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Therapeutic Class Overview
Ophthalmic Anti-Allergy

INTRODUCTION

- Conjunctivitis can be classified as noninfectious or infectious, and as acute, chronic, or recurrent. Types of noninfectious conjunctivitis are allergic, mechanical/irritative/toxic, immune-mediated, and neoplastic. Causes of infectious conjunctivitis are viruses and bacteria *(American Academy of Ophthalmology [AAO] 2018)*.
- Types of allergic conjunctivitis include atopic keratoconjunctivitis, seasonal or perennial conjunctivitis, vernal conjunctivitis, and giant papillary conjunctivitis. Atopic keratoconjunctivitis is a severe, chronic, external ocular inflammation associated with atopic dermatitis. Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea *(AAO 2018, Bielory et al 2020)*.
- Allergic conjunctivitis results from classic Type I immunoglobulin E (IgE)-mediated hypersensitivity, where the immediate response to allergens is mediated predominantly by mast cells. The mast cells are present in the conjunctiva in high concentrations and release chemical mediators when activated by allergen-IgE cross-linkage. During the early response, histamine is the main mediator, and it 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 (*Bielory et al 2020, Bielory et al 2012*). Symptoms of allergic conjunctivitis include itching, tearing, mucoid discharge, chemosis, hyperemia, and redness. Most commonly, symptoms are present in both eyes, but they may also occur unilaterally *(Hamrah and Dana 2020a, Bielory et al 2012)*.
- The ophthalmic anti-allergy therapeutic class overview details the efficacy and safety of the ophthalmic antihistamines and ophthalmic mast cell stabilizers.
  - The ophthalmic antihistamines are Food and Drug Administration (FDA)-approved for the management of the signs and symptoms associated with allergic conjunctivitis *(Micromedex 2.0 2021, Facts & Comparisons 2021)*.
    - All ophthalmic antihistamines are available by prescription with the exception of ketotifen. OTC products include ketotifen and olopatadine and are indicated for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander.
  - The ophthalmic mast cell stabilizers include cromolyn sodium (previously marketed under the brand name, Opticrom), Alomide (lodoxamide) and Alocril (nedocromil). Nedocromil is approved for the treatment of itching associated with allergic conjunctivitis while cromolyn and lodoxamide are the only agents in this review that are FDA-approved for the treatment of vernal conjunctivitis (*Drugs@FDA 2021, Hamrah and Dana 2020b*).
  - Alrex (loteprednol etabonate 0.2%) ophthalmic suspension, an ophthalmic corticosteroid, is also indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis in adults. Acular (ketorolac 0.5%) ophthalmic solution, an ophthalmic non-steroid anti-inflammatory drug (NSAID), is also FDA-approved for the treatment of ocular pruritus due to seasonal allergic conjunctivitis (ages ≥ 2 years) (*Micromedex 2.0 2021*). These 2 agents are reviewed in separate class reviews.
- Medispan Therapeutic Class: Ophthalmic Antiallergic

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ophthalmic Antihistamines	
Alaway†, Zaditor† (ketotifen 0.025% ophthalmic solution)	✔
Bepreve (bepotastine besilate 1.5% ophthalmic solution)	-§
Elestat (epinastine HCl 0.05% ophthalmic solution)	✔
Lastacaft (alcaftadine 0.25% ophthalmic solution)	-
Optivar* (azelastine HCl 0.05% ophthalmic solution)	✔
Pataday* (olopatadine HCl 0.2% ophthalmic solution) Patanol* (olopatadine HCl 0.1% ophthalmic solution)	✔ ‡ ✔ ‡
Pataday Once Daily Relief† (olopatadine HCl 0.2%, 0.7%** ophthalmic solution)	-

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Drug	Generic Availability
Pataday Twice Daily Relief† (olopatadine HCl 0.1% ophthalmic solution)	-
Zerviate (cetirizine 0.24% ophthalmic solution)	-
Ophthalmic Mast Cell Stabilizers	
Alocril (nedocromil 2% ophthalmic solution)	-§
Alomide (lodoxamide 0.1% ophthalmic solution)	-
cromolyn sodium 4% ophthalmic solution	✔

