OPTUMRx

Therapeutic Class Overview
Ophthalmic Antihistamines

INTRODUCTION

- The ophthalmic antihistamines are Food and Drug Administration (FDA)-approved for the management of the signs and symptoms associated with allergic conjunctivitis and include Lastacaft (alcaftadine); Optivar (azelastine); Bepreve (bepotastine); Zerviate (cetirizine); Emadine (emedastine); Elestat (epinastine); the ketotifen-containing products (eg, Alaway and Zaditor); and the olopatadine-containing products Pataday, Patanol, and Pazeo *(Micromedex 2.0 2018)*.
- All products are available by prescription with the exception of ketotifen, which is available over-the-counter (OTC). Ketotifen is approved for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander.
- 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] 2013)*.
- Types of allergic conjunctivitis include atopic keratoconjunctivitis, simple allergic conjunctivitis, 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 *(American Optometric Association [AOA] 2007)*. None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis.
- 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 *(AOA 2007)*.
- Most of these agents have been shown to have both histamine type 1 (H_1-antihistamine) and mast cell stabilizing properties *(AAO 2013, Hamrah et al 2017)*. The ophthalmic antihistamines reduce itching and redness through competitive binding with histamine receptor sites and by inhibiting the degranulation of mast cells, thus limiting the release of inflammatory mediators associated with the development of allergy symptoms *(Micromedex 2.0 2018)*.
- The ophthalmic antihistamines with mast cell-stabilizing properties are the agents of choice in treating seasonal and perennial allergic conjunctivitis as they address both the acute and chronic aspects of these conditions *(Hamrah et al 2017)*. While the onset of action is within minutes for most of these agents, patients with seasonal allergies may benefit from early therapy initiation (ie, at least 2 weeks before expected symptom onset) since control of inflammation and symptom resolution often takes some time *(Hamrah et al 2017)*.
- Medispan Therapeutic Class: Ophthalmics - Miscellaneous

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alaway† (ketotifen), Zaditor† (ketotifen)	✔
Bepreve (bepotastine besilate ophthalmic solution) 1.5%	-
Elestat (epinastine HCl ophthalmic solution) 0.05%	✔
Emadine (emedastine difumarate ophthalmic solution) 0.05%	-
Lastacaft (alcaftadine ophthalmic solution) 0.25%	-
Optivar (azelastine HCl ophthalmic solution, 0.05%)	✔
Pataday (olopatadine HCl ophthalmic solution) 0.2%, Patanol (olopatadine HCl ophthalmic solution) 0.1%, Pazeo (olopatadine HCl ophthalmic solution) 0.7%	✔ ✔ -
Zerviate (cetirizine ophthalmic solution) 0.24%‡	-

Key: HCl = hydrochloride
† Products contain ketotifen 0.025% (equivalent to ketotifen fumarate 0.035%) and are available over-the-counter.
‡ Zerviate contains cetirizine 0.24% (equivalent to cetirizine hydrochloride 0.29%) and was approved in May 2017; however, the product has not yet launched.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	**Alaway, Zaditor** (ketotifen)	**Bepreve** (bepotastine)	**Elestat** (epinastine)	**Emadine** (emedastine)	**Lastacaft** (alcaftadine)	**Optivar** (azelastine)	**Pataday, Patanol, Pazeo** (olopatadine)	**Zerviate** (cetirizine)
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 the signs and symptoms of allergic conjunctivitis				✔				
Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander	✔							

* 0.2% and 0.7% strengths
† 0.1% strength

(Prescribing information: Alaway 2015, Bepreve 2018, Elestat 2011, Emadine 2009, Lastacaft 2015, Optivar 2008, Pataday 2010, Patanol 2007, Pazeo 2017, Zaditor 2015, Zerviate 2017)

- 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

- 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. Clinical data supporting the FDA approval of cetirizine

ophthalmic solution were from 3 unpublished, placebo-controlled trials that showed improvement in ocular itching with cetirizine *(Nicox 2017)*.

- 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 agents in this class 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 short-term. Data for the long-term use of topical antihistamines are lacking *(Castillo et al 2015)*.

CLINICAL GUIDELINES

- According to the AAO, mild allergic conjunctivitis may be treated with an OTC ophthalmic antihistamine/vasoconstrictor or a prescription ophthalmic antihistamine. 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. The use of ophthalmic vasoconstrictors should be limited due to their short duration of action and potential to cause rebound hyperemia and conjunctivitis medicamentosa. Ophthalmic mast cell stabilizers may be used if the condition is recurrent or persistent *(AAO 2013)*.

SAFETY SUMMARY

- 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 topical 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.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alaway, Zaditor (ketotifen)	Both: Ophthalmic solutions	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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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*
Emadine (emedastine)	Ophthalmic solution	Ophthalmic	Up to 4 times daily	Instill 1 drop into affected eye(s) up to 4 times 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 B*
Lastacaft (alcaftadine)	Ophthalmic solution	Ophthalmic	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. Pregnancy Category B*
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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				years of age have not been established. Pregnancy Category C*
Pataday, Patanol, Pazeo (olopatadine)	All: Ophthalmic solutions	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%, Pazeo 0.7%: Instill 1 drop in 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, Patanol: Pregnancy Category C* Pazeo: Unclassified†
Zerviate (cetirizine)	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†

†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 ophthalmic antihistamines are FDA-approved for the management of the signs and symptoms associated with allergic conjunctivitis, the most common form of ocular allergy.
- 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 agents in this class are administered 2 to 4 times daily. In addition, ophthalmic alcaftadine and ophthalmic emedastine are classified as pregnancy category B; other agents in this class are pregnancy category C or were not studied in pregnant patients *(Micromedex 2.0 2018)*. Currently, ophthalmic formulations of azelastine, epinastine, ketotifen, and olopatadine are available generically. Ophthalmic formulations of ketotifen are also available generically in OTC formulations. Due to the ophthalmic

administration of these agents, relatively few adverse reactions have been reported; the most common adverse reactions are ocular burning and stinging and headache.

- 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. 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. 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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Publication Date: March 15, 2018