Ophthalmic-1s: Antihistamine and Dual Acting Antihistamine/Mast Cell Stabilizers

DHA Formulary Management Branch

Executive Summary

- **For the MTF Formulary Management Document with the formulary recommendation from the May 2017 P&T Committee meeting, see http://www.health.mil/DoDPTResources.**
- The ophthalmic Antihistamine and Dual Acting Antihistamine/Mast Cell Stabilizers (AH/MCS) are indicated for the treatment and prevention of ocular itching associated with allergic conjunctivitis (AC).
- Allergic conjunctivitis treatment guidelines recommend treatment with dual acting AH/MCS, and do not prefer one agent over another.
- New data since the previous DoD P&T Committee drug class review in 2010 does not change the conclusion that there is insufficient evidence to suggest clinically relevant differences in efficacy between the AH/MCS agents.
- A 2015 Cochrane review and a 2016 meta-analysis conclude there is insufficient evidence to discern which AH/MCS agent is more effective than another. Olopatadine may be more effective than ketotifen, but less effective than alcaftadine; however, these differences between products are of questionable clinical relevance.
- Three olopatadine products are marketed. Generic olopatadine 0.1% BID (Patanol) formulations are available. In terms of efficacy and safety, olopatadine 0.1% BID is comparable to olopatadine 0.2% QD (Pataday). The newest product, olopatadine 0.7% QD (Pazeo) is purported to have less ocular itching when compared to Pataday. Although the results were statistically significant 24 hours after administration, when the next dose is due, the clinical relevance of this result is questionable.

Background

- The antihistamine and dual acting AH/MCS are a subclass of the Ophthalmic-1 Drug Class. See Table 1 for drugs in the subclass.

Table 1. Ophthalmic-1s: Antihistamine and Dual Acting Antihistamine/Mast Cell Stabilizers Drugs in the Subclass

Subclass	Generic Name	Brand	Manufacturer	Generic as of April 2017	Strength	FDA Approval	Patent Expiration
Antihistamine	Emedastine	Emadine	Alcon	No	0.05%	1997	2013
Dual Acting Antihistamine / Mast Cell Stabilizer	Alcaftadine	Lastacaft	Allergan	No	0.25%	2010	2015
	Azelastine	Optivar	-	Yes	0.05%	2000	-
	Bepotastine	Bepreve	Bausch + Lomb	No	1.5%	2009	2014
	Epinastine	Elestat	-	Yes	0.05%	2003	-
	Ketotifen*	Zaditor, Alaway	-	Yes (OTC)	0.025%	1999	-
	Olopatadine	Patanol	-	Yes	0.1%	1996	-
		Pataday	Alcon	No	0.2%	2004	2017
		Pazeo	Alcon	No	0.7%	2015	2032

*Ketotifen is OTC and not part of the TRICARE Pharmacy benefit; the formulary recommendation does not apply.

- The full Ophthalmic-1 Drug Class was reviewed in August 2010 by the DoD P&T Committee. The Basic Core Formulary (BCF) choice is olopatadine 0.1% (Patanol, generics). Ketotifen (Zaditor) is now available over-the-counter (OTC); it is not part of the formulary recommendation. See Table 2 for the formulary status of the ophthalmic dual acting AH/MCS agents recommended at the May 2017 DoD P&T Committee meeting.
- Several generic formulations of olopatadine 0.1% BID (Patanol) are commercially available. Generic formulations of olopatadine 0.2% QD (Pataday) are expected in the second quarter of 2017; however, only one company has a generic tentatively approved by the FDA.
- Current Military Health System (MHS) prescription data show that Patanol, generic Patanol, and Pataday account for over 80% of the utilization in the class.

