CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-565

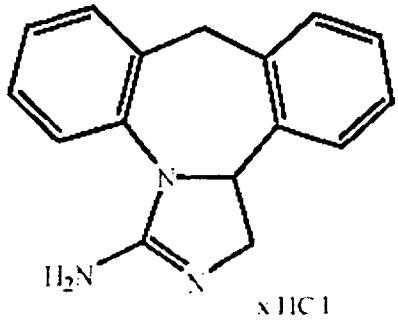
MEDICAL REVIEW

CLINICAL REVIEW of NDA 21-565

Original Application

Submitted:	December 19, 2002
Significant Clinical Amendments:	April 18, 2003, July 18, 2003
Review completed:	October 3, 2003
Reviewer:	Wiley A. Chambers, MD

Proposed Name: ELESTAT (epinastine HCl ophthalmic solution) 0.05%



Molecular Formula: $C_{16}H_{15}N_3 \bullet HCl$
Molecular Weight 285.8 g
Chemical Name: [redacted]3-Amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride

Pharmacologic Category: H1-receptor antagonist with antihistamine activity

Proposed Indication: Prevention of [redacted] allergic conjunctivitis.

Reviewer's Comments: *Text listed in italics throughout this review is intended to be comments and conclusions of this reviewer.*

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

Clinical studies have demonstrated that the benefits of using this drug product outweigh the risks for the indication of treatment of ocular itching associated with allergic conjunctivitis. The labeling as originally proposed contains sections which are not supported by the application. NDA 21-565 is recommended to be approved from a clinical perspective for the indication of the treatment of ocular itching associated with allergic conjunctivitis, after labeling revisions are made consistent with the recommendations listed in this review.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no recommended Phase 4 or Risk Management steps for this application.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Elastat (epinastine HCl ophthalmic solution) is a H1-receptor antagonist with antihistamine activity for topical ophthalmic administration. The application consists of principally of 5 US studies and 10 European/South African studies. These studies were designed to support the indication of the prevention of [redacted] Approximately 800 patients were treated with epinastine HCl ophthalmic solution 0.05% and another 150 patients were treated with higher concentrations of Epinastine HCl including concentrations up to 0.5%.

B. Efficacy

The agency considers effectiveness for [redacted] itching [redacted] critical for support of an application for the prevention [redacted]
The signs and symptoms of allergic conjunctivitis resolve spontaneously in minutes if there is no ongoing contact with an allergen. Treatment involves preventing ongoing allergen response, and therefore, the terms prevention and treatment are effectively the same for this indication. Three different types of studies are considered acceptable. These types of studies include the allergen challenge model, the allergen room model and environmental studies. The agency has reviewed well over 100 studies for drug products seeking an indication of allergic conjunctivitis. Historically, most environmental studies evaluating effectiveness of a drug product for allergic conjunctivitis fail to demonstrate a statistically significant difference in drug effect compared to vehicle. As a result of this phenomenon the agency does not accept equivalence

to any other product as sufficient evidence of equivalence. When conducting antigen challenge studies, a change of one unit or more compared to vehicle is considered clinically significant. The submitted NDA includes studies using all three models. Two of these models demonstrated effectiveness for itching [redacted] Clinically significant effectiveness for itching was demonstrated in the antigen challenge model and several environmental studies. Evidence of either superiority or inferiority compared to other approved new drug products for this indication was not reproducibly demonstrated.

C. Safety

Testing was completed in over 800 patients. Over 300 patients received the drug product for six weeks or more. Adverse events were generally concentration dependent. The most frequent events were burning upon instillation, conjunctival injection and ocular discomfort. The most frequent of these events occurred in less than 10% of patients and was generally self limited. The reporting of adverse events for this product was consistent with other products approved for this indication. There are no unresolved safety issues.

D. Dosing

The drug product is administered topically to the affected eye. Concentrations as high as 10 times the proposed concentration have been studied. The selected concentration appears appropriate for this indication. There are no unresolved issues related to dosing.

E. Special Populations

No special populations have been identified with this product. No gender, age, ethnic, racial, iris color or other subgroup differences were noted in the clinical studies. Pediatric patients have been studied down to the lowest age that the indication is thought to exist (age 3 years). Eleven pregnant patients have received this drug product and while no adverse events have been reported in either the patients or their children, the reporting is not sufficiently complete (duration and timing of treatment) reach definitive conclusions.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Proposed Name:	ELESTAT (epinastine HCl ophthalmic solution) 0.5%
Pharmacologic Category:	H1-receptor antagonist with antihistamine activity
Proposed Indication:	Prevention of the [redacted] of allergic conjunctivitis.
Dose Regimen:	One drop in the affected eye twice a day

B. State of Armamentarium for Indication(s)

The following products are approved for the treatment of allergic conjunctivitis:
Alrex (loteprednol etabonate ophthalmic suspension) 0.2%
Emadine (emedastine difumarate ophthalmic solution) 0.05%
Livostin (levocabastine hydrochloride ophthalmic solution) 0.05%
Lotemax (loteprednol etabonate ophthalmic suspension) 0.5%
Patanol (olopatadine hydrochloride ophthalmic solution) 0.1%
Vasocon-A (naphazoline/antazoline ophthalmic solution) 0.05%/0.5%
Naphcon-A (naphazoline/phenirmaine ophthalmic solution) 0.025%/0.3%
Visine-A (naphazoline/phenirmaine ophthalmic solution) 0.025%/0.3%
Pred Forte (prednisolone acetate ophthalmic suspension) 1%
Pred Mild (prednisolone acetate ophthalmic suspension) 0.12%
Decadron (dexamethasone phosphate ophthalmic solution) 0.1%

The following products are approved for the treatment of itching associated with allergic conjunctivitis:
Alamast (pemirolast potassium ophthalmic solution) 0.1%
Alocril (nedocromil sodium ophthalmic solution) 2%
Optivar (azelastine hydrochloride ophthalmic solution) 0.05%
Zaditor (ketotifen fumarate ophthalmic solution) 0.025%

C. Important Milestones in Product Development

The drug product was originally developed by Boehringer Ingelheim Pharma KG, Germany (BI) and was subsequently licensed to Allergan, Inc. in 1999. As part of the agreement, Allergan acquired numerous ocular and systemic studies in animals and humans and supplemented these data as discussed during the August 29, 2000, pre-IND/End of Phase 2 meeting for IND 61,025. The Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (DAAODP) raised concern at this meeting over the lack of support for a claim of [redacted]

The NDA has been organized as discussed in the Pre-NDA meeting held on July 24, 2002.

D. Other Relevant Information

Epinastine HCl 0.05% ophthalmic solution was approved in Sweden on October 18, 2002, under the trade name RELESTAT™. This product has also been submitted by Allergan for marketing approval in [redacted]

Epinastine HCl film-coated tablets (10 mg and/or 20 mg) have been approved for marketing in Argentina, Brazil, China, Japan, Korea, and Mexico, as well as 17 other countries, under the trade names ALESION and FLURINOL. A new drug application for Epinastine HCl tablets has not been submitted in the United States.

Epinastine HCl syrup (200 mg/mL) has been approved for marketing in Argentina, Brazil, Japan, and Mexico, as well as 13 other countries, under the trade names ALESION, FLURINOL, EPINAS, and TALERC. [redacted]

Epinastine HCl ophthalmic solution, tablets and syrup have not been withdrawn from the market in any country.

E. Important Issues with Pharmacologically Related Agents

Epinastine is reported to have a binding affinity for the H_1-receptor and 400 times lower affinity for the histamine H_2-receptor. The antihistaminic H_1-receptor activity was confirmed in functional assays using histamine-induced contractions in isolated guinea pig ileum. Besides its affinity for the H_1-receptor, epinastine is reported to possess affinity for the α_1-, α_2-, and the 5-HT_2–receptor. Affinity for cholinergic (affinity for ^{3}H-QNB labeled receptors), dopaminergic and a variety of other receptor sites was reported as low). Alpha-receptor blocking activity of epinastine was reported in binding studies in isolated blood vessels of the guinea pig and rat, in rat seminal vesicles and in isolated vas deferens of guinea pig. The antihistaminic potency of epinastine is believed to be approximately 6 to 22 times higher than its adrenergic activity. Systemic use of this drug in previous animal studies does show some alpha receptor activity, i.e., an increase in peripheral vascular resistance.

As epinastine is a racemic mixture, the pharmacological characteristics of both the (+)-enantiomer and (-)-enantiomer. While the H_1-receptor affinity was nearly identical between epinastine and both optical isomers, the (+)-enantiomer and the (-)-enantiomer differed somewhat with respect to their affinity for the α_1-, α_2- and the 5-HT_2-receptor. The (-)-enantiomer had a somewhat lower affinity for the α_1-receptor (IC_{50}=350 nM) and a very low affinity for the α_2-receptor compared to

epinastine. The receptor affinities of the (+)-enantiomer resembled those of epinastine.

Toxicology studies with 0.5 mg/mL epinastine eye drops TID did not demonstrate any significant alpha effects, vasodilation, or intraocular pressure (IOP) changes. Miosis was observed in rabbits at 30 mg/kg (30,000 higher dose than recommended daily clinical dose) and in humans after instillation of 0.3% epinastine TID (9 times higher than recommended daily clinical dose). In that alpha effects are not expected in the 0.5 mg/mL topical formulation, there is no real advantage to either enantiomer of epinastine. Because of the similar binding affinities observed for both enantiomers at the H_1-receptor, separation of the enantiomers was deemed unnecessary. Neither stereoisomer showed a receptor binding advantage over the racemate, and there is presumed to be no difference in efficacy considering the low doses utilized in ocular administration.

