutes 10, 15 and 20 for loteprednol compared to placebo (*P* value not reported). Olopatadine was significantly more effective for preventing ocular

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				redness at 10, 15 and 20 minutes compared to placebo (*P*<0.001, *P*=0.012 and *P*=0.027, respectively). There was a statistically significant increase in IOP during the third visit with loteprednol compared to both olopatadine and placebo (*P*<0.001 for both). There were no adverse events reported during the course of study. Secondary: Not reported

*Agent not available in the United States.
The conjunctival allergen challenge model usually consisted of three visits. At visit one, the allergen concentration that elicited the desired ocular allergic response was determined, and this concentration was confirmed at visit two. At visit three, the study drugs were administered prior to the allergen challenge.
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-labeled, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SB=single-blind, SC=single center, XO=cross over
Miscellaneous abbreviations: CAC=conjunctival allergen challenge, IOP=intraocular pressure, ITT=intent to treat population, MAR=Minimum angle of resolution, SAC=seasonal allergic conjunctivitis, PAC=perennial allergic conjunctivitis, PP=per-protocol population

Special Populations

Table 5. Special Populations[2-11]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Alcaftadine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and effectiveness in children <2 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	B	Unknown
Azelastine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and effectiveness in children <3 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown
Bepotastine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and effectiveness in children <2 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown
Emedastine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and effectiveness in children <3 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	B	Unknown
Epinastine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and effectiveness	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	in children <2 years of age have not been established.				
Ketotifen	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and effectiveness in children <3 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown
Olopatadine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and effectiveness in children <3 years (0.1%) and <2 years (0.2%) of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown

Adverse Drug Events

Table 6. Adverse Drug Events[2-11]

Adverse Event(s)	Alcaftadine	Azelastine	Bepotastine	Emedastine	Epinastine	Ketotifen	Olopatadine
Central Nervous System							
Abnormal dreams	-	-	-	<5	-	-	-
Asthenia	-	-	-	<5	-	-	<5
Fatigue	-	1 to 10	-	-	-	-	-
Headache	<3	15	2 to 5	11	1 to 3	10 to 25	<7
Dermatological							
Dermatitis	-	-	-	<5	-	-	-
Pruritus	<4	1 to 10	-	<5	1 to 10	-	<5
Rash	-	-	-	-	-	<5	-
Gastrointestinal							
Nausea	-	-	-	-	-	-	<5
Taste perversion	-	10	25	<5	-	-	<5
Ocular							
Blurred vision	-	1 to 10	-	<5	-	-	<5
Burning	<4	30	-	<5	1 to 10	<5	<5

Adverse Event(s)	Alcaftadine	Azelastine	Bepotastine	Emedastine	Epinastine	Ketotifen	Olopatadine
Conjunctival injection	-	-	-	-	-	10 to 25	-
Conjunctivitis	-	1 to 10	-	-	-	<5	<5
Corneal infiltrates	-	-	-	<5	-	-	-
Corneal staining	-	-	-	<5	-	-	-
Discharge	-	-	-	-	-	<5	-
Discomfort	-	-	-	<5	-	-	-
Dry eye	-	-	-	<5	-	<5	<5
Eyelid disorder/edema	-	-	-	-	-	<5	<5
Folliculosis	-	-	-	-	1 to 10	-	-
Foreign body sensation	-	-	-	<5	-	-	<5
Hyperemia	-	-	-	<5	1 to 10	-	<5
Irritation	<4	-	2 to 5	-	-	-	-
Itching	-	-	-	-	1 to 10	<5	<5
Keratitis	-	-	-	<5	-	<5	<5
Lacrimation disorder	-	-	-	<5	✔	<5	-
Mydriasis	-	-	-	-	-	<5	-
Pain	-	1 to 10	-	-	-	<5	<5
Photophobia	-	-	-	-	-	<5	-
Redness	<4	-	-	-	-	-	-
Stinging	<4	30	-	<5	-	<5	<5
Tearing	-	-	-	<5	-	-	-
Respiratory							
Asthma	-	1 to 10	-	-	-	-	-
Cold/flu symptoms	-	1 to 10	-	-	10	<5	<10
Cough	-	-	-	-	1 to 3	-	<5
Dyspnea	-	1 to 10	-	-	-	-	-
Nasopharyngitis	<3	-	2 to 5	-	-	-	-
Pharyngitis	-	1 to 10	-	-	1 to 3	<5	<10
Rhinitis	-	1 to 10	-	<5	1 to 3	10 to 25	<5
Sinusitis	-	-	-	<5	1 to 3	-	<5
Other							
Allergic reaction	-	-	-	-	-	<5	<5
Back pain	-	-	-	-	-	-	<5
Bitter taste	-	10	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	-	<5
Infection	-	-	-	-	10	-	<5
Influenza	<3	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications

Table 7. Contraindications[2-11]

Contraindication(s)	Alcaftadine	Azelastine	Bepotastine	Emedastine	Epinastine	Ketotifen	Olopatadine
Known or suspected hypersensitivity to any components of the product	-	✔	✔	✔	-	✔	✔

Warnings/Precautions

Table 8. Warnings and Precautions[2-11]

Warning/Precaution	Alcaftadine	Azelastine	Bepotastine	Emedastine	Epinastine	Ketotifen	Olopatadine
Contact lens use: patients should not wear a contact lens if eye is red	✔	✔	✔	✔	✔	✔	✔
Contact lens use; remove contact lenses prior to instilling this product, as the preservative, benzalkonium chloride may be absorbed by soft contact lenses	✔	✔	✔	✔	✔	✔	✔
Contamination of tip and solution; do not to touch eyelids or surrounding areas with the dropper tip of the bottle	✔	✔	✔	✔	✔	✔	✔
For topical use only	✔	✔	✔	✔	✔	✔	✔

Drug Interactions

No drug interactions have been reported for ophthalmic antihistamines.[4-11]

Dosage and Administration

Table 9. Dosing and Administration[2-11]

Generic Name	Adult Dose	Pediatric Dose	Availability
Alcaftadine	Allergic conjunctivitis: Ophthalmic solution: instill one drop into affected eye(s) once daily	Allergic conjunctivitis: Children ≥2 years of age, refer to adult dose. Safety and effectiveness in children <2 years of age have not been established.	Ophthalmic solution: 0.25% (5 mL)
Azelastine	Allergic conjunctivitis:	Allergic conjunctivitis:	Ophthalmic

Generic Name	Adult Dose	Pediatric Dose	Availability
	Ophthalmic solution: instill one drop in affected eye(s) twice daily	Children ≥3 years of age, refer to adult dose. Safety and effectiveness in children <3 years of age have not been established.	solution: 0.05% (10 mL)
Bepotastine	Allergic conjunctivitis: Ophthalmic solution: instill one drop in affected eye(s) twice daily	Allergic conjunctivitis: Children ≥2 years of age, refer to adult dose. Safety and effectiveness in children <2 years of age have not been established.	Ophthalmic solution: 1.5% (5, 10 mL)
Emedastine	Allergic conjunctivitis: Ophthalmic solution: instill one drop in affected eye(s) up to four times daily	Allergic conjunctivitis: Children ≥3 years of age, refer to adult dose. Safety and effectiveness in children <3 years of age have not been established.	Ophthalmic solution: 0.05% (5 mL)
Epinastine	Allergic conjunctivitis: Ophthalmic solution: instill one drop in affected eye(s) twice daily	Allergic conjunctivitis: Children ≥2 years of age, refer to adult dose. Safety and effectiveness in children <2 years of age have not been established.	Ophthalmic solution: 0.05% (10 mL)
Ketotifen	Allergic conjunctivitis, ocular itching: Ophthalmic solution: instill 1 drop in affected eye(s) twice daily	Allergic conjunctivitis, ocular itching: Children ≥3 years of age, refer to adult dose. Safety and effectiveness in children <3 years of age have not been established.	Ophthalmic solution: 0.025% (over-the-counter, prescription) (5, 10 mL)
Olopatadine	Allergic conjunctivitis: Ophthalmic solution: initial, instill one drop (0.1%) in affected eye(s) twice daily or one drop (0.2%) in affected eye(s) once daily	Allergic conjunctivitis: Children ≥2 (0.2%) and ≥3 (0.1%) years of age, refer to adult dose. Safety and effectiveness in children <3 years (0.1%) and <2 years (0.2%) of age have not been established.	Ophthalmic solution: 0.1% (5 mL) 0.2% (4 mL)