Table 2. Formulary Status Recommended at the May 2017 DoD P&T Committee Meeting

Basic Core Formulary (BCF)	Uniform Formulary (UF)	Nonformulary (NF)
• olopatadine 0.1% (Patanol generic)	• azelastine (Optivar generic) • epinastine (Elestat generic) • **olopatadine 0.7% (Pazeo)**	• alcaftadine 0.25% (Lastacaft) • bepotastine 1.5% (Bepreve) • emedastine 0.05% (Emadine) • **olopatadine 0.2% (Pataday)**

Epidemiology of Allergic Conjunctivitis

- Seasonal and perennial allergic conjunctivitis are non-infectious types of conjunctivitis and are among the most common ophthalmic problems. Within the United States, the incidence of ocular allergies is estimated at 15-25% of the population with some data suggesting the incidence is as high as 40% (Abelson, Shetty, et al. 2015).
- Pathophysiology includes activation of mast cells, release of histamine, and activation of inflammatory pathways by the antigen in the eye which causes the primary symptom of ocular itching (Abelson, Shetty, et al. 2015).
- Allergic conjunctivitis is a highly seasonal condition, and MHS utilization of the AH/MCS agents reflects this variability.

AH/MCS Mechanism of Action

- Dual acting agents are both histamine H1 antagonists and mast cell stabilizers (Hamrah and Dana. 2017).
- Antihistamines competitively and reversibly block histamine receptors in the conjunctiva and eyelids, thus inhibiting the action of the primary mast cell-derived mediator. This also helps reduce the late phase of the allergic response (Hamrah and Dana. 2017).
- Mast cell stabilizers inhibit mast cell degranulation, limiting the release of histamine, tryptase, and prostaglandin D2. Release of these pro-inflammatory mast cell mediators is the first step in the allergic cascade. These drugs also inhibit leukocyte activity and dampen mediator release from basophils, eosinophils, and neutrophils (Hamrah and Dana. 2017).

Clinical Practice Guidelines

- American Optometric Association (Quinn, Mathews, et al. 2002)
  - Allergic conjunctivitis is effectively treated with dual acting medications
  - Olopatadine may be more effective than other mast cell stabilizer agents
  - Olopatadine is more effective than ketotifen in relieving itchiness and redness
- American Academy of Ophthalmology (Ophthalmology 2013)
  - Mild allergic conjunctivitis can be treated with OTC products (ketotifen or vasoconstrictor agents) or with the more effective legend AH/MCS agents
  - AH/MCS can be utilized for either acute or chronic allergic conjunctivitis
  - No specific agent recommended over others

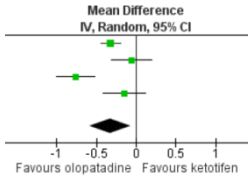
Efficacy Endpoints

- The main measure of ocular allergy symptoms is itching, although hyperemia, chemosis, and lid swelling have also been measured as secondary outcomes.
- The Conjunctival Allergan Challenge (CAC) model uses titrated quantities of allergen to induce the signs and symptoms of allergic conjunctivitis in a standardized, precise, and reproducible manner. Pre-determined concentrations of allergen are used to elicit an allergic response, eliminating much of the variability associated with environmental models. The method allows for evaluation of safety, comfort, and efficacy using standardized symptom grading scales (Abelson, Shetty, et al. 2015). The treated eye is compared to the contralateral untreated eye as an internal control.
- Grading is as follows:
  - Patient-assessed symptoms at specific time intervals
  - Investigator-assessed conjunctival hyperemia at specific time intervals
  - A 5-unit (9 step) grading scale with ½ unit increments is used to score symptoms (0 = none to 4 = severe)
  - Redness is scored with a 4-unit scale allowing ½ unit increments
- Clinical significance in the CAC test is defined as ≥ 1.0-U between-group difference in mean ocular symptom or observation score at the majority of time points at a study visit.