Key: HCl = hydrochloride
* Brand name has been discontinued; generics are available.
† Available over-the-counter.
‡ Generic prescription products containing olopatadine HCl 0.1% or 0.2% remain available.
** This prescription brand, Pazeo, has been discontinued; olopatadine HCl 0.7% became available over-the-counter as Pataday Once Daily Relief in September 2020.
§ A generic product has received FDA approval but is not yet commercially available.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications – Ophthalmic Antihistamines

Indication	**Alaway, Zaditor** (ketotifen)	**Bepreve** (bepotastine)	**Elestat** (epinastine)	**Lastacaft** (alcaftadine)	**Optivar** (azelastine)	olopatadine prescription	**Pataday Once or Twice Daily Relief** (olopatadine) OTC	**Zerviate** (cetirizine)
Prevention of ocular itching associated with allergic conjunctivitis			✔	✔				
Treatment of ocular itching associated with allergic conjunctivitis		✔			✔	✔ (0.2%)		✔
Treatment of signs and symptoms of allergic conjunctivitis						✔ (0.1%)		
Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander	✔						✔	

(Prescribing information: Alaway 2020, Azelastine 2019, Bepreve 2019, Elestat 2011, Lastacaft 2020, Pataday 2010, Pataday Once Daily Relief 2020, Pataday Twice Daily Relief 2020, Patanol 2018, Zaditor 2020, Zerviate 2020)

Table 3. Food and Drug Administration Approved Indications – Ophthalmic Mast Cell Stabilizers

Indication	Alocril (nedocromil)	Alomide (lodoxamide)	cromolyn sodium
Treatment of itching associated with allergic conjunctivitis	✔		
Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis		✔	✔

(*Prescribing information: Alocril 2018, Alomide 2020, cromolyn sodium ophthalmic solution 2016*)

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- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Ophthalmic Antihistamines

- 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 these trials demonstrated improvements in symptoms, especially for itching, in those treated with ophthalmic antihistamines and antihistamines/mast cell stabilizers compared to placebo.
- 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 *(Avunduk et al 2005, Berdy et al 2000, Borazan et al 2009, Ganz et al 2003, Leonardi et al 2004)*. There are limited head-to-head studies that compare the clinical efficacy of the other ophthalmic antihistamines to one another, and all are considered equally efficacious at improving ocular allergy symptoms. 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. A Cochrane review of topical antihistamines for treatment of allergic conjunctivitis concluded that topical antihistamines and mast cell stabilizers reduce symptoms temporarily. Data for the long-term use of topical antihistamines are lacking *(Castillo et al 2015)*.
- A study compared efficacy of daily use of alcaftadine (n = 60), olopatadine (n = 60), and bepotastine (n = 60) for 14 days in 180 patients with mild-to-moderate allergic conjunctivitis. At day 14, the total ocular symptom score (TOSS) had significantly reduced from baseline scores in all 3 groups. Although the authors describe a statistically significant difference between groups in mean TOSS score at day 14, this was a post hoc assessment and the clinical significance of this difference is unclear. No significant differences in adverse events were observed between the 3 groups (*Ayyappanavar et al 2021*).
- Clinical data supporting the FDA approval of cetirizine ophthalmic solution were from two Phase 3 studies that evaluated the efficacy and safety of the drug compared with vehicle in the treatment of allergen-induced conjunctivitis using a conjunctival allergen challenge model (*Malhotra et al 2019, Meier et al 2018*). Approximately 100 subjects were randomized in each study. Results revealed that ophthalmic cetirizine administered 15 minutes or 8 hours before the challenge results in significantly reduced ocular itching at all time points post-challenge ($p < 0.0001$) compared to vehicle in both studies. Additionally, significant improvement in chemosis, eyelid swelling, tearing, ciliary redness, episcleral redness, and nasal symptoms were observed with cetirizine. The ophthalmic solution was well-tolerated and was associated with a low incidence of mild adverse events.