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Ophthalmology: **Preferred Practice Pattern: Conjunctivitis (2011)**[2]	Seasonal allergic conjunctivitis • Treatment of conjunctivitis is ideally directed at the root cause. Indiscriminate use of topical antibiotics or corticosteroids should be avoided because antibiotics can induce toxicity, and corticosteroids can potentially prolong adenoviral infections and worsen herpes simplex virus infections. • Treat mild allergic conjunctivitis with an over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H_1-receptor antagonist. The guideline does not give preference to one OTC antihistamine/vasoconstrictor or antihistamine vs another. The

Clinical Guideline	Recommendations
	guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. • If the condition is frequently recurrent or persistent, use mast-cell stabilizers. The guideline does not give preference to one mast-cell stabilizer vs another. • Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. The guideline does not give preference to one antihistamine/mast-cell stabilizer vs another. • If the symptoms are not adequately controlled, a brief course (one to two weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used. • Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), is also Food and Drug Administration (FDA)-approved for the treatment of allergic conjunctivitis. • Additional measures include allergen avoidance and using cool compresses, oral antihistamines and artificial tears, which dilute allergens and treat coexisting tear deficiency. Frequent clothes washing and bathing before bedtime may also be helpful. • Consultation with an allergist or dermatologist may be helpful for patients with disease that cannot be adequately controlled with topical medications and oral antihistamines. <u>Vernal/atopic conjunctivitis</u> • General treatment measures include modifying the environment to minimize exposure to allergens or irritants and using cool compresses and ocular lubricants. Topical and oral antihistamines and topical mast-cell stabilizers may be beneficial in maintaining comfort. • For acute exacerbations, topical corticosteroids are usually necessary to control severe symptoms. The minimal amount of corticosteroid should be used based on patient response and tolerance. Topical cyclosporine is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis. For entities such as vernal keratoconjunctivitis, which may require repeat short-term therapy with topical corticosteroid, patients should be informed about potential complications of corticosteroid therapy, and general strategies to minimize corticosteroid use should be discussed. • For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, systemic immunosuppression may be warranted. Eyelid involvement may be treated with pimecrolimus or tacrolimus. Patients should be told to keep these medications away from the conjunctival and corneal surface and from the tear film. Both agents are rarely associated with the development of skin cancer and lymphoma. • Frequency of follow-up visits is based on the severity of disease presentation, etiology and treatment. Consultation with a dermatologist is often helpful. If corticosteroids are prescribed, baseline and periodic measurement of intraocular pressure and papillary dilation should be performed to evaluate for glaucoma and cataract(s).

