

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), EMADINE® (emedastine), ELESTAT® (epinastine), ALAWAY®, ZADITOR® (ketotifen) and PATADAY™, PATANOL®, PAZEO® (olopatadine) (Micromedex, 2017).
- All products are available by prescription only except for ketotifen, which is available as an over-the-counter (OTC) product. 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 (H₁-antihistamine) and mast cell stabilizing properties (AAO, 2013). 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 mediators associated with the development of allergy symptoms (Micromedex, 2017).
- Medispan Therapeutic Class: Ophthalmics - Miscellaneous

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ALAWAY*, ZADITOR* (ketotifen)	various	12/01/2006 07/02/1999	✓
BEPREVE (bepotastine)	Bausch & Lomb	09/08/2009	-
ELESTAT (epinastine)	various	10/16/2003	✓
EMADINE (emedastine)	Alcon	12/29/1997	-
LASTACAFT (alcaftadine)	Allergan	07/28/2010	-
OPTIVAR (azelastine)	various	05/22/2000	✓
PATADAY, PATANOL, PAZEO (olopatadine)	various, Alcon (PAZEO)	12/22/2004 12/18/1996 01/30/2015	✓ ✓ -

* Over-the-counter product

(DRUGS@FDA, 2017, Orange Book, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ALAWAY, ZADITOR (ketotifen)	BEPREVE (bepotastine)	ELESTAT (epinastine)	EMADINE (emedastine)	LASTACRAFT (alcaftadine)	OPTIVAR (azelastine)	PATADAY, PATANOL, PAZEO (olopatadine)
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, 2016; ELESTAT, 2011; EMADINE, 2009; LASTACRAFT, 2015; OPTIVAR, 2009; PATADAY, 2010; PATANOL, 2007; PAZEO 2015; ZADITOR, 2015)

Information on indications, mechanism of action, pharmacokinetics, and safety information 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 most 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 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. The data and study results lack for long-term use of topical antihistamines (Castillo et al, 2015).

- 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; AAO, 2016).

SAFETY SUMMARY

- 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 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	Dosage Form: Strength	Usual Recommended Dose
ALAWAY, ZADITOR (ketotifen)	Ophthalmic solution: 0.025% (OTC) (5, 10 mL)	<u>Allergic conjunctivitis, ocular itching:</u> Ophthalmic solution: instill one drop into affected eye(s) twice daily, every eight to 12 hours, no more than twice per day
BEPREVE (bepotastine)	Ophthalmic solution: 1.5% (5, 10 mL)	<u>Allergic conjunctivitis:</u> Ophthalmic solution: instill one drop into affected eye(s) twice daily
ELESTAT (epinastine)	Ophthalmic solution: 0.05% (5 mL)	<u>Allergic conjunctivitis:</u> Ophthalmic solution: instill one drop into affected eye(s) twice daily
EMADINE (emedastine)	Ophthalmic solution: 0.05% (5 mL)	<u>Allergic conjunctivitis:</u> Ophthalmic solution: instill one drop into affected eye(s) up to four times daily
LASTACAFT (alcaftadine)	Ophthalmic solution: 0.25% (3 mL)	<u>Allergic conjunctivitis:</u> Ophthalmic solution: instill one drop into affected eye(s) once daily
OPTIVAR (azelastine)	Ophthalmic solution: 0.05% (6 mL)	<u>Allergic conjunctivitis:</u> Ophthalmic solution: instill one drop into affected eye(s) twice daily
PATADAY, PATANOL, PAZEO (olopatadine)	Ophthalmic solution: 0.2% (2.5 mL) 0.1% (5 mL) 0.7% (2.5 ml)	<u>Allergic conjunctivitis:</u> PATANOL 0.1% ophthalmic solution: instill one drop into affected eye(s) twice daily at an interval of six to eight hours PATADAY 0.2%, PAZEO 0.7% ophthalmic solution: instill one drop in affected eye(s) once daily

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ALAWAY, ZADITOR (ketotifen) ophthalmic	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	<u>Allergic conjunctivitis, ocular itching</u> : Children \geq 3 years of age, refer to adult dose. Safety and effectiveness in children < 3 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	Not studied in pregnant patients Unknown whether excreted in breast milk; use with caution.
BEPREVE (bepotastine) ophthalmic	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	<u>Allergic conjunctivitis</u> : Children \geq 2 years of age, refer to adult dose. Safety and effectiveness in children < 2 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
ELESTAT (epinastine) ophthalmic	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	<u>Allergic conjunctivitis</u> : Children \geq 2 years of age, refer to adult dose. Safety and effectiveness in children < 2 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
EMADINE (emedastine) ophthalmic	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	<u>Allergic conjunctivitis</u> : Children \geq 3 years of age, refer to adult dose. Safety and effectiveness in children < 3 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	Pregnancy Category B* Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
LASTACFT (alcaftadine) ophthalmic	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	<u>Allergic conjunctivitis:</u> Children ≥ 2 years of age, refer to adult dose. Safety and effectiveness in children < 2 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	Pregnancy Category B* Unknown whether excreted in breast milk; use with caution.
OPTIVAR (azelastine) ophthalmic	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	<u>Allergic conjunctivitis:</u> Children ≥ 3 years of age, refer to adult dose. Safety and effectiveness in children < 3 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
PATADAY, PATANOL, PAZEO (olopatadine) ophthalmic	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	<u>Allergic conjunctivitis:</u> 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.	No dosage adjustment is required.	No dosage adjustment is required.	Pregnancy Category C* PAZEO was not studied in pregnant women; use recommended only if a potential benefit outweighs a potential harm. Unknown whether excreted in breast milk; use with caution.

*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.

(Micromedex® 2.0, 2017, Clinical Pharmacology, 2017)

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 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 or were not studied in pregnant patients (Micromedex® 2.0, 2017). 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 being 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.

Table 5. Advantages and Disadvantages of Ophthalmic Antihistamines

Drug	Advantages	Disadvantages
LASTACAFT (alcaftadine)	Once daily dosing Pregnancy category B	Branded product
OPTIVAR (azelastine)	Generic	-
BEPREVE (bepotastine)	-	Branded product
ELESTAT (epinastine)	Generic	-
EMADINE (emedastine)	Pregnancy category B	Dosing up to four times daily Branded product
ALAWAY, ZADITOR (ketotifen)	Available as OTC products	-
PATADAY, PATANOL, PAZEO (olopatadine)	Once daily dosing (0.2%, 0.7%)	Branded product for PAZEO

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