Ophthalmic Mast Cell Stabilizers

- Clinical studies have demonstrated that ophthalmic mast cell stabilizers are safe and effective for their FDA-approved indications.
- Ophthalmic formulations of cromolyn and lodoxamide are FDA-approved for the treatment of vernal conjunctivitis, which is a severe form of allergic conjunctivitis that may involve the cornea. A study confirmed that ophthalmic cromolyn 4% was significantly more effective than placebo in treating the signs and symptoms of vernal conjunctivitis, such as conjunctival and limbal injection, limbal edema, and tearing (n = 65) (*Foster et al 1988*). In a few small studies (N = 30 to 120) conducted over 10 to 28 days, ophthalmic lodoxamide was reported to be more effective than ophthalmic cromolyn 4% in improving clinical signs and symptoms of vernal conjunctivitis (*Avunduk et al 2000, Caldwell et al 1992, Leonardi et al 1997*).
- Clinical studies have shown that ophthalmic formulations of cromolyn, lodoxamide, azelastine, and nedocromil were more effective than placebo for managing symptoms of seasonal and perennial allergic conjunctivitis (*James et al 2003, Kjellman et al 1995, Leino et al 1992, Orfeo et al 2002, Owen et al 2004*). Pooled data showed that patients using ophthalmic mast-cell stabilizers were 4.9 times more likely to perceive benefit than those using placebo (*Owen et al 2004*).
- A meta-analysis of 4 trials found that patients were 1.3 times more likely to perceive their treatment response as “good” with ophthalmic antihistamines and ophthalmic antihistamines/mast-cell stabilizers compared to patients receiving pure

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ophthalmic mast-cell stabilizers. However, this difference in response failed to reach statistical significance (*Owen et al 2004*).

- Single-acting mast cell stabilizers are now rarely used in the treatment of acute allergic conjunctivitis because of their slow onset of action (ie, 3 to 5 days may be required for symptom abatement). Dual-acting antihistamine/mast cell stabilizers reduce allergic inflammation by preventing mast cell release of inflammatory mediators and by selectively blocking the H_1-receptor, thus countering the effects of histamine that has already been released and enabling a relatively rapid onset of action and an effect on the late-phase response (*Bielory et al 2013*).

CLINICAL GUIDELINES

- According to the AAO, mild allergic conjunctivitis may be treated with an OTC antihistamine/vasoconstrictor or with the more effective second-generation topical histamine H_1 receptor antagonists (*AAO 2018*). Because ophthalmic vasoconstrictors have a short duration of action and may cause rebound hyperemia and conjunctivitis medicamentosa, they should only be used short-term. Ophthalmic mast-cell stabilizers can be utilized if the condition is recurrent or persistent. Newer medications that combine antihistamine activity with mast cell stabilizing properties can be utilized for either acute or chronic disease. If symptoms are not adequately controlled, a brief course of low-potency topical corticosteroids can be added. Additional measures include artificial tears, cool compresses, and allergen avoidance. Oral antihistamines are commonly used as well but may induce or worsen dry eye syndrome, impair the tear film's protective barrier, and worsen allergic conjunctivitis.
- For vernal/atopic conjunctivitis, general treatment measures include minimizing exposure to allergens or irritants and using cool compresses and ocular lubricants. Topical and oral antihistamines and topical mast cell stabilizers can be used to maintain comfort. For acute exacerbations of vernal/atopic conjunctivitis, topical corticosteroids are usually necessary to control severe symptoms (*AAO 2018*).
- The guideline does not recommend one specific ophthalmic antihistamine or mast cell stabilizer over another (*AAO 2018*). There are limited head-to-head trials comparing the agents in these classes to each other. While a few studies reported some differences, the overall clinical significance of these differences is not known since many trials were conducted using single doses of study medication (conjunctival allergen challenge model), in a small number of patients, and/or with comparisons to products that are no longer commercially available.

SAFETY SUMMARY

Ophthalmic Antihistamines

- Contact lens use: patients should not wear a contact lens if the eye is red; 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 touch eyelids or surrounding areas with the dropper tip of the bottle.
- Products are for ophthalmic use only.
- Adverse events are primarily ocular in nature with burning/stinging upon instillation, ocular irritation, ocular pruritus, and redness. Systemic adverse events include mild taste upon instillation, headache, rhinitis, and potential hypersensitivity reactions.
- Due to the topical application of the ophthalmic antihistamines, drug interactions have not been reported.