Efficacy

- Since the last DoD P&T Committee review, two meta-analyses are available. A Cochrane review evaluated the topical ophthalmic agents for allergic conjunctivitis (Castillo, Scott, et al. 2015) and a meta-analysis evaluated olopatadine in comparison with other AH/MCS (Kam, Chen, et al. 2016).
- **Cochrane Review:** The 2015 Cochrane review compared 30 randomized, controlled randomized trials (RCTs) enrolling over 4,300 patients. Both placebo-controlled and head-to-head studies were included. The main efficacy endpoints were ocular itching, irritation, watering eye, and photophobia. The authors concluded that there was insufficient evidence to discern which topical ophthalmic agents were most effective. Azelastine, bepotastine, and ketotifen all showed superiority to placebo, with the differences from placebo considered clinically relevant. Bepotastine compared with olopatadine 0.2% did not have sufficient evidence to compare efficacy. Olopatadine 0.1% studied against ketotifen favored olopatadine statistically, but did not meet the one unit meaningful clinically important difference (MCID) (Castillo, Scott, et al. 2015). See Table 3 for additional information from the Cochrane review.
- **2016 Systematic Review and Meta-Analysis**: Another publication evaluated 23 RCTs enrolling 1,700 patients and included studies with olopatadine (0.1% and 0.2%), epinastine, ketotifen, alcaftadine, and placebo. The authors concluded that olopatadine (both strengths) were superior to placebo, based on the primary endpoint of ocular itch based on the CAC. The differences between olopatadine versus epinastine and ketotifen were not statistically significant. Alcaftadine showed statistical significance in reducing ocular itching when compared to olopatadine, but the difference (0.39 units) did not meet the MCID of 1 unit change (Kam, Chen, et al. 2016).
- **Patanol versus Pataday**: A head-to-head study compared olopatadine 0.1% BID with olopatadine 0.2% QD. The study design was a 24-hour CAC challenge in 23 patients evaluating prevention of ocular itching associated with allergic conjunctivitis. The results of both products were statistically significant at 24 hours in reducing ocular itching compared to placebo. The difference from placebo for both products was also clinically relevant, in that there was a 1 unit difference over placebo (Abelson, Shetty, et al. 2015).

Table 3. 2015 Cochrane Review Summary

Medications	Design	n	Outcomes	Conclusion
azelastine vs. placebo	9 studies	1404	Itch, irritation, watering eyes and photophobia	Only one study showed statistically significant improvement for itching. Other endpoints did not reach statistical significance
bepotastine vs. olopatadine 0.2% bepotastine vs. placebo	1 crossover 1 randomized	30 245	Itch 5-point Likert scale: Bep 2.30; Olo 2.15 (p<0.0001) Reflective Itching Improvement: Bep 28.0%; Pbo 21.101%	Insufficient evidence to compare efficacies Evidence in itching improvement
ketotifen (Ket) vs. placebo (Pbo)	1 study	33	Itching: Ket mean 1.08, SD 0.2; Pbo mean 0.17, SD 0.1 (p<0.05) Watering eyes: Ket mean 0.17, SD 0.1; Pbo 1.07, SD 0.2 (p<0.05)	Ketotifen more effective than placebo
olopatadine 0.1% vs. ketotifen	4 studies	182	Itch (day 14): MD -0.32 (-0.59, -0.06) 	Olopatadine may be more effective than ketotifen in improving itching

MD: Mean Difference; SD: Standard Deviation

- **Pazeo**: Two CAC studies were conducted with olopatadine 0.7% to gain FDA approval. The FDA Medical Review of olopatadine 0.7% included studies comparing olopatadine 0.7% with both olopatadine 0.1% and 0.2%. Table 4 summarizes the results. The studies evaluated ocular itching and redness over 24 hours. In both studies, Pazeo was statistically and clinically superior ($p<0.0001$) to vehicle for treating ocular itching associated with allergic conjunctivitis (AC) at onset of acting, and 24-hour duration-of action. Pazeo produced statistically superior results compared to Pataday with ocular itching and redness; however, the results were not clinically significant. The manufacturer of olopatadine 0.7% (Pazeo) is marketing the product as providing 24 hours of eye allergy itch relief. However, the clinical relevance of these results is questionable, as the reduced ocular itching was noted at the end of the 24-hour study period, when the next dose is due. Redness was also evaluated and all three olopatadine strengths were superior to vehicle, with 0.7% was producing statistically significant reductions in redness up to 24 hours (FDA Review Document. 2014).