With respect to ocular findings and with ocular dosing, epinastine is similar to other members of the antihistamine class.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Quantitative Composition of Epinastine HCl 0.05% Ophthalmic Solution			
			Amount (g) for Commercial-Scale Batch
Ingredient	Concentration (% w/v)	Concentration (mg/mL)	[redacted]
Epinastine HCl	0.05	0.5	[redacted]
Benzalkonium Chloride	0.01	0.1	[redacted]
Monobasic Sodium Phosphate	[redacted]	[redacted]	[redacted]
Sodium Chloride	[redacted]	[redacted]	[redacted]
Edetate Disodium	[redacted]	[redacted]	[redacted]
Sodium Hydroxide	[redacted]	[redacted]	[redacted]
[redacted] HCl and/or [redacted] NaOH	[redacted]		
Purified Water	[redacted]	[redacted]	[redacted]

[redacted]

Reviewer's Comments: *Acceptable.*

Product Tests and Specifications for Epinastine HCl 0.05% Ophthalmic Solution			
Test	**Release Specification**	**Regulatory Specification**	**Method**
Epinastine HCl Assay	[redacted]	0.0465-0.0550% w/v	[redacted]
[redacted]	[redacted]	[redacted]	
Epinastine HCl Identification			
[redacted] Method	[redacted]	Performed at release only	[redacted]
[redacted] Method	[redacted]	Performed at release only	[redacted]
Impurities	% w/w of epinastine HCl label strength	% w/w of epinastine HCl label strength	[redacted]
[redacted]	NMT [redacted]	NMT [redacted]	
[redacted]	NMT [redacted]	NMT [redacted]	
Individual Unspecified	NMT 0.1%	NMT 0.1%	
Total Impurities: Sum of All	NMT 1.0%	NMT 1.0%	
Benzalkonium Chloride Assay	[redacted]	0.0085 – 0.0115% w/v	[redacted]
	[redacted]	(85.0 – 115.0% of label strength)	
Benzalkonium Chloride Identification	[redacted]	Performed at release only	[redacted]
Edetate Disodium Assay	[redacted]	0.0450 – 0.0575% w/v (90.0 – 115.0% of label strength)	[redacted]
Osmolality	[redacted]	250 – 310 mOsm/kg	USP <785>
Physical Appearance			
Color	[redacted]	Colorless solution (Not more intensely colored than reference solution B8)	Ph Eur 2.2.2
Clarity	Clear solution (Not more opalescent than reference suspension I)	Clear solution (Not more opalescent than reference suspension I)	Ph Eur 2.2.1
pH	[redacted]	6.5 – 7.5	USP <791>
Antimicrobial Preservative Effectiveness Test	[redacted]	Meets current USP	USP <51>
Sterility	Meets current USP	Meets current USP	USP <71>
Particulate Matter	NMT 50 Particles/mL 10 µm NMT 5 Particles/mL 25 µm NMT 2 Particles/mL 50 µm	NMT 50 Particles/mL 10 µm NMT 5 Particles/mL 25 µm NMT 2 Particles/mL 50 µm	[redacted]

Reviewer's Comments: *Acceptable from a clinical prospective.*

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The pharmacokinetics following single and multiple-dose administration of epinastine HCl 0.05% ophthalmic solution was studied in 14 patients with allergic conjunctivitis PK-01-126). Systemic epinastine exposure was low following ophthalmic dosing. The maximum plasma concentration in patients was 0.5 ± 0.008 ng/mL (T_{max} 4.46 ± 2.87 hr) following a single dose and 0.042 ± 0.014 ng/mL (T_{max} 1.81 ± 0.93 hr) following twice-daily dosing. The pharmacokinetics of topical epinastine were linear, with single-dose AUC predictive of the multiple-dose AUC value. Terminal plasma elimination half-life after single-dose (9.26 ± 4.28 hr) and twice-daily dosing (11.9 ± 11.6 hr) was similar to that observed after oral and intravenous administration. Tear epinastine concentrations peaked

rapidly, and local drug concentration was substantial (C_{max} 27.1 ± 46.2 µg/mL T_{max} 0.033 ± 0.043 hr). Subsequently, drug concentrations in tear declined rapidly until 30 minutes after dosing, beyond which a slower exponential phase was apparent.

Following ophthalmic dosing with epinastine HCl, the plasma concentrations in humans are less than the exposure following oral dosing. Following a single dose of epinastine HCl 0.05% ophthalmic solution in patients with allergic conjunctivitis, the C_{max} and AUC value is approximately 600 and 300 times less than the C_{max} and AUC following a single 20 mg oral dose in humans (C_{max} [redacted] and AUC 143 – 468 ng·hr/mL).

B. Pharmacodynamics

The Pharmacodynamics section is not applicable for this product since the plasma levels do not correlate with clinical efficacy or ocular safety.

IV. Description of Clinical Data and Sources

A. Overall Data

The clinical data source consists entirely of full study reports submitted by the applicant. Clinical trials were either dose ranging, vehicle controlled or levocabastine controlled.

Reviewer's Comments: *The Division does not consider equivalence to levocabastine as supportive of efficacy. In clinical studies reviewed by the Division, levocabastine was sometimes superior to its vehicle and sometimes not.*

B. Tables Listing the Clinical Trials in Allergic Conjunctivitis

Study ID	Country	Study Type/Phase	Epinastine HCl	Control(s)	Duration
001	US	CAC (randomized by eye) / Phase 3	0.05% (194 eyes)	Vehicle (192 eyes)	2 doses
003	US	Environmental with CAC screen / Phase 3	0.05% (118)	Levocabastine (118) Vehicle (62)	56 days BID
214.6	Austria Germany	Environmental / Phase 3	0.05% (77)	Vehicle (81)	14 days BID
214.7	South Africa	Environmental / Phase 2	0.05% (68)	Vehicle (64)	14 days BID
214.10	South Africa	Environmental / Phase 3	0.05% (168)	Levocabastine (85)	42 days BID
214.4	Austria Germany	Environmental / Phase 2	[redacted]	Vehicle	14 days TID
214.3	Austria	VCC (crossover) / Phase 2	[redacted] 0.05%	Vehicle	4 doses each treatment
214.5	Austria	VCC (crossover) / Phase 2	[redacted]	Levocabastine Vehicle	4 doses each treatment
214.8	Austria	VCC (crossover) / Phase 2	0.05%	Levocabastine Vehicle	4 doses each treatment
214.11	Austria	VCC / Phase 2	0.05%	Vehicle	42 days BID
004	US	Pharmacokinetics / Phase 2	0.05%	None	8 days
Studies in Healthy Subjects					
002	US	Safety / Phase 1	0.05%	Vehicle	42 days BID
005	US	Safety / Phase 1	0.05%	Vehicle	42 days BID
214.1	Germany	Safety / Phase 1	0.5%, 0.3%, 0.1%	Vehicle	single dose
214.2	Germany	Safety (randomized by eye) / Phase 1	0.3%	Vehicle	21 days TID

BID = 2 times daily, CAC = conjunctival allergen challenge, TID = 3 times daily, VCC = Vienna challenge chamber

C. Postmarketing Experience

The postmarketing data has been reviewed. The events reported are consistent with the events reported in the clinical studies.

D. Literature Review

There was no significant new information found in the published literature.

V. Clinical Review Methods

A. How the Review was Conducted

All trials listed in the table above were reviewed separately. Environmental study designs are well known to frequently fail even when testing effective drug products. The antigen challenge model tends to provide more reproducible results. Small changes will be statistically significant with this model however, products failing to demonstrate a 1 unit change are not considered to be clinically effective.

B. Overview of Materials Consulted in Review

The majority of the application was submitted in electronic PDF format. Additionally reference was made to IND 61,025, where the results of some additional trials were reported.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI was involved in an audit of some of the clinical sites. Additionally, the data was reviewed for consistency with other applications in this class.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials were conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

There were no investigators identified meeting the criteria for financial reporting. However, many of the studies were conducted prior to the Financial Disclosure regulation, and there is no continuing relationship between the investigator and the applicant.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The clinical studies support the treatment of itching associated with allergic conjunctivitis. The studies do not support the [redacted] associated with allergic conjunctivitis.

