EXECUTIVE SUMMARY

- Antihistamine ophthalmic drops provide quick relief from allergic conjunctivitis (AC) symptoms such as itching and redness, without the potential adverse effects associated with systemic absorption.
- Epinastine is the fourth ophthalmic antihistamines/mast cell stabilizer approved for the itching associated with AC. Other ophthalmic preparations for allergic conjunctivitis include antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory agents (NSAIDs), corticosteroids, decongestants, and decongestant/antihistamines.
- An ideal agent would offer improved efficacy and safety, reduce polypharmacy as a combination product or through replacing oral agents, and provide evidence for chronic AC prevention.

INTRODUCTION[1]

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating epinastine ophthalmic solution for possible addition to the VA National Formulary (VANF); (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

PHARMACOLOGY/PHARMACOKINETICS[1, 2]

Antihistamines are receptor antagonists used to avoid the inflammatory effects of histamine. Taken orally, these agents have been shown to be effective for treating allergic symptoms such as pruritis (itching). Epinastine in particular has been found to have a rapid onset of action.[3] Topical antihistamine eye drops provide relief from ocular symptoms without systemic absorption or related adverse events, allowing for the combination of oral and topical agents when indicated.

Ophthalmic antihistamine/mast cell stabilizers such as epinastine combine H_1-receptor actions to block ocular itching and redness with H_2-receptor affinity. The H_2-receptor activity limits vasodilatation, stabilization of mast cell and basophil surfaces, vascular permeability, and mucous discharge which all contribute to the inflammatory response of further redness. Additionally, epinastine has affinity for the α_1-, α_2-, and 5-HT_2-receptors, however ocular effects on glaucoma or serotonin-related congestion have not been studied.[4,5] Epinastine ophthalmic solution does not penetrate the blood/brain barrier.

	Azelastine 0.05% (Optivar, MedPointe)[6]	Epinastine 0.05% (Elestat, Allergan/Inspire)	Ketotifen 0.025%, (Zaditor, CIBA Vision)[7]	Olopatadine 0.1% (Patanol, Alcon)[8]
Onset	n/a	Rapid, 3-5 minutes	n/a	n/a
Duration	n/a	8 hours	n/a	>8 hours
Metabolism	cP450	< 10%	n/a	Minimal
Elimination	Clearance 0.5L/hr/kg; 75% in feces, 10% unchanged	Total clearance 56 L/hr; IV dose excreted unchanged renal (55%) via active tubular secretion; 30% fecal elimination	n/a	60-70% unchanged renal
Half-life	22 hours	Plasma 12 hours	n/a	Plasma 3 hours
Protein Binding/	88%, metabolite 97% bound	64%	n/a	n/a

h=hour; IV=intravenous; kg=kilogram; L=liter min.=minutes; n/a= not available

ADVERSE EVENTS[2]

Ocular adverse events occurred in 1-10% of patients studied, including burning sensation in the eye, folliculosis (inflammation of the eyelid causing pain, swelling or irritation), hyperemia (redness), and pruritis. Non-ocular events included cold symptoms and upper respiratory infections in approximately 10% of patients, and headache, rhinitis, sinusitis, increased cough, and pharyngitis reported in 1-3%. Most of the adverse effects reported are expected in the allergic patient.

Warnings

Contraindicated if hypersensitivity to epinastine or any of the vehicle's components. Elestat™ ophthalmic solution is for topical use only.

Precautions

Contact lenses should not be worn if eye is red and epinastine should not be used for contact lens irritation. Prior to epinastine use, contact lenses should be removed; patients should wait 10 minutes before reinserting due to the risk of the benzalkonium chloride preservative absorbing into the lenses.

Epinastine is pregnancy category C**;** animal models have shown conflicting outcomes and should only be used in pregnant or nursing mothers if the potential benefit outweighs the risk.

Special Populations

There is insufficient published data on pediatric patients under the age of 3 years. Geriatric patients >65 years of age have been included in clinical trials with no differences in safety or efficacy compared to the other subjects. Co-morbidities, race, and concomitant medications have not been studied.