Ophthalmic Mast Cell Stabilizers

- Contraindications to these products include hypersensitivity to any component of the medications.
- Contact lenses should not be worn during use of these medications.
- Contact of dropper tip to any surface should be avoided to minimize risk of contamination and ocular infection.
- Products are for ophthalmic use only.
- The most common adverse effects of the ophthalmic mast cell stabilizers are ocular burning, stinging and headache. In general, drug interactions are limited due to low systemic bioavailability by the ocular route.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ophthalmic Antihistamines				

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alaway, Zaditor (ketotifen)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily, every 8 to 12 hours, no more than twice per day. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Not studied in pregnancy.
Bepreve (bepotastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy: Unclassified†
Elestat (epinastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop in each eye twice daily. Treatment should be continued throughout the period of exposure (ie, until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy Category C*
Lastacaft (alcaftadine)	Ophthalmic solution	Ophthalmic	Once daily	Instill 1 drop in each eye once daily. If more than 1 topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified†
Optivar (azelastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Pregnancy Category C*
Pataday, Patanol, (olopatadine)	Ophthalmic solution	Ophthalmic	Once or twice daily (varies by product)	Patanol 0.1%: Instill 1 drop into affected eye(s) twice daily at an interval of 6 to 8 hours. Pataday 0.2%, 0.7%: Instill 1 drop into affected eye(s) once daily For children ≥ 2 (0.2%, 0.7%) 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%, 0.7%) of age have not been established. Pregnancy Pataday: Pregnancy Category C* Patanol: Unclassified†
Pataday Once Daily Relief and Pataday Twice Daily Relief (olopatadine)	Ophthalmic solution	Ophthalmic	Once or twice daily (varies by product)	Pataday Twice Daily Relief 0.1%: Instill 1 drop into affected eye(s) twice daily at an interval of 6 to 8 hours, no more than twice per day Pataday Once Daily Relief 0.2%, 0.7%: Instill 1 drop into affected eye(s) once daily, no more than once daily and for the 0.7% formulation, no more than 1 drop in each eye For aged ≥ 2 years, use adult dosage for either OTC Pataday product. Not studied in pregnancy.
Zerviate (cetirizine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy: Unclassified†
Ophthalmic Mast Cell Stabilizers				
Alocril (nedocromil)	Ophthalmic Solution	Ophthalmic	Twice daily	Instill 1 or 2 drops into each affected eye(s) twice daily. Use at regular intervals. Treatment should be continued throughout the period of exposure, even when symptoms are absent. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established Pregnancy: Unclassified†
Alomide (lodoxamide)	Ophthalmic solution	Ophthalmic	4 times a day for up to 3 months	Instill 1 to 2 drops into each affected eye(s) four times daily for up to 3 months. For children > 2 years of age, refer to adult dose; safety and effectiveness in children ≤ 2 years of age have not been established. Pregnancy: Unclassified†
cromolyn sodium	Ophthalmic solution	Ophthalmic	4 to 6 times daily	Instill 1 or 2 drops into each affected eye(s) 4 to 6 times daily at regular intervals. Symptomatic response is usually evident within a few days, but up to 6 weeks may be required; therapy should be continued if needed to sustain improvement. For children ≥ 4 years of age, refer to adult dose; safety and effectiveness in children < 4

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				years of age have not been established. Pregnancy Category B*.

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

See the current prescribing information for full details.

CONCLUSION

- The most common form of ocular allergy is allergic conjunctivitis (*Bielory et al 2012, Hamrah and Dana 2020a*). Ophthalmic mast cell stabilizers and antihistamines are FDA-approved for the management of signs and symptoms associated with allergic conjunctivitis. The ophthalmic mast cell stabilizers cromolyn and lodoxamide are the only agents in this class that are FDA-approved for the treatment of vernal conjunctivitis.
- Few distinguishing characteristics exist among the available ophthalmic antihistamines, but alcaftadine and olopatadine 0.2% and 0.7% may be administered once daily, while the remaining ophthalmic antihistamines are administered 2 to 4 times daily. Currently, ophthalmic formulations of azelastine, epinastine, ketotifen, and olopatadine are available generically. Ophthalmic formulations of ketotifen and olopatadine are also available in OTC formulations. Due to the ophthalmic administration of these agents, relatively few adverse effects have been reported; the most common adverse reactions are ocular burning and stinging and headache.
- Regarding the ophthalmic mast cell stabilizers, all are approved for use in children (> 2 to 4 years of age depending on the product). The most common adverse effects of these agents are ocular burning, stinging, and headache. The administration schedule of these ophthalmic products ranges from twice daily to 6 times daily. Ophthalmic cromolyn is the only mast cell stabilizer currently available as a generic formulation.
- The AAO conjunctivitis guideline does not recommend one specific ophthalmic antihistamine or mast cell stabilizer over another (*AAO 2018*). There are limited head-to-head trials comparing the agents in these classes to each other. While a few studies reported some differences, the overall clinical significance of these differences is not known since many trials were conducted using single doses of study medication (conjunctival allergen challenge model), in a small number of patients, and/or with comparisons to products that are no longer commercially available.