Table 4. Pazeo FDA Efficacy Review

	Ocular Itching		**Conjunctival Redness**	
Study	0.7% vs vehicle	0.7% vs 0.2%	0.7% vs vehicle	0.7% vs 0.2%
Torkildsen, et al. 0.7% (N=66) vs 0.2% (N=68) vs vehicle (N=68)	olopatadine 0.7% superior compared to vehicle ($p<0.001$) at onset, at 16- and 24-hour duration of action ($p<0.001$ for all)	olopatadine 0.7% superior to 0.2% at 24 hours after dosing MD -0.48 (-0.76,to -0.20) $p<0.05$	olopatadine 0.7% superior ($p<0.01$) vs vehicle at 16- and 24-hr assessments	olopatadine 0.7% superior to 0.2% at treating redness at 24 hours after dosing ($p<0.05$)
McLaurin, et al. 0.7% QD (N=98) vs 0.2% QD (N=99) vs 0.1% QD (N=99) vs vehicle (N=49)	olopatadine 0.7% superior vs vehicle ($p<0.0001$) at onset, and at 24-hour duration of action ($p<0.001$ for all)	olopatadine 0.7% superior to 0.2% at 24 hours after dosing at 2 out of 3 endpoints. MD -0.31 (-0.57, -0.06) $p<0.05$ Also superior to 0.1% QD at all time points ($p<0.05$)	olopatadine 0.7% was superior vs vehicle ($p<0.05$) at all three post-CAC time points	olopatadine 0.7% superior to 0.2% and 0.1% at onset ($p<0.05$), but not stat sig at 24-hr duration

Safety

- The previous P&T Committee review in 2010 concluded there was insufficient evidence to suggest clinically relevant differences in safety between the AH/MCS agents. Overall the incidence of adverse events is low with these products, and primarily includes blurred vision, dry eye, and dysgeusia.
- A comparison of the adverse events listed in the package inserts is notable for the following: the incidence of taste pervasion with bepotastine (25%) and the incidence of headache with emedastine (11%), compared to the other AC/MCS. All other adverse reactions (e.g., ocular burning, dry eye, redness, and blurred visions) occurred at an incidence of 10% or lower. All of the products are rated a pregnancy category C, with the exception of alcaftadine and emedastine which are rated as pregnancy category "B".
- Pediatric use is generally safe for those 2 years and older with all the products, with the exception that emedastine and olopatadine 0.1% are recommended in patients 3 years and older.
- For all the products, contact lenses should be avoided if there is hyperemia and contacts should only be inserted after waiting 10 minutes post medication administration.

Other Factors

- All of these agents contain benzalkonium chloride as the preservative and add to the incidence of side effects.
- The pH and recommended storage requirements are relatively similar for all the products.

Conclusion

- There was no new evidence to change the previous conclusions from the August 2010 DoD P&T Committee meeting which determined that there was insufficient evidence to suggest clinically relevant differences in efficacy between the AH/MCSs.
- The newest olopatadine 0.7% QD formulation (Pazeo) was statistically superior to olopatadine 0.2% QD (Patanol) in reducing itchiness and redness, but this change did not translate into a meaningful clinical difference.
- Overall, for relief of ocular itching due to AC, there do not appear to be clinically relevant differences in efficacy or safety between olopatadine 0.7% (Pazeo) and the other dual acting AH/MCS agents.

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Abbreviations

The following abbreviations are used in this review:

AC	allergic conjunctivitis
AH	antihistamine
AH/MCS	antihistamine/mast cell stabilizer
CAC	Conjunctival Allergan Challenge
MCID	meaningful clinically important difference
RCT	randomized controlled trial