CLINICAL TRIALS

Citation	Whitcup S, Bradford R, Lue J, et al. Efficacy and tolerability of ophthalmic epinastine: A randomized, double-masked, parallel-group, active-and-vehicle-controlled environmental trial in patients with seasonal allergic conjunctivitis. Clin Ther. 2004; 26(1):29-34.
Study Goals	To assess the efficacy and tolerability of epinastine ophthalmic solution in patients with seasonal allergic conjunctivitis (SAC).
Methods	**Study Design:** Multicenter, double masked, parallel-group, active- and vehicle-controlled, environmental trial. Patients were randomized (block stratified by age) in a 2:2:1 ratio to 1 drop/eye bid (morning and afternoon) of epinastine 0.05% solution, levocabastine 0.05% suspension, or vehicle of epinastine for 8 weeks. Bottles were masked for blinding. Washouts: 14-days for steroids and mast cell stabilizers; 7 days for fexofenadine, loratadine and cetirizine; 3-days for ASA, H_1 –receptor antagonist antihistamines or any other topical ophthalmics. Primary analysis was average worst daily ocular itching (scale of 0-4), based on two 1-week periods with the highest pollen counts and assessed tid as mean of worst all-day and bedtime scores. Secondary end points included ocular hyperemia (redness) with a scale of 0-4 and photos, chemosis, ocular mucous discharge (scale 0-4); eyelid swelling (scale 0-3) and tearing (present or absent). **Baseline:** 298 patients, 53.4% female, 46.3% Asian, mean age 32.7 (range 9-71 years), prestudy NS differences in population. Conducted March 20, 2001 - July 17, 200 in West, Midwest, South and East Coast centers. Lowest mean pollen counts 8.2 grains/m^3, highest 97.5 grains/m^3. **Data Analysis:** Performed in intent-to-treat (ITT) population. Wilcoxon rank-sum test instead of ANOVA for between group diaries due to skewed distribution. Noninferior defined as UL of 2-sided 95% CI of epinastine minus levocabastine group <0.4. Null hypothesis of no difference between groups at $p \leq 0.05$. Slit-lamp and AEs (mild, moderate or severe) by Pearson chi-square or Fisher exact test (if 25% of cell counts were <5); visual acuity data by Fisher exact test.
Criteria	**Inclusions:** ≥9 years of age, history of SAC or rhinoconjunctivitis; allergen sensitivity=positive grass skin-prick test within 2 years prior and bilateral ocular response to low dose grass pollen with the conjunctival allergen challenge (CAC); best-corrected visual acuity using Early Treatment Diabetic Retinopathy Study (ETDRS) chart, calculated logarithm of the minimal angle of resolution (logMAR) ∃0.7 and avoided contact lenses 15 minutes after administration and study visits. **Exclusions:** Pregnant or nursing, ocular infection or condition such as blepharitis, follicular conjunctivitis, iritis, diagnosis of dry eye, retinal detachment or disease, history of asthma to study antigens, systemic autoimmune disease.
Results	**Primary end point:** Ocular itching p=0.045 epinastine vs. vehicle, UL 95% CI median shift of epinastine and levocabastine was <0.4, 0.00 (-0.20 to 0.10) therefore epinastine was noninferior. **Secondary end points**: Ocular hyperemia was NS versus vehicle and noninferior to levocabastine (median shift, 95% CI= -0.10 (-0.30 to 0.10). Chemosis, ocular mucous discharge, eyelid swelling and tearing NS. **Tolerability:** AEs reported in 1.7 - 3.6% of patients, most common reaction was stinging in <1.6% of patients. Slit-lamp biomicroscopy, visual acuity, other AEs NS; 3 patients withdrew due to AEs.
Conclusion	Marginally statistically significant difference between epinastine and vehicle for worst ocular itching. Noninferior to levocabastine for ocular itching.
Critique	**Strengths:** Multi-center across all regions, environmental study is realistic clinical setting, efficacy and tolerability by ITT. **Limitations:** The pollen counts were low, wide-ranging, and varied among sites. Worst ocular itching (SD) was very low on scale 0-4: epinastine 0.77 (0.86), levocabastine 0.86 (0.86), and vehicle 0.93(0.76). Sponsored by the manufacturer.