B. General Approach to Review of the Efficacy of the Drug

Summary of Ocular Itching by Study

Study ID (Type)			Epinastine	Levocabastine		
Treatments	Endpoint	Variable/Visit	0.05%	0.05%	Vehicle	P-value
001 (CAC)	Itching graded by patient post challenge from 0=none to 4=incapacitating	Day 21 (3, 5, 10 min) Day 35 (3, 5, 10 min)	Mean (N=127) 0.59, 0.70, 0.63 1.02, 1.05, 0.88		Mean (N=125) 1.97, 2.06, 1.76 1.74, 1.92, 1.69	< 0.001 < 0.001
003 (Environmental with CAC screen)	Average worst daily itching based on grading by patient, 3 times daily for each eye from 0=absent to 4=extremely severe	Averaged over 2-week peak pollen period for each patient	Median (N=118) 0.45	Median (N=118) 0.60	Median (N=62) 0.85	Epi vs Vehicle p=0.045 Epi vs Levo P=0.364
214.7 (Environmental)	Itching graded by patient from 0=absent to 4=very severe	Median proportion of days with itching reported as absent or mild	83% (N=68)		68% (N=64)	< 0.01
214.10 (Environmental)	Itching graded by patient from 0=absent to 3=severe	Average for days 7 to 42	Mean (N=168) 0.79	Mean (N=85) 0.97		0.048
214.6 (Environmental)	Itching graded by patient from 0 = absent to 4 = very severe	Proportion of drug days with itching reported as absent or slight (mild)	74% (783/1053 days) (N=77)		72% (776/1081 days) (N=81)	NS
214.8 (VCC)	Itching graded by patient at 15-minute intervals on 100-mm VAS from 0 = none to 100 = extremely severe	Scores summed across time intervals VCC test + CPT CPT	Mean (N=23) 114 22	Mean (N=23) 157 24	Mean (N=23) 186 44	NS
214.11 (VCC)	Itching graded by patient at 15-minute intervals on 100-mm VAS from 0 = none to 100 = very severe	Scores summed across time intervals on day 42 VCC test + CPT CPT	Mean (N=42) 126 33		Mean (N=40) 156 58	NS

Reviewer's Comments: *Protocols 1, 3, 214.7 and 214.10 support the indication of itching associated with allergic conjunctivitis.*

Summary of [redacted] by Study

Study ID (Type)			Epinastine	Levocabastine		
Treatments	**Endpoint**	**Variable/Visit**	**0.05%**	**0.05%**	**Vehicle**	**P-value**
001 (CAC)	Itching graded by patient post challenge from 0=none to 4=incapacitating	Day 21 (3, 5, 10 min) Day 35 (3, 5, 10 min)	Mean (N=127) [redacted]		Mean (N=125) [redacted]	
003 (Environmental with CAC screen)	Average worst daily itching based on grading by patient, 3 times daily for each eye from 0=absent to 4=extremely severe	Averaged over 2-week peak pollen period for each patient	Median (N=118)	Median (N=118)	Median (N=62)	NS
214.7 (Environmental)	Itching graded by patient from 0=absent to 4=very severe	Median proportion of days with itching reported as absent or mild	%(N=68)		% (N=64)	NS
214.10 (Environmental)	Itching graded by patient from 0=absent to 3=severe	Average for days 7 to 42	Mean (N=168)	Mean (N=85)		NS
214.6 (Environmental)	Itching graded by patient from 0 = absent to 4 = very severe	Proportion of drug days with itching reported as absent or slight (mild)	(N=77)		(N=81)	NS
214.8 (VCC)	Itching graded by patient at 15-minute intervals on 100-mm VAS from 0 = none to 100 = extremely severe	Scores summed across time intervals VCC test + CPT CPT	Mean (N=23)	Mean (N=23)	Mean (N=23)	NS
214.11 (VCC)	Itching graded by patient at 15-minute intervals on 100-mm VAS from 0 = none to 100 = very severe	Scores summed across time intervals on day 42 VCC test + CPT CPT	Mean (N=42)		Mean (N=40)	NS

Reviewer's Comments: [redacted] *is not supported by these submitted studies. Study 001, which* [redacted]

C. Detailed Review of Trials by Indication

Reviewer Study #1: Protocol 001: A Single-Center, Double-Masked, Randomized, Vehicle-Controlled Study of the Efficacy and Safety of Epinastine Hydrochloride 0.05% Ophthalmic Solution Used as a Single Dose on Two Occasions in the Conjunctival Antigen Challenge Model in Patients with History of Allergic Conjunctivitis

Study Design:

This study was randomized, double-masked, vehicle-controlled, and used a CAC model at a single center. The study treatments were randomly assigned by eye. Approximately 140 patients at least 10 years of age with a known history of allergic conjunctivitis who manifested a positive CAC reaction were to be enrolled to complete approximately 120 patients. Patients' individual eyes were randomly assigned to receive either epinastine or its vehicle in a 1:1 ratio. There were 3 treatment combinations: epinastine in both eyes, contralateral administration of epinastine in one eye and vehicle in the other eye, and vehicle in both eyes.

Using the CAC model, patients with a history of atopy who were not currently exhibiting signs and symptoms of allergy were administered controlled quantities of antigen instilled in each eye. Antigens were selected based on allergy history and a skin test. At visit 1 (day 0), screening antigen challenge was performed to determine an antigen concentration that would elicit a positive response, defined as a ≥ 2 hyperemia score in the conjunctival vessel bed and a ≥ 2 ocular itching score in both eyes. At visit 2 (day 7), patients underwent a confirmatory antigen challenge with the antigen and dilution determined at visit 1. At visit 3 (day 21), patients received 1 drop of study medication in each eye 15 minutes prior to antigen challenge to determine onset of action. At visit 4 (day 35), patients received 1 drop of study medication in each eye 8 hours prior to antigen challenge to determine duration of action.

The study population consisted of patients at least 10 years old with a positive allergic history to cat hair/dander, ragweed, tree, dust mite and/or grass pollens with calculated logMAR visual acuity (VA) score (best-corrected visual acuity using an Early Treatment of Diabetic Retinopathy Study [ETDRS] chart) of 0.70 or better in each eye. Patients were excluded if they had clinically active allergic conjunctivitis at the start of study day 0, 7, or 21, the presence of preauricular lymphadenopathy, an active bacterial or viral ocular infection, a history of dry eye syndrome or used medications (topical, systemic, or ocular) that might have interfered with the study parameters (i.e., H_1–selective or nonselective antihistamines, mast cell stabilizers, aspirin, and corticosteroids).

This study was conducted at a single center in the United States. The principal investigator was Henry Jerome Crampton, MD (North Andover, Massachusetts).

Reviewer's Comments: *Jerome Crampton was also involved in Protocol 003, reviewed as Study #2 in this review.*

Schedule of Assessments	Visit 1	Visit 2	Visit 3	Visit 4
	Screening	Confirmation	Onset	Duration
	Day 0	Day 7 ±2	Day 21 ±3	Day 35 ±3
Informed consent/ assent	X			
Medical & ophthalmic history	X			
Medical & ophthalmic history update		X	X	
Pregnancy test (if female of childbearing potential)	X	X[a]	X[a]	X
Biomicroscopy	X	X	X[b]	X[b]
Visual acuity	X	X	X[b]	X[b]
Antigen challenge	X	X	X	X
Conjunctivitis evaluation	X[c]	X[d]	X[d]	X[d]
In-office administration of study medication			X	X
Assessment of adverse events			X	X
Assessment of concomitant medications	X	X	X	X

a Only for premenarchal patients who experienced onset of menses prior to study visit.

b All patients were to be evaluated before dosing, and patients ≤ 17 years also at the end of the visit.

c Patient evaluation of ocular itching pre-challenge and 10 minutes post-challenge; examiner evaluation of chemosis, eyelid swelling, tearing, mucous discharge, and [redacted] pre-challenge and 10 minutes post-challenge.

d Patient evaluation of ocular itching pre-challenge and 3, 5, and 10 minutes post-challenge; examiner evaluation of chemosis, eyelid swelling, tearing, mucous discharge, and [redacted] pre-challenge and 5, 10, and 20 minutes post-challenge.

Efficacy Criteria:

Itching was evaluated by the patient on a scale from 0 to 4 (allowing 0.5-grade increments), as follows:

0 None
1 An intermittent tickle sensation involving more than just the corner of the eye
2 A mild continuous itch (can be localized) without desire to rub
3 A severe itch with desire to rub
4 An incapacitating itch with an irresistible urge to rub

[redacted]

Disposition of Patients

A total of 126 patients were enrolled in the study: 30 patients randomly assigned to receive epinastine in both eyes (epi/epi), 67 patients randomly assigned to receive epinastine in one eye and vehicle in the contralateral eye (epi/veh), and 29 patients randomly assigned to receive vehicle in both eyes (veh/veh). All patients completed the study with the exception of patient 3153-1021, who received epi/veh on day 21 and was lost to follow-up before day 35.

	Epi/Epi	Epi/Veh	Veh/Veh	p-value
	(N=30)	(N=67)	(N=29)	
Age (years)				
N	30	67	29	0.324
Mean ± SD	36.8 ± 13.4	38.4 ±14.2	40.0 ±10.9	
Median	40.0	37.0	42.0	
Min	11	12	11	
Max	60	67	54	
<= 17 years	4 (13.3%)	5 (7.5%)	1 (3.4%)	
18 - 64 years	26 (86.7%)	58 (86.6%)	28 (96.6%)	
>= 65 years	0 (0.0%)	4 (6.0%)	0 (0.0%)	
Sex				
N	30	67	29	0.497
Male	14 (46.7%)	30 (44.8%)	11 (37.9%)	
Female	16 (53.3%)	37 (55.2%)	18 (62.1%)	
Race				
N	30	67	29	
Caucasian	28 (93.3%)	64 (95.5%)	28 (96.6%)	
Black	0	0 (0.0%)	0 (0.0%)	
Asian	1 (3.3%)	1 (1.5%)	0 (0.0%)	
Hispanic	1 (3.3%)	2 (3.0%)	0 (0.0%)	
Other	0 (0.0%)	0 (0.0%)	1 (3.4%)	
White	28(93.3%)	64 (95.5%)	28 (96.6%)	>0.999
Non-White	2 (6.7%)	3 (4.5%)	1 (3.4%)	
Iris Color				
N	30	67	29	126
Blue	7 (23.3%)	19 (28.4%)	9 (31.0%)	35 (27.8%)
Brown	15 (50.0%)	28 (41.8%)	15 (51.7%)	58 (46.0%)
Green	3 (10.0%)	6 (9.0%)	2 (6.9%)	11 (8.7%)
Hazel	5 (16.7%)	14 (20.9%)	3 (10.3%)	22 (17.5%)