REFERENCES

- Alaway [package insert]. Bridgewater, NJ: Bausch & Lomb, Inc.; January 2020.
- Alocril [package insert], Madison, NJ: Allergan USA, Inc.; June 2018.
- Alomide [package insert], Fort Worth, TX: Alcon Laboratories; August 2020.
- American Academy of Ophthalmology. Conjunctivitis Preferred Practice Pattern [guideline on the internet]. 2018. https://www.aao.org/preferred-practice-pattern/conjunctivitis-ppp-2018. Accessed February 12, 2021.
- Avunduk AM, Avunduk MC, Kapicioglu Z, et al. Mechanisms and comparison of anti-allergic efficacy of topical lodoxamide and cromolyn sodium treatment in vernal keratoconjunctivitis. *Ophthalmology*. 2000;107(7):1333-1337.
- Avunduk AM, Tekelioglu Y, Turk A, Akyol N. Comparison of the effects of ketotifen fumarate 0.025% and olopatadine HCl 0.1% ophthalmic solutions in seasonal allergic conjunctivitis: a 30-day, randomized, double-masked, artificial tear substitute-controlled trial. *Clin Ther*. 2005;27(9):1392-1402.
- Ayyappanavar S, Sridhar S, Kumar K, et al. Comparative analysis of safety and efficacy of alcaftadine 0.25%, olopatadine hydrochloride 0.2%, and bepotastine besilate 1.5% in allergic conjunctivitis. *Indian J Ophthalmol*. 2021;69(2):257-261. doi: 10.4103/ijo.IJO_2083_20.
- Azelastine solution/drops [package insert]. Apotex Corp. Weston, FL; July 2019.
- Bepreve [package insert]. Bridgewater, NJ: Bausch & Lomb, Inc.; September 2019.
- Berdy GJ, Spangler DL, Bensch G, et al. A comparison of the relative efficacy and clinical performance of olopatadine hydrochloride 0.1% ophthalmic solution and ketotifen fumarate 0.025% ophthalmic solution in the conjunctival antigen challenge model. *Clin Ther*. 2000;22(7):826-33.
- Bielory BP, O'Brien TP, Bielory L. Management of seasonal allergic conjunctivitis: guide to therapy. *Acta Ophthalmologica*. 2012;90:399-407.
- Bielory L, Delgado L, Katelaris CH, Leondardi A, Rosario N, Vichyanoud P. ICON: diagnosis and management of allergic conjunctivitis. *Ann Allergy Asthma Immunol*. 2020;124(2):118-134. doi: 10.1016/j.anai.2019.11.014.
- Bielory L, Meltzer EO, Nichols KK, et al. An algorithm for the management of allergic conjunctivitis. *Allergy Asthma Proc*. 2013;34:408-420.