Clinical Guideline	Recommendations
	Mild bacterial conjunctivitis • Mild bacterial conjunctivitis may be self-limited and resolve spontaneously without treatment in immunocompetent adults. • Ophthalmic antibacterial therapy is associated with earlier clinical and microbiological remission compared to placebo at days two to five of treatment. The advantages persist over six to 10 days, but the benefit over placebo lessens over time. • The choice of ophthalmic antibiotic is usually empirical. • A five to seven day course of ophthalmic broad-spectrum antibiotic is usually effective. • The most convenient or least expensive option can be selected. Severe bacterial conjunctivitis • Severe bacterial conjunctivitis is characterized by copious purulent discharge, pain and marked inflammation of the eye. • The choice of ophthalmic antibiotic is guided by the results of laboratory tests. • Methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated with increasing frequency from patients with bacterial conjunctivitis. Many MRSA organisms are resistant to commercially available ophthalmic antibiotics. • Systemic antibiotic therapy is necessary to treat conjunctivitis due to *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. • If corneal involvement is present, the patient should also be treated topically for bacterial keratitis. Herpes simplex virus conjunctivitis • Topical and/or oral antiviral treatment is recommended for herpes simple virus conjunctivitis to prevent corneal infection. • Possible options include topical ganciclovir 0.15% gel applied three to fiv times per day, trifluridine 1% solution applied five to eight times per day, or oral acyclovir 200 to 400 mg administered five times per day. • Oral valacyclovir and famciclovir also can be used. • Topical antiviral agents may cause toxicity if used for more than two weeks. • Topical corticosteroids potentiate herpes simplex virus infection and should be avoided. • Follow-up care management within one week of treatment is advised an should include an interval history, visual acuity measurement and slit-lamp biomicroscopy. • Neonates require prompt consultation with the pediatrician or primary care physician, because systemic herpes simplex virus infection is a life-threatening condition.
American Optometric Association: **Optometric Clinical Practice Guideline: Care of the Patient With Conjunctivitis (2007)**[3]	Allergic conjunctivitis (includes atopic keratoconjunctivitis, simple allergic conjunctivitis, seasonal or perennial conjunctivitis and vernal conjunctivitis) • The treatment of allergic conjunctivitis is based upon identification of specific antigens and elimination of specific pathogens, when practical, and upon the use of medications that decrease or mediate the immune response. The use of supportive treatment, including unpreserved lubricants and cold compresses, may provide symptomatic relief. • The following agents are useful in treating allergic conjunctivitis:

Clinical Guideline	Recommendations
	topical corticosteroids (numerous products listed), vasoconstrictors/antihistamines (specific products not listed), antihistamines (azelastine, emedastine and levocabastine*), NSAIDs (ketorolac), mast cell stabilizers (cromolyn, lodoxamide, nedocromil and pemirolast), antihistamines/mast cell stabilizers (ketotifen and olopatadine) and immunosuppressants; and systemic immunosuppressants and antihistamines. • Topical corticosteroids are effective in relieving the acute symptoms of allergy; however, their use should be limited to the acute suppression of symptoms because of the potential for adverse side effects with prolonged use (e.g., cataract formation and elevated intraocular pressure). • Topical vasoconstrictors/antihistamines cause vascular constriction, decrease vascular permeability and reduce ocular itching by blocking histamine H_1 receptors. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. • Topical antihistamines competitively bind with histamine receptor sites and reduce itching and vasodilation. Azelastine, emedastine and levocabastine* are effective in reducing the symptoms of allergic conjunctivitis, and emedastine may be more efficacious than levocabastine*. • Topical diclofenac and ketorolac, which are both NSAIDS, are effective in reducing the signs and symptoms associated with allergic conjunctivitis, although only ketorolac is FDA approved for this indication. • Nedocromil, an effective treatment for seasonal allergic conjunctivitis, is more effective than cromolyn (2%†) in treating vernal conjunctivitis. Nedocromil was less effective than fluorometholone in treating severe vernal keratoconjunctivitis but has fewer side effects. Lodoxamide has demonstrated a greater improvement in the signs and symptoms of allergic eye disease, including vernal keratoconjunctivitis, than cromolyn (2† or 4%). Pemirolast has FDA approval as a treatment to relieve (to prevent) itching associated with allergic conjunctivitis. • Ketotifen and olopatadine are selective histamine H_1-receptor antagonists that also have mast cell stabilizing properties. Olopatadine may be more effective than other mast cell stabilizing agents in targeting the subtype of mast cell found in the conjunctiva. Compared to ketorolac or ketotifen, olopatadine is more effective in relieving the itching and redness associated with acute allergic conjunctivitis. • Systemically administered cyclosporine may be an effective treatment for patients with severe atopic keratoconjunctivitis. Topical cyclosporine is an alternative to topical corticosteroids for treatment of patients with severe atopic keratoconjunctivitis. Topical cyclosporine may also be beneficial in patients with vernal keratoconjunctivitis who have failed conventional therapy. • Systemic antihistamines are useful when the allergic response is associated with lid edema, dermatitis, rhinitis or sinusitis. They should be used with caution because of the sedating and anticholinergic effects of some first-generation antihistamines. Newer antihistamines are much less likely to cause sedation, but their use may result in increased ocular surface dryness.