Reviewer's Comments: *Baseline groups are comparable.*

Mean Ocular Itching Scores (Parallel-Eyes Comparison)				
	Epinastine (N = 127)	Vehicle (N = 125)	Difference[a]	P-Value[b]
Day 7 (Rechallenge)				
Pre-challenge	0.00	0.00	0.00	0.991
3 minutes	2.46	2.49	0.03	0.663
5 minutes	2.78	2.70	0.08	0.399
10 minutes	2.67	2.61	0.06	0.439
Day 21 (onset)				
Pre-challenge	0.00	0.00	0.00	> 0.999
3 minutes	0.59	1.97	-1.39	< 0.001
5 minutes	0.70	2.06	-1.36	< 0.001
10 minutes	0.63	1.76	-1.13	< 0.001
Day 35 (8 hours)				
Pre-challenge	0.00	0.00	0.00	> 0.999
3 minutes	1.02	1.74	-0.72	< 0.001
5 minutes	1.05	1.92	-0.87	< 0.001
10 minutes	0.88	1.69	-0.80	< 0.001
a	Difference = epinastine minus vehicle; a negative difference favors epinastine.			
b	P-value based on Wilcoxon rank sum test on the mean values.			

Reviewer's Comments: *The differences in mean ocular itching scores are considered clinically significant at onset and marginally significant at 8 hours after administration.*

Mean [redacted] Scores (Parallel-Eyes Comparison)				
	Epinastine (N = 127)	Vehicle (N = 125)	Difference[a]	p-Value[b]
[redacted]				

Reviewer's Comments: *The differences in [redacted], are not considered clinically significant at either onset or 8 hours after administration. They did not reach 1 unit of difference.*

Reviewer Study #2: Protocol 003: A Multi-Center, Randomized, Double-Masked, Parallel Group Study Evaluating the Efficacy and Safety of Epinastine Hydrochloride 0.05% Ophthalmic Solution Compared to Vehicle of Epinastine or to Levocabastine 0.05% Ophthalmic Suspension Used Twice Daily for 8 Weeks in an Environmental Study in Adult and Pediatric Patients with Seasonal Allergic Conjunctivitis

Study Design/Plan

This was a multicenter, randomized, double-masked, vehicle- and active-controlled, parallel group, refined (CAC screen) environmental study in adult and pediatric patients with seasonal allergic conjunctivitis. Patients at least 9 years old with a known history of seasonal allergic conjunctivitis who manifested a positive CAC response at screening were enrolled. Patients were randomly assigned to receive epinastine HCl 0.05% ophthalmic solution (epinastine), levocabastine 0.05% ophthalmic suspension (levocabastine), or the vehicle of epinastine (vehicle) in a 2:2:1 ratio. Treatment was administered as 1 drop into each eye BID for 56 days (8 weeks).

Patient self-assessments of ocular itching [redacted] were collected 3 times daily in a take-home diary. Patients were asked to evaluate their symptoms in the morning prior to instillation of the eye drops, in the afternoon before the second instillation, and at bedtime at least 2 hours after the second instillation. The third evaluation was used for the assessment of evening ocular itching [redacted]. For each patient, the worst daily ocular itching [redacted] scores for analysis were taken from the highest of 6 scores (3 evaluations for each eye) recorded by the patient each day. The worst evening ocular itching and [redacted] scores for analysis were taken from the highest of 2 scores (one for each eye) recorded by the patient each evening. These scores were averaged over the 2-week period of peak pollen count for each patient for most analyses, and over the 2-week period of peak ocular itching for a supplemental analysis. Itching was evaluated both in the diary and at study visits using the following scale (allowing 0.5-grade increments):

Absent (0)	
Mild (1):	An intermittent tickle sensation involving more than just the corner of the eye.
Moderate (2):	A continuous itch (can be localized) without desire to rub.
Severe (3):	A severe itch with desire to rub.
Extremely severe (4):	Incapacitating itch with an irresistible urge to rub.

[redacted]

The investigator evaluated hyperemia, chemosis, and ocular mucous discharge with slit lamp at each study visit [redacted] was evaluated using the following scale, [redacted]

Pollen Counts

Daily grass pollen counts throughout the study were obtained from independent pollen counting stations near each study center. A list of the pollen stations by center and the pollen data were provided.

Schedule of Assessments	Screening	Randomization	Treatment			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Days –42 to -7	Day 0	Day 14	Day 28	Day 42	Day 56
Medical and ophthalmic history/update	X	X				
Urine pregnancy test	X	X	X[d]	X[d]	X[d]	X
Visual acuity	X	X	X	X	X	X
Biomicroscopy	X	X	X	X	X	X
Conjunctival antigen challenge	X					
Evaluation of hyperemia[b]	X	X	X	X	X	X
Evaluation of chemosis[b]	X	X	X	X	X	X
Evaluation of ocular mucous discharge[b]	X	X	X	X	X	X
Visit day tearing[c]	X	X	X	X	X	X
Visit day itching[c]	X	X	X	X	X	X
Visit day lid swelling[c]	X	X	X	X	X	X
Randomization		X				
Study drug dispensing		X	X	X	X	
Collection of returned study drug			X	X	X	X
Issue diary card		X	X	X	X	
Compliance review			X	X	X	X
Assessment of AEs		X	X	X	X	X
Assessment of concomitant medications	X	X	X	X	X	X
Eye Allergy Pt Assessment Questionnaire	X	X		X		X
Mini-Rhinoconjunctivitis QOL Questionnaire	X	X	X	X	X	X

All visits were to have a window of ±5 days to the extent possible.
[b] Investigator assessment at each study visit.
[c] Patient assessment at each study visit.
[d] Only for premenarchal patients who experienced onset of menses after day 0 (visit 2).

Principal Investigator Name (Number), Address	Subinvestigators Name, Degree
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Reviewer's Comments: *Henry Jerome Crampton is also an investigator in Protocol 001, reviewed as Study #1 in this review.*

	Epinastine	Levocabastine	Vehicle	
	(N=118)	(N=118)	(N=62)	P-value
Age (years)				
N	118	118	62	0.622
Mean	33.6	32.5	31.5	
SD	15.29	13.55	15.18	
Median	33.5	33.0	30.0	
Min	9	9	11	
Max	71	66	71	
<= 17 years	21 (17.8%)	20 (16.9%)	13 (21.0%)	
18-64 years	92 (78.0%)	97 (82.2%)	47 (75.8%)	
>= 65 years	5 (4.2%)	1 (0.8%)	2 (3.2%)	
Sex				
N	118	118	62	0.700
Male	57 (48.3%)	56 (47.5%)	26 (41.9%)	
Female	61 (51.7%)	62 (52.5%)	36 (58.1%)	
Race				
N	118	118	62	
Caucasian	51 (43.2%)	52 (44.1%)	28 (45.2%)	
Black	4 (3.4%)	6 (5.1%)	1 (1.6%)	
Asian	57 (48.3%)	53 (44.9%)	28 (45.2%)	
Hispanic	2 (1.7%)	4 (3.4%)	5 (8.1%)	
Other	4 (3.4%)	3 (2.5%)	0 (0.0%)	
Iris Color				
N	118	118	62	
Blue	18 (15.3%)	21 (17.8%)	16 (25.8%)	
Brown	75 (63.6%)	81 (68.6%)	38 (61.3%)	
Green	10 (8.5%)	4 (3.4%)	1 (1.6%)	
Hazel	13 (11.0%)	11 (9.3%)	7 (11.3%)	
Other	2 (1.7%)	1 (0.8%)	0 (0.0%)	
Dark	75 (63.6%)	81 (68.6%)	38 (61.3%)	0.557
Light	43 (36.4%)	37 (31.4%)	24 (38.7%)	

Reviewer's Comments: *There are no imbalances between groups.*

Summary Statistics of Average Worst Daily Ocular Itching Score Based on 2-Week Peak Pollen Count (Nonparametric Analysis) (Intent-to-Treat Population)

	Epinastine (N=118)	Levocabastine (N=118)	Vehicle (N=62)	Epinastine vs. Vehicle p-value, Median Shift, (CI) [a,b]	Levocabastine vs. Vehicle p-value, Median Shift, (CI) [a,b]	Epinastine vs. Levocabastine p-value, Median Shift, (CI) [a,b]
N	118	118	62	0.045	0.27	0.36
Mean	0.77	0.86	0.93	-0.20	-0.10	0.00
SD	0.856	0.860	0.760	(-0.4,0.0)	(-0.3, 0.1)	(-0.2, 0.1)
Median	0.45	0.60	0.85			
Min	[redacted]					
Max						

Summary Statistics of Average Worst Daily [redacted] Score Based on 2-Week Peak Pollen Count (Nonparametric Analysis) (Intent-to-Treat Population)

	Epinastine (N=118)	Levocabastine (N=118)	Vehicle (N=62)	Epinastine vs. Vehicle p-value, Median Shift, (CI) [a,b]	Levocabastine vs. Vehicle p-value, Median Shift, (CI) [a,b]	Epinastine vs. Levocabastine p-value, Median Shift, (CI) [a,b]
N	118	118	62	0.126	0.327	0.524
Mean	[redacted]					
SD						
Median						
Min						
Max						

Note: The difference of treatment A versus treatment B is calculated as treatment A minus treatment B. Thus, a positive difference between the groups indicates a higher severity for treatment A. Itching scored using the following scale: 0=absent/ 1=mild/ 2=moderate/ 3=severe/ 4=extremely severe. Half-grade increments were allowed. [redacted] scored using the following scale: [redacted]

[a] P-values are based on the Wilcoxon rank-sum test. The median shift is based on the differences of the individual scores of treatment A minus treatment B. Note: The median shift is not the difference in median scores.
[b] The 95% confidence interval of the median shift (Hodges-Lehmann estimate). The CIs are based on large sample approximation.