Citation	Abelson M, Gomes P, Crampton H, et al. Efficacy and tolerability of ophthalmic epinastine assessed using the conjunctival antigen challenge model in patients with a history of allergic conjunctivitis. Clin Ther. 2004; 26(1):35-47.
Study Goals	To assess the efficacy and tolerability of epinastine ophthalmic solution in patients with allergic conjunctivitis using the conjunctival antigen challenge (CAC) model.
Methods	**Study Design:** Single-center, double masked, parallel-group, vehicle-controlled trial. Randomized (computer-generated) by eye to a single dose of 1 drop of epinastine 0.05% solution and 1 drop of vehicle of epinastine in the other eye 15 minutes before antigen challenge for onset and 8 hours before antigen to assess duration. Bottles were masked for blinding. Primary assessment of itching (scale 0-4) made at 3, 5, and 10 minutes after antigen. Primary assessment of conjunctival hyperemia (redness) and secondary objectives assessed 5, 10, and 20 minutes after antigen on a scale of 0-4; lid swelling (scale 0-3), tearing and mucous discharge (present or absent). Clinically effective if ≥1 grade less than vehicle. **Baseline:** 67 patients, 55% female, mean age 38.4 (range 12-67 years), 7.5% ≤17 years. Pre-study NS differences or difference in randomized eyes for itching, hyperemia, swelling, chemosis, tearing or discharge. Conducted Nov 2000 - June 2001 in Massachusetts. **Data Analysis:** Primary analysis powered for sample size of 10 for detecting a 1-grade difference with SD 1 and p= 0.05. Data compared in intent-to-treat (ITT) population by Wilcoxin signed rank tests. Tearing and discharge % assessed with McNemar test for correlated proportions. AEs assessed by slit-lamp biomicroscopy (examination of eyelids, tear meniscus, conjunctiva, cornea, lens, and anterior chamber), visual acuity using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, weeks 0,1,3,5, evaluated with Pearson chi-square test or Fisher exact test for 3x2 tables.
Criteria	**Inclusions :** ≥10 years of age, ≥1 allergy to cat hair, cat dander, dust mites, ragweed, tree, or grass pollens with positive CAC (ocular itching ≥2/5) at 2/3 time points in each eye; willing to avoid contact lenses beginning 3 days prior to study; calculated logarithm of the minimum angle of resolution (logMAR) visual acuity score (best-corrected visual acuity using ETDRS chart) of ≥0.70 in each eye. **Exclusions:** Active allergic conjunctivitis (hyperemia or redness >1 or any ocular itching) at weeks 0, 1 or 3; active ocular infection or serious condition, diagnosis of dry eye**,** any condition limiting completion of the study, intraocular surgery within past 2 months, or using interfering topical, systemic, or ocular medications (antihistamines, mast cell-stabilizing agents, ASA, or corticosteroids).

Results- Primary end point: Ocular itching was lower for epinastine than vehicle for onset and duration ($p<0.001$) at all time points of (3, 5, and 10 minutes). Conjunctival hyperemia was lower with epinastine $p<0.001$ at all time points (5, 10, and 20 minutes). **Secondary end points**: Measured at 5, 10, and 20 minutes; see table below:

	SCALE	ONSET 5 minutes		SIG.	DURATION 5 minutes	
		Epinastine	Vehicle		Epinastine	Vehicle
Ocular itching (3 minutes)	0-4	0.45 (0.77)	1.99 (1.03)	p<0.001	0.92 (0.93)	1.86 (0.93)
Conjunctival hyperemia	0-4	1.28 (0.86)	2.03 (0.78)	p<0.001	1.37(0.78)	1.93(0.77)
Eyelid swelling	0-3	0.16 (0.40)	0.53 (0.77)	p<0.001	0.14 (0.38)	0.39 (0.63)
Episcleral hyperemia	0-4	1.17-1.85	1.93-2.37	p<0.001	1.38-1.83	1.89-2.30
Ciliary hyperemia	0-4	1.11-1.85	1.94-2.36	p<0.001	1.21-1.80	1.77-2.30
Chemosis	0-4	0.54-0.93	0.79-1.12	p≤0.009	0.30-0.57	0.58-0.90
Tearing	p≤0.021***all significant except 5 minutes after duration challenge**					
Ocular mucous discharge	NS					
Tolerability	No ocular AEs reported, only AE was symptoms of upper respiratory infection in 5/67 (7.5%) and considered unrelated. Slit-lamp biomicroscopy, visual acuity, NS. No withdrawals due to AEs, 1 patient (1.5%) lost to follow-up.					

****** lid swelling, episcleral and ciliary hyperemia, and chemosis were significantly different at all time points

Conclusions	Ocular itching and hyperemia significantly lower for epinastine than vehicle for onset and duration.
Critique	**Strengths:** CAC method calibrates threshold to antigen and rechallenges after administration of a study agent, which consistently and reproducibly assesses therapeutic effect. ITT analysis performed . **Limitations:** Clinical effectiveness predetermined if ≥1 grade less than vehicle; clinical superiority of primary end point should pre-specify margin of 95% CI. Sponsored by manufacturer**.**

FDA APPROVED INDICATION

Elestat ™ was approved on October 16, 2003 for the prevention of itching associated with AC.

DOSAGE AND ADMINISTRATION

One drop in each eye twice a day. Treatment should continue in the absence of symptoms until the allergen exposure is over.

CONCLUSIONS

An ideal agent for AC would block ocular itching, redness, and have a quick onset with sufficient duration of action without systemic absorption. Epinastine is the fourth ophthalmic antihistamine/mast cell stabilizer marketed for the itching associated with AC.

Epinastine's only published comparative trial has confirmed noninferiority to the antihistamine levocabastine, which is the VANF's highest utilized ophthalmic for AC. Mast cell stabilizers and over-the-counter antihistamine/decongestants also have significant usage. Corticosteroids and NSAIDs are represented on the VANF however they have many other indications beyond AC (refer to table 1 for products, pricing and dispensing data). Formulary usage patterns may vary among warmer climates or seasons when AC is most prevalent.

An ophthalmic antihistamine/mast cell stabilizer such as epinastine offers less frequent daily dosing and may prevent chronic AC through mast cell stabilization; this could explain the significant non-formulary utilization in this class. Reduction of polypharmacy as a combination product or replacing an oral agent for patients with ocular symptoms alone would also be an advantage, however it would likely be used in addition to a nasal or oral product for other allergic manifestations such as rhinitis or cough.

RECOMMENDATIONS

Epinastine has only been marketed for the last few months. The DoD has decided to wait before considering this agent for formulary addition. Gaining input from specialists in Allergy or Ophthalmology would provide further insight, namely:

1. Is there a difference between ophthalmic antihistamine/mast cell stabilizers (azelastine, epinastine, ketotifen, or olopatadine) in efficacy or safety?

2. Would adding an ophthalmic antihistamine/mast cell stabilizer offer higher efficacy, safety, or improved patient management than current formulary antihistamine or mast cell stabilizing agents alone or in combination for treating AC?

3. Is there evidence to support a significant improvement in quality of life by administering these agents chronically to prevent AC?

Prepared 04/04 Chris Chandler, Pharm D.