Clinical Guideline	Recommendations
	Viral conjunctivitis • Most viral conjunctivitis is related to adenoviral infection; however, no antiviral agent has been demonstrated to be effective in treating these infections. • Topical NSAID therapies have shown no benefit in reducing viral replication, decreasing the incidence of sub-epithelial infiltrates or alleviating symptoms. • Topical antibiotics are not routinely used to treat viral conjunctivitis, unless there is evidence of secondary bacterial infection. • The treatment of herpes simplex conjunctivitis may include the use of antiviral agents such as trifluridine, although there is no evidence that this therapy results in a lower incidence of recurrent disease or keratitis. • Supportive therapy, including lubricants and cold compresses, which may be as effective as antiviral drugs, eliminates the potential for toxic side effects. • Topical steroids are specifically contraindicated for treating herpes simplex conjunctivitis.

*Product is not available in the United States.
†Cromolyn 4% but not 2% is available in the United States. The concentrations of cromolyn that were used in the original clinical studies are noted in this table.

Conclusions

The ophthalmic antihistamines are Food and Drug Administration-approved for the management of the signs and symptoms associated with allergic conjunctivitis, the most common form of ocular allergy. The class of ophthalmic antihistamines includes alcaftadine (Lastacaft®), azelastine (Optivar®), bepotastine (Bepreve®), emedastine (Emadine®), epinastine (Elestat®), ketotifen (Alaway®, Zaditor®) and olopatadine (Pataday®, Patanol®). Most of these agents have been shown to have both histamine type 1 (H_1-antihistamine) and mast cell stabilizing properties. The ophthalmic antihistamines reduce itching and redness through competitive binding with histamine receptor sites and inhibiting the degranulation of mast cells, thus limiting the release of inflammatory mediator associated with the development of allergy symptoms.[14]

Few distinguishing characteristics exist between the available ophthalmic antihistamines, but alcaftadine and olopatadine 0.2% may be administered once daily, while remaining agents in this class are administered two to four times daily. In addition, ophthalmic alcaftadine and ophthalmic emedastine are classified as pregnancy category B; other agents in this class are pregnancy category C.[2-11] Currently ophthalmic formulations of azelastine, epinastine and ketotifen are available generically. Ophthalmic formulations of ketotifen are also available in over-the-counter (OTC) formulations. Due to the ophthalmic administration of these agents, relatively few adverse reactions have been reported, the most common being ocular burning and stinging and headache.

According to the American Academy of Ophthalmology, mild allergic conjunctivitis may be treated with an OTC ophthalmic antihistamine/vasoconstrictor or ophthalmic antihistamine.[16] Ophthalmic allergy preparations with dual antihistamine and mast cell stabilizing properties may be used for either acute or chronic disease, with no preference given to one agent over another.[16] The use of ophthalmic vasoconstrictors including phenylephrine, should be limited due to their short duration of action and potential to cause rebound hyperemia and conjunctivitis medicamentosa.[13] Ophthalmic mast cell stabilizers may be used if the condition is recurrent or persistent, but they have a slower onset of action than other agents.[13,16]

Several studies have been conducted to directly compare ophthalmic ketotifen and ophthalmic olopatadine. These studies have produced mixed results, generally demonstrating no difference between the agents. Results of some studies suggest that ophthalmic olopatadine may be preferred and better

tolerated by patients.[29-32] There are limited head-to-head studies that compare the clinical efficacy of the other agents in this class to one another, and all are considered equally efficacious at improving ocular allergy symptoms.[18,25-28,33] While some studies reported statistically significant differences in symptom scores, the overall clinical significance of these differences is not known, as many of these trials were conducted using single doses of study medication (in the conjunctival allergen challenge model) and generally enrolled a small number of patients.

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