Reviewer's Comments: *The results reported in the tables above are dependent on the type of analysis performed. They are marginally statistically significant for itching and* [redacted] *If p-values are taken from pairwise contrasts from the two-way ANOVA model (including the factors of treatment, investigator, treatment by-investigator interaction) then the itching differences are not statistically significant.*

Reviewer Study #3: Protocol 214.7: Placebo-controlled multicenter double-blind trial for 2 weeks to investigate the efficacy and tolerability of WAL 801 Cl (0.05%) eye drops in acute allergic conjunctivitis

This was a double-blind, placebo-controlled, randomized, parallel group comparison. One hundred and thirty nine patients with confirmed allergic conjunctivitis caused by grass pollen were screened to be included in the trial. After enrolment the patients received at random either epinastine eye drops or placebo, and administered the medication twice daily for 14 days, one drop into each eye The trial was performed between February 1996 and May 1996 in 10 centers.

One drop with an estimated volume of about 30 µl was instilled into each eye twice daily for 14 days. The eye drops were administered in the morning and in the evening independent of meals.

Schedule of Assessments

Assessment	Visit 1	Visit 2	Visit 3
	Day 0	Day 7±2	Day 14±2
Informed consent	X		
Inclusion criteria	X		
Exclusion criteria	X		
Clinical history	X		
RAST	X		
Prick Test	X		
Examination of lid and conjunctiva	X	X	X
Adverse event		X	X
Assessment of global efficacy			X
Assessment of global tolerability			X

Primary endpoint

The final assessment of global efficacy by the investigator is the primary efficacy parameter. The final assessment of global effectiveness was graded as:

Excellent=0
Good=1
Moderate=2
Poor=3
Very poor=4

Secondary endpoints

The subjective symptoms itching, tearing, foreign body sensation, photophobia and erythema were recorded daily in a diary. The responses of the patients with regard to above mentioned ocular symptoms were scored and documented as follows:

Absent=0
Mild=1
Moderate=2
Severe=3
Very severe=4

Edema and hyperemia (erythema) of the conjunctiva bulbi and tarsi were also assessed and documented as below:

Absent=0
Mild=1
Moderate=2
Severe=3
Very severe=4

Centre Number	Investigator	Address	Area
001			Milnerton
002			Delmas/ Ermelo
003			Milnerton
004			Pretoria/Brits
005			Milnerton
006			Pretoria/Brits
007			Pretoria/Brits
008			Pretoria/Brits
009			Pletoria/Brits
010			Pretoria/Brits
011			PretoriaBrits

* No patients recruited at this centre

Characteristic	Statistic	Placebo	Epinastine
Gender	Total (n)	64 (100%)	68 (100%)
	Male	31 (48%)	33 (49%)
	Female	33 (52%)	35 (51%)
Age (years) Males	*N*	31	33
	Mean	34.3	31.4
	Range	18.0-61.0	18.0-61.0
Age (years) Females	*N*	33	35
	Mean	39.6	37.5
	Range	18.0-66.0	20.0-62.0
Color of Iris	Brown	23 (36%)	29 (43%)
	Blue	25 (39%)	24 (35%)
	Green	16 (25%)	15 (22%)

Reviewer's Comments: *The groups are equally balanced.*

Overall Symptoms	Placebo	Epinastine
	(n = 64)	(n = 68)
Excellent (Free / almost free of symptoms)	15 (23%)	22 (32%)
Good (Definite improvement)	13 (20%)	21 (31%)
Moderate (moderate improvement)	10 (16%)	19 (28%)
Poor (Frequent symptoms)	12 (19%)	3 (4%)
Very Poor (No effect)	13 (20%)	3 (4%)
Missing	1 (2%)	-

Reviewer's Comments: *The Epinastine group was statistically superior to the placebo group in overall symptom score.*

Days with an absent or mild score - Intent to Treat

	Placebo (n = 64)	Epinastine (n = 68)	Difference ("Epinastine-Placebo")*	95% CI** for difference	p-values
Itching (days)	68%	83%	7%	0% to 25%	<0.01
Tearing (days)	86%	92%	0%	0% to 8%	0.21
Foreign Body Sensation (days)	69%	92%	8%	0% to 26%	<0.01
Photophobia (days)	61%	76%	0%	0% to 18%	0.24
Median Sum Score	6.1	4.9	-1.4	-2.7 to -0.2	<0.05

*: Non-parametric point estimate (median difference)
**: Non-parametric confidence interval for median difference

Days with an absent or mild score - Per-Protocol

	Placebo (n = 52)	Epinastine (n = 56)	Difference ("Epinastine-Placebo")*	95% CI** for difference	p-values
Itching (days)	69%	83%	8%	0% to 29%	<0.01
Tearing (days)	92%	92%	0%	-1 to 7%	0.38
Foreign Body Sensation (days)	71%	92%	8%	0% to 23%	0.02
Photophobia (days)	77%	79%	0%	-8% to 8%	0.63
Median Sum Score	6.2	4.9	-1.3	-2.8 to 0.0	<0.05

*: Non-parametric point estimate (median difference)
**: Non-parametric confidence interval for median difference

Reviewer's Comments: *The epinastine group is statistically superior to the placebo group with respect to itching. With respect to*

Reviewer Study #4: Protocol 214.10: Double-blind, randomized, active-controlled clinical trial to investigate the safety of epinastine eye drops (0.05%) bid in patients with seasonal allergic conjunctivitis over a 6-week period in comparison to levocabastine eye drops

Assessment	**Initiation visit**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
	Day 0	Day 7±2	Day 14±2	Day 28±4	Day 42±4
Informed consent	X				
Inclusion criteria	X				
Exclusion criteria	X				
Demographics	X				
Medical history	X				
Prick test	X				
Randomization	X				
Distribution of eye drops	X	X	X	X	
Examination of lid and conjunctiva	X	X	X	X	X
Assessment of global tolerability		X	X	X	
Assessment of ocular symptoms	X	X	X	X	X
Assessment of side effects	X	X	X	X	X
Compliance		X	X	X	X
Adverse events		X	X	X	X
Concomitant therapy	X	X	X	X	X
Assessment of overall tolerability					X
Assessment of overall efficacy					X

Scoring

Overall efficacy was assessed after 6 weeks of treatment (visit 5) (or at study termination) by both patient and investigator by means of a 4-point rating scale: 0=excellent/very good; 1=good, 2=moderate; 3=poor. Score for itching: 0=absent, 1=mild, 2=moderate, 3=severe.

CLINICAL REVIEW

Clinical Review Section

Centre	Investigator	Centre	No of Patients
01	[redacted]		95
02			Counted in Centre 01
03			0
04			0
05			7
06			11
07			2
08			No drugs assigned
09			No drugs assigned
10			5
11			85
12			0
13			36
14			6
15			0
16			1
17			6
18			0
19			0
20			1
21			0
22			2
23			Did not participate

			Levocabastine 0.05%	Epinastine 0.05%
Safety Population Age (years)	Male	Mean	35.5	33.9
		Range	18-61	18-56
		N	38	69
	Female	Mean	37.6	35.8
		Range	18-56	18-64
		N	49	101
ITT Population Age (years)	Male	Mean	359	338
		Range	18-61	18-56
		N	37	68
	Female	Mean	379	359
		Range	18-56	18-64
		N	48	100

Reviewer's Comments: *The groups are equally matched.*

Assessment of Overall Efficacy of Trial Medication by Patient and Investigator Percentage of Ratings- ITT

	Investigator		Patient	
	Levocabastine	Epinastine	Levocabastine	Epinastine
	N =85 (100%)	N =168 (100%)	N =85 (100%)	N =168 (100%)
Very Good	35%	55%	34%	53%
Good	25%	13%	28%	15%
Moderate	16%	14%	21%	13%
Poor	24%	17%	16%	18%
Missing values	0%	1 %	0%	1%
Mean Score	1.29	0.93	1.18	0.96
P value (chi square)	0.017 favoring Epinastine		0.008 favoring Epinastine	

Reviewer's Comments: *Epinastine was shown to be superior to Levocabastine in overall efficacy score.*

Itching

Day	Itching Score	
	Levocabastine (n=85)	Epinastine (n=168)
0	2.06	2.08
7	1.25	1.04
14	0.94	0.79
28	0.85	0.74
42	0.84	0.60
Average Day 7 – 42	0.97	0.79
Wilcoxon Rank Sum Test	p=0.048	

Reviewer's Comments: *Epinastine was shown to be superior to Levocabastine with respect to itching.*

Reviewer Study #5: Protocol 2: A Multi-Center, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of Epinastine Hydrochloride 0.05% Ophthalmic Solution Used Twice Daily in Normal Pediatric Subjects

This study was a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study of epinastine in pediatric subjects. Approximately 120 subjects 3 to 12 years of age were to be enrolled and randomized in a ratio of 2:1 to treatment with epinastine or vehicle at a regimen of 1 drop into each eye twice daily for 42 days (6 weeks). Visits were on days 0 (baseline), 7, 21, and 42.