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- Borazan M, Karalezli A, Akova YA, et al. Efficacy of olopatadine HCl 0.1%, ketotifen fumarate 0.025%, epinastine HCl 0.05%, emedastine 0.05% and fluorometholone acetate 0.1% ophthalmic solutions for seasonal allergic conjunctivitis: a placebo-controlled environmental trial. *Acta Ophthalmol.* 2009;87(5):549-554.
- Caldwell DR, Verin P, Hartwich-Young R, et al. Efficacy and safety of lodoxamide 0.1% vs cromolyn sodium 4% in patients with vernal keratoconjunctivitis. *Am J Ophthalmol*. 1992;113(6):632-637.
- Castillo M, Scott NW, Mustafa MZ, et al. Topical antihistamines and mast cell stabilizers for treating seasonal and perennial allergic conjunctivitis (Review). *Cochrane Database Syst Rev*. 2015 (6): CD009566.
- Cromolyn sodium ophthalmic solution [package insert], Lake Forest, IL: Akorn, Inc.; June 2016.
- Drugs@FDA [database on the Internet]. Rockville, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2021. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed February 9, 2021.
- Elestat [package insert]. Allergan. Irvine, CA. December 2011.
- Facts & Comparisons eAnswers [database online]. St. Louis, MO: Wolters Kluwer Heath, Inc.; 2021. https://online.factsandcomparisons.com. Accessed February 9, 2021.
- FDA drug shortages [database on the Internet]. Rockville, MD: Food and Drug Administration (US); 2021. https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Emedastine+Difumarate+%28Emadine%29+0.05per+Ophthalmic+Solution&st=d&tab=tabs-2. Accessed February 12, 2021.
- Foster CS. Evaluation of topical cromolyn sodium in the treatment of vernal keratoconjunctivitis. *Ophthalmology*. 1988;95(2):194-201.
- Ganz M, Koll E, Gausche J, et al. Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. *Adv Ther*. 2003;20(2):79-91.
- Hamrah P, Dana R. Allergic conjunctivitis: clinical manifestations and diagnosis. UpToDate Web site. www.uptodate.com. Updated May 15, 2020a. Accessed February 12, 2021.
- Hamrah P, Dana R. Allergic conjunctivitis: management. UpToDate Web site. www.uptodate.com. Updated May 15, 2020b. Accessed February 12, 2021.
- James IG, Campbell LM, Harrison JM, et al. Comparison of the efficacy and tolerability of topically administered azelastine, sodium cromoglycate and placebo in the treatment of seasonal allergic conjunctivitis and rhinoconjunctivitis. *Curr Med Res Opin*. 2003;19(4):313-320.
- Kjellman NI, Stevens MT. Clinical experience with Tilavist: an overview of efficacy and safety. *Allergy*. 1995;50(21 Suppl):14-22;discussion 34-38.
- Lastacaft [package insert]. Madison, NJ: Allergan; June 2020.
- Leino M, Ennevaara K, Latvala AL, et al. Double-blind group comparative study of 2% nedocromil sodium eye drops with 2% sodium cromoglycate and placebo eye drops in the treatment of seasonal allergic conjunctivitis. *Clin Exp Allergy*. 1992;22(10):929-932.
- Leonardi A, Borghesan F, Avarello A, et al. Effect of lodoxamide and disodium cromoglycate on tear eosinophil cationic protein in vernal keratoconjunctivitis. *Br J Ophthalmol*. 1997;81(1):23-26.
- Leonardi A, Zafirakis P. Efficacy and comfort of olopatadine vs ketotifen ophthalmic solutions: a double-masked, environmental study of patient preference. *Curr Med Res Opin*. 2004;20(8):1167-1173.
- Malhotra RP, Meier E, Torkildsen G, Gomes PJ, Jasek MC. Safety of cetirizine ophthalmic solution 0.24% for the treatment of allergic conjunctivitis in adult and pediatric subjects. *Clin Ophthalmol*. 2019;13:403-413. doi: 10.2147/OPTH.S186092.
- Meier EJ, Torkildsen GL, Gomes PJ, Jasek MC. Phase III trials examining the efficacy of cetirizine ophthalmic solution 0.24% compared to vehicle for the treatment of allergic conjunctivitis in the conjunctival allergen challenge model. *Clin Ophthlamol*. 2018;12:2617-2628.
- Micromedex 2.0 [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; 2021. http://www.micromedexsolutions.com/home/dispatch. Accessed February 9, 2021.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2021. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 9, 2021
- Orfeo V, Vardaro A, Lena P, et al. Comparison of emedastine 0.05% or nedocromil sodium 2% eye drops and placebo in controlling local reactions in subjects with allergic conjunctivitis. *Eur J Ophthalmol*. 2002;12(4):262-266.
- Owen CG, Shah A, Henshaw K, et al. Topical treatments for seasonal allergic conjunctivitis: systematic review and meta-analysis of efficacy and effectiveness. *Br J Gen Pract*. 2004;54:451-456.
- Pataday [package insert]. Fort Worth, TX: Alcon Labs; December 2010.
- Pataday Once Daily Relief [drug facts]. Fort Worth, TX: Alcon Labs; February 2020.
- Pataday Twice Daily Relief [drug facts]. Fort Worth, TX: Alcon Labs; February 2020.
- Patanol [package insert]. Fort Worth, TX: Alcon Labs; April 2018.
- Zaditor [package insert]. Fort Worth, TX: Alcon Labs; October 2020.
- Zerviate [package insert]. Fort Worth, TX: Eyevance Pharmaceuticals, LLC; June 2020.

Publication Date: March 30, 2021

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