Table 1.[9] VA CLASS/ OPHTHALMIC AGENTS FOR ALLERIC CONJUNCTIVITIS	ALLERGIC INDICATION	DOSE	3/03-2/04 30DAY RX	STATUS	VA COST /VIAL ($)	COST/ DAY†
OP900 ANTIHISTAMINES/MAST CELL STABILIZERS						
Azelastine 0.05% (Optivar, MedPointe)	Treat itching AC	1 drop OU bid	35	NF	38.27 6ml	$1.70
Epinastine HCl 0.05% (Elestat, Allergan/Inspire)	Prevent itching AC	1 drop OU bid	0	NF	59.01 5ml	$3.15
Ketotifen 0.025% (Zaditor, CIBA)	Prevent itching AC	1 drop OU bid	354	NF	24.14 5ml	$1.29
Olopatadine 0.1% (Patanol, Alcon)	Prevent itching AC	1-2 drops OU bid	9,754	NF	24.00 5ml	$.64-1.3♣
OP900 ANTIHISTAMINES						
Emedastine 0.05% (Emadine, Alcon)	Relief AC	1 drop OU qid	1	NF	30.96 5ml	$3.30
Levocabastine 0.05% (Livostin, Novartis)	Relief SAC	1 drop OU qid max. 2 weeks	19,671	F	4.59 5 ml	$0.49
OP900 MAST CELL STAILIZERS *Indications beyond AC, however a benefit would be afforded through standardization to the generic if applicable						
Cromolyn 4%, generic	Treat AC (vernal)	1-2 drops OU q4-6h	*11,537	F	3.50 10ml	$0.19-.37
Lodoxamide 0.1% (Alomide, Alcon)	Treat SAC (vernal)	1-2 drops OU qid max.3 months	*5,249	F	37.5 10ml	$2-4.00
Nedocromil 2% (Alocril, Allergan)	Treat itching AC	1-2 drops OU bid	*44	NF	35.09 5ml	$1.9-3.74
Pemirolast 0.1% (Alamast, Santen)	Prevent itching AC	1-2 drops OU qid	*2	NF	24.3 10ml	$1.3-2.60
OP300 NSAIDS **Also post-op indications						
Ketorolac 0.5% (Acular, Allergan)	Relief itching SAC	1 drop OU qid	**37,981	F	29.11 5ml	$3.11
OP300 CORTICOSTEROIDS ***Many non-AC indications						
Dexamethasone 0.1%, various	Treat inflammation AC	1-2 drops OU tid-qid		F		
Loteprednol etabonate 0.2 and 0.5% (Alrex, Lotemax, Bausch & Lomb)	Relief , treat 0.5% SAC	1 drop OU qid		NF ***		
Medrysone 1% (HMS, Allergan)	Treat AC, SAC (vernal)	1 drop OU q4h		NF		
Prednisolone 0.12, 0.125. 1%, various	Treat inflammation AC	1-2 drops OU tid-qid		F		
OP600 DECONGESTANTS/COMBINATIONS ****High non-formulary use of decongestants alone and in combination, which may cause dependence						
Naphazoline HCl RX 0.1% , various	Soothe, remove redness	1-2 drops OU qid	****10,973	NF	3.14 15ml	$0.11-0.21
Oxymetazoline HCl (OTC) 0.025% , various, Visine L.R.	Relief redness	1-2 drops OU qid	0	OTC	2.96 15ml	$0.11-0.21
Phenylephrine (OTC) 0.12% , various	Relief minor irritation	1-2 drops OU qid	13	OTC	1.36 3ml	$0.24-0.48
Tetrahydrozoline HCl (OTC) 0.05% , various	Relief redness	1-2 drops OU qid	307	OTC	0.84 30ml	$0.015-.03
Naphazoline .01,.02,.12%,naphazoline .025%/pheniramine .3%,naphazoline .027%/pheniramin .315%, +naphazoline .05%/antazoline phosphate.5%, various	Relief itching/redness AC	varied	****19,057	OTC	+3.87 15ml	varied

AC=allergic conjunctivitis, AWP=average wholesale price; bid=twice daily, F=formulary, FSS= federal supply schedule; max= maximum; mg=milligrams; ml=milliliter, N=non-formulary, NSAIDS nonsteroidal anti-inflammatory agents, SAC= seasonal allergic conjunctivitis, OTC=over-the-counter, qid=4 times daily, RX=by prescription only, tid=three times daily, †15 drops/ml; ♣ reflects BPA pricing for 40% Market Share

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