Study Plan

Assessment or Procedure	Visit 1 (Baseline) Day 0	Visit 2 Day 7 ±1	Visit 3 Day 21 ±2	Visit 4 Day 42 ±2
Informed consent/ assent	X			
Medical and ophthalmic history	X			
Body weight determination	X			
Physical examination	X			X
Visual acuity[a]	X	X	X	X
Biomicroscopy pre-drug instillation	X	X	X	X
Intraocular pressure[b]	X			X
Ophthalmoscopy[c]	X			X
Instill study medication at office	X	X	X	X
Biomicroscopy post-drug instillation	X	X	X	X
Dispense study medication	X	X	X	
Collect returned study medication		X	X	X
Assessment of adverse events	X[d]	X	X	X
Assessment of concomitant medications	X	X	X	X

a Correction was necessary, best-correct visual acuity was to be determined .
b Measured for subjects ≥9 years old, if possible.
c Dilated if necessary to observe the posterior pole.
d Evaluated 1 hour after first instillation of study medication in the investigator's office

Age Stratum (years)	Number of Subjects Enrolled	
	Epinastine	Vehicle
3	8	5
4	6	4
5	10	3
6 to 9	21	10
10 to 12	19	10

Reported Adverse Events

Body System COSTART Term	**Epinastine (N = 64)**	**Vehicle (N = 32)**	**Between-group p-value***
Infection (Body as a Whole)	12 (18.8%)	5 (15.6%)	0.705
Headache	4 (6.3%)	1 (3.1%)	0.662
Flu syndrome	2 (3.1%)	1 (3.1%)	> 0.999
Fever	2 (3.1%)	0 (0.0%)	0.551
Gastroenteritis	1 (1.6%)	1 (3.1%)	> 0.999
Cough increased	3 (4.7%)	1 (3.1%)	> 0.999
Rhinitis	2 (3.1%)	2 (6.3%)	0.599
Pharyngitis	2 (3.1%)	0 (0.0%)	0.551
Infection	0 (0.0%)	1 (3.1%)	0.333
Skin and Appendages			
Inflammation cutaneous	1 (1.6%)	0 (0.0%)	> 0.999
Urticaria	1 (1.6%)	0 (0.0%)	> 0.999
Conjunctival folliculosis	5 (7.8%)	2 (6.3%)	> 0.999
Conjunctival hyperemia	1 (1.6%)	1 (3.1%)	> 0.999
Otitis media	1 (1.6%)	0 (0.0%)	> 0.999

*Pearson's chi-square test was used for the calculation of the p-value for Infection, all other p-values are reported as calculated by Fisher's exact test.

Reviewer's Comments: *The reported adverse events are consistent with other products in this class.*

Biomicroscopy Findings: Number (Percent) of Subjects with ≥1 Grade Increase in Severity			
	Epinastine	**Vehicle**	
	(N = 64)	**(N = 32)**	**p-value**
Pre-Drug Instillation Increase from Baseline:			
Conjunctiva			
Overall	16 (25.0%)	5 (15.6%)	0.295[a]
Other pathology[c]	15 (23.4%)	4 (12.5%)	0.205[a]
Erythema/hyperemia	5 (7.8%)	2 (6.3%)	> 0.999[b]
Chemosis	0 (0.0%)	1 (3.1%)	0.333[b]
Lid and Lid Margin			
Overall	5 (7.8%)	3 (9.4%)	> 0.999[b]
Other pathology[d]	5 (7.8%)	3 (9.4%)	> 0.999[b]
Erythema	1 (1.6%)	0 (0.0%)	> 0.999[b]
Post-Drug Instillation, Increase from Pre-Drug Instillation:			
Conjunctiva			
Overall	1 (1.6%)	0 (0.0%)	> 0.999[b]
Other pathology (papillae)	1 (1.6%)	0 (0.0%)	> 0.999[b]
Lid and Lid Margin			
Overall	2 (3.1%)	0 (0.0%)	> 0.551[b]
Other pathology (meibomian secretion)	2 (3.1%)	0 (0.0%)	> 0.551[b]

a Pearson's chi-square test.
b Fisher's exact test.
c Described as follicles for 14.1% (9/64) of epinastine-treated subjects and 9.4% (3/32) of vehicle-treated subjects and as papillae for 10.9% (7/64) of epinastine-treated subjects and 3.1% (1/32) of vehicle-treated subjects.
d Described as meibomian secretion in all cases, with posterior blepharitis also reported for one subject.

Reviewer's Comments: *The reported adverse events are consistent with other products in this class.*

D. Efficacy Conclusions

The agency considers effectiveness for itching critical for support of an application for the prevention

The signs and symptoms of allergic conjunctivitis resolve spontaneously in minutes if there is no ongoing contact with an allergen. Treatment involves preventing ongoing allergen contact and therefore the terms prevention and treatment are effectively the same for this indication. Three different types of studies are considered acceptable. These types of studies include the allergen challenge model, the allergen room model and environmental studies. The agency has reviewed well over 100 studies for drug products seeking an indication of allergic conjunctivitis. Historically, most environmental studies evaluating effectiveness of a drug product for allergic conjunctivitis fail to demonstrate a statistically significant difference compared to vehicle. As a result of this phenomenon the agency does not accept equivalence to any other product as sufficient evidence of equivalence. When conducting antigen challenge studies, a change of one unit or more compared to vehicle is considered clinically significant. The submitted NDA includes studies using all three models. Two of these models demonstrated effectiveness for itching Clinically significant effectiveness for itching was demonstrated in the antigen challenge model in study 1 above. Evidence of effectiveness for itching is also demonstrated in the environmental studies 2, 3 and 4 above. Evidence of either superiority or inferiority compared to other approved new drug products for this indication was not reproducibly demonstrated.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The drug product has been adequately studied. The observed adverse events were generally self limited and consistent with other products in this class.

B. Description of Patient Exposure

Study ID	Treatment Duration	Epinastine HCl				Levocabastine	Vehicle
		0.5%	0.3%	0.1%	0.05%		
Studies in Patients and Subjects with 8 Days or Less Treatment Duration (N = 223)[b]							
001	2 doses	--	--	--	epi/epi 30 epi/veh 67[a]	--	veh/veh 29 epi/veh 67[a]
214.3	4 doses[b]	[redacted]			23[c]	--	23[c]
214.5	4 doses	[redacted]			--	24[c]	23[c]
214.8	4 doses	--	--	--	23[c]	24[c]	24[c]
214.1	single dose	3	3	3	--	--	3
004	8 days	--	--	--	14	--	--
Studies in Patients with 2 Weeks Treatment Duration (N = 458)							
214.4	14 days BID	[redacted]			--	--	70
214.6	14 days BID	--	--	--	89	--	93
214.7	14 days BID	--	--	--	69	--	65
Study in Healthy Subjects with 21 Days Treatment Duration (N = 17)[d]							
214.2	21 days[d]	--	17[a]	--	--	--	17[a]
Studies in Healthy Subjects with 6 Weeks Treatment Duration (N = 276)							
002	42 days BID	--	--	--	64	--	32
005	42 days BID	--	--	--	120	--	60
Studies in Patients with at Least 6 Weeks (42 or 56 Days) Treatment Duration (N = 639)							
003	56 days BID	--	--	--	118	118	62
214.10	42 days BID	--	--	--	170	87	--
214.11	42 days BID	--	--	--	42	--	42
TOTAL		3	115	49	829	253	610

[a] Participants who received epinastine in 1 eye and vehicle in contralateral eye are counted in each group.
[b] One patient discontinued before the first study period and is not counted in this table.
[c] Patients who received multiple treatments in crossover design study are counted in each group.
[d] Two subjects did not receive study medication and are not counted in this table.

C. Methods and Specific Findings of Safety Review

All submitted adequate and well controlled studies were reviewed.

D. Adequacy of Safety Testing

The submitted studies included studies of adequate duration (6 weeks or longer) to assess the safety and efficacy of the drug product. The evaluation methods were appropriate for the drug product and the indication.

E. Summary of Critical Safety Findings and Limitations of Data

Ocular Adverse Events Reported by more than 2 patients or subjects in any treatment group with at least 2 weeks treatment duration

Population, Duration	Epinastine HCl	Epinastine HCl	Levocabastine	
Adverse Event	0.3% TID	0.05% BID	BID	Vehicle
Patients, 2 Weeks[a]				
Burning sensation in the eye	17/72 (23.6%)	12/158 (7.6%)		21/228 (9.2%)
Conjunctival hyperemia	3/72 (4.2%)	1/158 (0.6%)		0/228 (0.0%)
Eye dryness	4/72 (5.6%)	1/158 (0.6%)		1/228 (0.4%)
Headache	5/72 (6.9%)	5/158 (3.2%)		9/228 (3.9%)
Nausea	3/72 (4.2%)	0/158 (0.0%)		1/228 (0.4%)
Cough increased	2/72 (2.8%)	1/158 (0.6%)		3/228 (1.3%)
Pharyngitis	3/72 (4.2%)	1/158 (0.6%)		2/228 (0.9%)
Pruritus	5/72 (6.9%)	0/158 (0.0%)		2/228 (0.9%)
Taste perversion	16/72 (22.2%)	1/158 (0.6%)		2/228 (0.9%)
Subjects, 6 Weeks[b]				
Conjunctival folliculosis		5/184 (2.7%)		2/92 (2.2%)
Stinging sensation eye		1/184 (0.5%)		3/92 (3.3%)
Infection		18/184 (9.8%)		10/92 (10.9%)
Headache		6/184 (3.3%)		1/92 (1.1%)
Cough increased		3/184 (1.6%)		1/92 (1.1%)
Pharyngitis		3/184 (1.6%)		1/92 (1.1%)
Rhinitis		2/184 (1.1%)		3/92 (3.3%)
Patients, ≥6 Weeks[c]				
Burning sensation in the eye		10/330 (3.0%)	1/205 (0.5%)	0/104 (0.0%)
Conjunctival hyperemia		3/330 (0.9%)	1/205 (0.5%)	0/104 (0.0%)
Eye pruritus		3/330 (0.9%)	1/205 (0.5%)	3/104 (2.9%)
Foreign body sensation		1/330 (0.3%)	0/205 (0.0%)	3/104 (2.9%)
Infection		15/330 (4.5%)	9/205 (4.4%)	4/104 (3.8%)

Population, Duration	Epinastine HCl	Epinastine HCl	Levocabastine	
Adverse Event	0.3% TID	0.05% BID	BID	Vehicle
Headache		11/330 (3.3%)	5/205 (2.4%)	0/104 (0.0%)
Accidental injury		1/330 (0.3%)	5/205 (2.4%)	1/104 (1.0%)
Rhinitis		8/330 (2.4%)	3/205 (1.5%)	0/104 (0.0%)
Sinusitis		4/330 (1.2%)	1/205 (0.5%)	0/104 (0.0%)
Asthma		3/330 (0.9%)	0/205 (0.0%)	1/104 (1.0%)
Irritation nasal		1/330 (0.3%)	3/205 (1.5%)	0/104 (0.0%)
Pharyngitis		1/330 (0.3%)	5/205 (2.4%)	0/104 (0.0%)
Patients or Subjects, ≥6 Weeks with Biomicroscopy[d]				
Burning sensation in the eye		9/344 (2.6%)	0/118 (0%)	0/196 (0%)
Conjunctival folliculosis		5/344 (1.5%)	0/118 (0%)	2/196 (1.0%)
Conjunctival hyperemia		3/344 (0.9%)	0/118 (0%)	2/196 (1.0%)
Eye pruritus		3/344 (0.9%)	0/118 (0%)	5/196 (2.6%)
Stinging sensation eye		2/344 (0.6%)	1/118 (0.8%)	4/196 (2.0%)
Foreign body sensation		1/344 (0.3%)	0/118 (0%)	4/196 (2.0%)
Infection		26/344 (7.6%)	7/118 (5.9%)	14/196 (7.1%)
Headache		8/344 (2.3%)	4/118 (3.4%)	1/196 (7.1%)
Accidental injury		1/344 (0.3%)	3/118 (2.5%)	2/196 (1.0%)
Rhinitis		4/344 (1.2%)	0/118 (0%)	3/196 (1.5%)
Cough increased		3/344 (0.9%)	0/118 (0%)	2/196 (1.0%)
Pharyngitis		3/344 (0.9%)	1/118 (0.8%)	1/196 (0.5%)

BID = 2 times daily, TID = 3 times daily

a Studies 214.4, 214.6, and 214.7

b Studies 002 and 005

c Studies 003, 214.10, and 214.11

d Studies 002, 003, 005, and 214.11

Reviewer's Comments: *The specific adverse events are reported above. The events were generally self limited in scope and duration. The events are consistent with other products in this class.*

VIII. Dosing, Regimen, and Administration Issues

The drug product is administered topically to the affected eye. Concentrations as high as 10 times the proposed concentration have been studied. The selected concentration appears appropriate for this indication because there is an increased incidence of burning/irritation with higher concentrations. There are no unresolved issues related to dosing.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Comparison of safety and efficacy was evaluated in all studies with respect to gender. There are no significant differences with respect to gender for safety or efficacy.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Comparison of safety and efficacy was evaluated with respect to age, race, ethnicity and iris color. There are no significant differences with respect to age, race, ethnicity or iris color for safety or efficacy.

C. Evaluation of Pediatric Program

The agency did not issue a written request to study the pediatric population because there are already a number of ophthalmic drug products approved for this indication. Consistent with other products in this class, clinical studies included pediatric patients to the extent possible (evaluation of itching requires subjective evaluation generally limited to patients 10 years of age and older). Additional safety information was collected in pediatric patients down to 3 years of age (lower limit of the age of patients with the disease). There were no differences in safety or efficacy between pediatric and older patients.

D. Comments on Data Available or Needed in Other Populations

There is no reason to believe that additional information is needed from other populations.

X. Conclusions and Recommendations

A. Conclusions

The clinical studies support that the benefit outweighs the risk in using this drug product in the treatment of itching associated with allergic conjunctivitis. The studies do not support [redacted] *associated with allergic conjunctivitis. There are no unresolved scientific or regulatory issues.*

B. Recommendations

Clinical studies have demonstrated that the benefits of using this drug product outweigh the risks for the indication of treatment of ocular itching associated with allergic conjunctivitis. The labeling as originally proposed contains sections which are not supported by the application. NDA 21-565 is recommended to be approved from a clinical prospective for the prevention of ocular itching associated with allergic conjunctivitis after labeling revisions are made consistent with the recommendations listed in this review.

XI. Appendix

A. Original Proposed Labeling

[redacted]

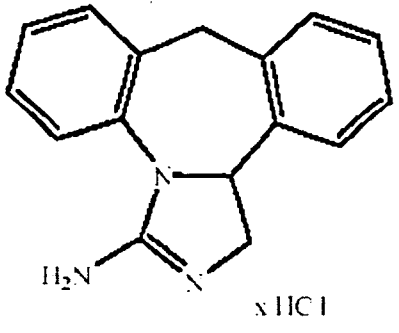
6 Draft Labeling Page(s) Withheld

B. Revised Labeling from Applicant:

ELESTAT™
(epinastine HCl ophthalmic solution) 0.05%

Sterile
DESCRIPTION
ELESTAT™ (epinastine HCl ophthalmic solution) 0.05% is a clear, colorless, sterile isotonic solution containing epinastine HCl, an antihistamine and an inhibitor of histamine release from the mast cell for topical administration to the eyes.

Epinastine HCl is represented by the following structural formula:



$C_{16}H_{15}N_3 \cdot HCl$ Mol. Wt. 285.78

Chemical Name: 3-Amino-9, 13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride
Each mL contains: Active: Epinastine HCl 0.05% (0.5 mg/mL) equivalent to epinastine 0.044% (0.44mg/mL); **Preservative:** Benzalkonium chloride 0.01%; **Inactives:** Edetate disodium; purified water; sodium chloride; sodium phosphate, monobasic; and sodium hydroxide and/or hydrochloric acid (to adjust the pH). ELESTAT™ has a pH of approximately 7 and an osmolality range of 250 to 310 mOsm/kg.

CLINICAL PHARMACOLOGY
Epinastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from the mast cell. Epinastine is selective for the histamine H_1-receptor and has affinity for the histamine H_2 receptor. Epinastine also possesses affinity for the α_1-, α_2-, and 5-HT_2 –receptors. Epinastine does not penetrate the blood/brain barrier and, therefore, is not expected to induce side effects of the central nervous system.

Fourteen subjects, with allergic conjunctivitis, received one drop of ELESTAT™ in each eye twice daily for seven days. On day seven, average maximum epinastine plasma concentrations of 0.04 ± 0.014 ng/ml were reached after about two hours indicating low systemic exposure. While these concentrations represented an increase over those seen following a single dose, the

day 1 and day 7 Area Under the Curve (AUC) values were unchanged indicating that there is no increase in systemic absorption with multiple dosing. Epinastine is 64% bound to plasma proteins. The total systemic clearance is approximately 56 L/hr and the terminal plasma elimination half-life is about 12 hours. Epinastine is mainly excreted unchanged. About 55% of an intravenous dose is recovered unchanged in the urine with about 30% in feces. Less than 10% is metabolized. The renal elimination is mainly via active tubular secretion.

Clinical studies: Epinastine HCl 0.05% has been shown to be significantly superior to vehicle for improving ocular itching in patients with allergic conjunctivitis in clinical studies using two different models: (1) conjunctival antigen challenge (CAC) where patients were dosed and then received antigen instilled into the inferior conjunctival fornix; and (2) environmental field studies where patients were dosed and evaluated during allergy season in their natural habitat. Results demonstrated a rapid onset of action for epinastine HCl 0.05% within 3 to 5 minutes after conjunctival antigen challenge. Duration of effect was shown to be 8 hours, making a twice daily regimen suitable. This dosing regimen was shown to be safe and effective for up to 8 weeks, without evidence of tachyphylaxis.

INDICATIONS AND USAGE
ELESTAT™ ophthalmic solution is indicated for the prevention of the itching associated with allergic conjunctivitis.

CONTRAINDICATIONS
ELESTAT™ ophthalmic solution is contraindicated in those patients who have shown hypersensitivity to epinastine or to any of the other ingredients.

WARNINGS
ELESTAT™ is for topical ophthalmic use only and not for injection or oral use.

PRECAUTIONS
Information for Patients: Patients should be advised not to wear a contact lens if their eye is red. ELESTAT™ should not be used to treat contact lens related irritation. The preservative in ELESTAT™, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of ELESTAT™ and may be reinserted after 10 minutes following its administration.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Bottle should be kept tightly closed when not in use.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
In 18-month or 2-year dietary carcinogenicity studies in mice or rats, respectively, epinastine was not carcinogenic at doses up to 40 mg/kg [approximately 30,000

times higher than the maximum recommended ocular human dose of 0.0014 mg/kg/day (MROHD) on a mg/kg basis, assuming 100% absorption in humans and animals].

Epinastine in newly synthesized batches was negative for mutagenicity in the Ames/*Salmonella* assay and *in vitro* chromosome aberration assay using human lymphocytes. Positive results were seen with early batches of epinastine in two *in vitro* chromosomal aberration studies conducted in 1980s with human peripheral lymphocytes and with V79 cells, respectively. Epinastine was negative in the *in vivo* clastogenicity studies, including the mouse micronucleus assay and chromosome aberration assay in Chinese hamsters. Epinastine was also negative in the cell transformation assay using Syrian hamster embryo cells, V79/HGPRT mammalian cell point mutation assay, and *in vivo/in vitro* unscheduled DNA synthesis assay using rat primary hepatocytes.

Epinastine had no effect on fertility of male rats. Decreased fertility in female rats was observed at an oral dose up to approximately 90,000 times the MROHD.

Pregnancy: Teratogenic Effects: Pregnancy Category C
In an embryofetal developmental study in pregnant rats, maternal toxicity with no embryofetal effects was observed at an oral dose that was approximately 150,000 times the MROHD. Total resorptions and abortion were observed in an embryofetal study in pregnant rabbits at an oral dose that was approximately 55,000 times the MROHD. In both studies, no drug-induced teratogenic effects were noted.

Epinastine had no effect on pup growth or behavior following an oral dose to pregnant or lactating rats that was approximately 90,000 times the MROHD.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ELESTAT™ ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: A study in lactating rats revealed excretion of epinastine in the breast milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ELESTAT™ ophthalmic solution is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
The most frequently reported ocular adverse events occurring in approximately 1 – 10%

of patients were burning sensation in the eye, folliculosis, hyperemia, and pruritus.

The most frequently reported non-ocular adverse events were infection (cold symptoms and upper respiratory infections) seen in approximately 10% of patients, and headache, rhinitis, sinusitis, increased cough, and pharyngitis seen in approximately 1 - 3% of patients.

Some of these events were similar to the underlying disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in each eye twice a day.

Treatment should be continued throughout the period of exposure (i.e., until the pollen season is over or until exposure to the offending allergen is terminated) even when symptoms are absent.

HOW SUPPLIED

ELESTAT™ (epinastine HCl ophthalmic solution) 0.05% is supplied sterile in opaque white LDPE plastic bottles with dropper tips and white high impact polystyrene (HIPS) caps as follows:

5 mL in 8 mL bottle NDC XXXX-XXXX-XX
10 mL in 15 mL bottle NDC XXXX-XXXX-XX

Storage: Store at 15-25°C (59-77°F). Keep bottle tightly closed and out of the reach of children.

Rx Only

October 2003

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wiley Chambers
10/6/03 11:02:39 AM
MEDICAL OFFICER

William Boyd
10/8/03 07:52:37 AM
MEDICAL OFFICER

Original Application Amendment

Review #2

Submitted: April 18, and October 10, 2003
Review completed: October 14, 2003
Reviewer: Wiley A. Chambers, MD

Proposed Name: ELESTAT (epinastine HCl ophthalmic solution) 0.05%

Submitted: Safety Update

No new safety information that would reasonably affect the statements of contraindications, warnings, precautions or adverse reaction sections.

Reviewer's Comments: *Concur.*

Submitted revised labeling from applicant:

ELESTAT™
(epinastine HCl ophthalmic solution) 0.05%

Sterile

DESCRIPTION

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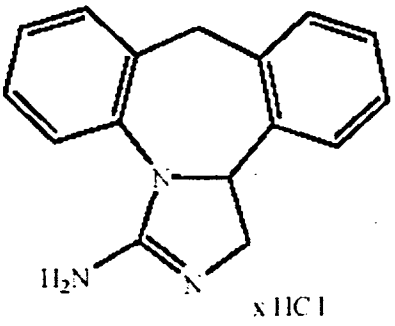
Epinastine HCl is represented by the following structural formula:



$C_{16}H_{15}N_3 \cdot HCl$ Mol. Wt. 285.78

Chemical Name: 3-Amino-9, 13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride

Each mL contains: Active: Epinastine HCl 0.05% (0.5 mg/mL) equivalent to epinastine 0.044% (0.44mg/mL); **Preservative:** Benzalkonium chloride 0.01%; **Inactives:** Edetate disodium; purified water; sodium chloride; sodium phosphate, monobasic; and sodium hydroxide and/or hydrochloric acid (to adjust the pH). ELESTAT™ has a pH of approximately 7 and an osmolality range of 250 to 310 mOsm/kg.

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Clinical studies: Epinastine HCl 0.05% has been shown to be significantly superior to vehicle for improving ocular itching in patients with allergic conjunctivitis in clinical studies using two different models: (1) conjunctival antigen challenge (CAC) where patients were dosed and then received antigen instilled into the inferior conjunctival fornix; and (2) environmental field studies where patients were dosed and evaluated during allergy season in their natural habitat. Results demonstrated a rapid onset of action for epinastine HCl 0.05% within 3 to 5 minutes after conjunctival antigen challenge. Duration of effect was shown to be 8 hours, making a twice daily regimen suitable. This dosing regimen was shown to be safe and effective for up to 8 weeks, without evidence of tachyphylaxis.

INDICATIONS AND USAGE

ELESTAT™ ophthalmic solution is indicated for the prevention of itching associated with allergic conjunctivitis.

CONTRAINDICATIONS

ELESTAT™ ophthalmic solution is contraindicated in those patients who have shown hypersensitivity to epinastine or to any of the other ingredients.

WARNINGS

ELESTAT™ is for topical ophthalmic use only and not for injection or oral use.

PRECAUTIONS

Information for Patients: Patients should be advised not to wear a contact lens if their eye is red. ELESTAT™ should not be used to treat contact lens related irritation. The preservative in ELESTAT™, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of ELESTAT™ and may be reinserted after 10 minutes following its administration.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Bottle should be kept tightly closed when not in use.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
In 18-month or 2-year dietary carcinogenicity studies in mice or rats, respectively, epinastine was not carcinogenic at doses up to 40 mg/kg [approximately 30,000 times higher than the maximum recommended ocular human dose of 0.0014 mg/kg/day (MROHD) on a mg/kg basis, assuming 100% absorption in humans and animals].

Epinastine in newly synthesized batches was negative for mutagenicity in the Ames/*Salmonella* assay and *in vitro* chromosome aberration assay using human lymphocytes. Positive results were seen with early batches of epinastine in two *in vitro* chromosomal aberration studies conducted in 1980s with human peripheral lymphocytes and with V79 cells, respectively. Epinastine was negative in the *in vivo* clastogenicity studies, including the mouse micronucleus assay and chromosome aberration assay in Chinese hamsters. Epinastine was also negative in the cell transformation assay using Syrian hamster embryo cells, V79/HGPRT mammalian cell point mutation assay, and *in vivo/in vitro* unscheduled DNA synthesis assay using rat primary hepatocytes.

Epinastine had no effect on fertility of male rats. Decreased fertility in female rats was observed at an oral dose up to approximately 90,000 times the MROHD.

Pregnancy: Teratogenic Effects: Pregnancy Category C
In an embryofetal developmental study in pregnant rats, maternal toxicity with no embryofetal effects was observed at an oral dose that was approximately 150,000 times the MROHD. Total resorptions and abortion were observed in an embryofetal study in pregnant rabbits at an oral dose that was approximately 55,000 times the MROHD. In both studies, no drug-induced teratogenic effects were noted.

Epinastine reduced pup body weight gain following an oral dose to pregnant rats that was approximately 90,000 times the MROHD.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response,

ELESTAT™ ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: A study in lactating rats revealed excretion of epinastine in the breast milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ELESTAT™ ophthalmic solution is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequently reported ocular adverse events occurring in approximately 1 – 10% of patients were burning sensation in the eye, folliculosis, hyperemia, and pruritus.

The most frequently reported non-ocular adverse events were infection (cold symptoms and upper respiratory infections) seen in approximately 10% of patients, and headache, rhinitis, sinusitis, increased cough, and pharyngitis seen in approximately 1 - 3% of patients.

Some of these events were similar to the underlying disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in each eye twice a day.

Treatment should be continued throughout the period of exposure (i.e., until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent.

HOW SUPPLIED

ELESTAT™ (epinastine HCl ophthalmic solution) 0.05% is supplied sterile in opaque white LDPE plastic bottles with dropper tips and white high impact polystyrene (HIPS) caps as follows:

5 mL in 8 mL bottle NDC XXXX-XXXX-XX
10 mL in 15 mL bottle NDC XXXX-XXXX-XX

Storage: Store at 15-25°C (59-77°F). Keep bottle tightly closed and out of the reach of children.

Rx Only

October 2003

Recommendation:

The labeling as submitted is acceptable. NDA 21-565, Elestat (epinastine HCl ophthalmic solution) 0.05% is recommended for approval for the prevention of itching associated with allergic conjunctivitis.

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/s/

Wiley Chambers
10/14/03 09:49:32 AM
MEDICAL OFFICER

William Boyd
10/14/03 09:55:34 AM
MEDICAL OFFICER