CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20706

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-706
Original and Safety Update

NDA # 20-706

Submission:	3/26/96
Safety Update:	7/22/96
Review Completed:	8/30/96

Drug name:	Emadine
Generic name:	Emedastine difumarate ophthalmic solution, (0.05%)
Proposed trade name:	Emadine™
Chemical name:	1H-Benzimidazole,1-(2-ethoxyethyl)-2(hexahydro-4-methyl-1,4-diazepin-1-yl), (E)-2-butenedioate (1:2)
Sponsor:	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, Texas 76134-2099
Pharmacologic Category:	Histamine H_1 antagonist
Proposed Indication(s):	Relief of the signs and symptoms of allergic conjunctivitis
Dosage Form and Route of Administration:	Topical, ophthalmic solution
NDA Drug Classification:	1-S
Related Drugs:	Livostin™ NDA 20-219 Approved

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4 Chemistry/Manufacturing Controls

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Emedastine[1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-1H-benzimidazole difumarate] is a selective histamine H_1 antagonist.

Following topical ocular dosing to pigmented Dutch Belted rabbits, emedastine showed higher concentrations and longer retention in pigmented ocular tissues relative to corresponding tissues from albino rabbits. The elimination half-lives from iris-ciliary, choroid and retina were approximately 23 days. These trends suggest melanin binding. This is not unexpected based on structural similarities of emedastine to drugs known to exhibit such interactions (Alcon Technical Report 027:38570:0695).

Reviewer's Comments: *The long elimination half-life from the uveal tract in Dutch Belted rabbits of 23 days suggesting melanin binding, raises some concern regarding melanin binding in the human. Phase 4 studies may need to be carried out to ensure no adverse effects will result.*

Clinical Background

6.1 Relevant human experience

Estimates of the prevalence of allergic conjunctivitis range from 10% to 20% of the American population. The disease is characterized by ocular redness and itching. Symptoms associated with allergic conjunctivitis persist through the allergy season. Treatment for the signs and symptoms of allergic conjunctivitis is available in many forms such as corticosteroids, vasoconstrictor/antihistamines and nonsteroidal anti-inflammatory drugs. These classes of drugs treat the signs and symptoms of the condition, but not the primary mechanisms of action of the allergic insult. Additionally, topical ocular steroids have the potential to elevate IOP which may result in damage to the optic nerve and subsequent irreversible visual field loss.

Antihistamines in combination with vasoconstrictors have long been recognized as being effective in the control of allergic conjunctivitis, however, very few antihistamines have been developed for this express indication. Lack of efficacy, local ocular irritation and hypersensitivity reactions are a few of the reasons for their lack of availability. Currently only one ocular antihistamine (Livostin™) is available on the market today.

6.3 Foreign experience

Emadine™ 0.05% (emedastine difumarate ophthalmic solution) is not marketed in any country. It has also not been withdrawn from marketing in any country due to safety or efficacy concerns.

An oral dosage form (1 and 2 mg capsules administered BID) of emedastine difumarate under the tradename DAREN® is marketed in Japan by
for the treatment of allergic rhinitis and urticaria. It is not marketed anywhere else outside of Japan. It has not been withdrawn in any market due to safety or efficacy.

6.4 Human Pharmacology, pharmacokinetics, pharmacodynamics

The pharmacokinetics of emedastine in man have been studied following both oral and topical ocular routes. A multiple dose topical ocular study was conducted by Alcon Laboratories, Inc. Topical ocular dosing of emedastine ophthalmic solution at 0.01, 0.05, 0.1 and 0.5% strengths BID for 15 days showed low plasma drug concentrations, with maximum concentrations for the highest topical dose similar to those seen with a 0.5 mg oral dose (i.e.,0.74 ng/mL).

In the topical ocular study, performed by Alcon Laboratories, normal volunteers were dosed with 0.01, 0.05, 0.1 and 0.5% Emedastine Ophthalmic Solution BID to both eyes for 15 days (10 subjects per dose group). Plasma samples were collected immediately prior to the morning dose and at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 hours postdose on Days 1 and 15. Emedastine plasma levels were low, with the highest concentration reported being 1.55 ng/mL from a 30 minute, Day 15 sample in the 0.5% dose group. Most samples in the three lower dose groups were below the quantitation limit (< 0.3 ng/mL), making quantitative evaluation of systemic exposure in these subjects difficult. The 0.5% dose group showed modest accumulation with mean C_{max} increasing from 0.64 ± 0.18 ng/mL on Day 1 to 0.94 ± 0.33 ng/mL on Day 15. The corresponding $AUC_{0\text{-}8\ hour}$ values were 3.77 ± 1.26 and 5.31 ± 1.41 ng.hour/mL, respectively. Mean $t_{1/2}$ values on both Day 1 and Day 15 were approximately 10 hours. For the therapeutic 0.05% dose strength, plasma concentrations on Day 15 were at least 10-fold lower than those found at steady-state in the 2 mg BID 15 day oral regimen conducted by . . . Emedastine Ophthalmic Solution is intended for QID administration.

7 Description of Clinical Data Sources

EMEDASTINE OPHTHALMIC SOLUTION CLINICAL STUDIES						
Study Type	**Protocol No.**	**Concentration**	**Dosing**	**Control**	**Duration of Dosing**	**No. of Patients**
SAFETY						
Comfort Study No. 1	C-93-12	0.5%,0.1%, 0.05%, and 0.01%	Single drop	ACULAR® (ketorolac tromethamine) and Placebo	1 drop	30
Comfort Study No. 2	C-95-13	0.05%	Single drop in one eye	ACULAR (ketorolac tromethamine) and LIVOSTIN™ (levocabastine HCl)	1 drop	30
Comfort Study No. 3	C-95-35	0.05%	Single drop in one eye	ACULAR (ketorolac tromethamine) and LIVOSTIN (levocabastine HCl)	1 drop	30
Pupil Diameter Study	C-95-11	0.05%	single drop	Placebo	1 drop	40
Multidose Safety	C-93-16	0.5%,0.1%, 0.05%, and 0.01%	Two drops BID in both eyes	None	15 days	40
Long Term Safety	C-94-93	0.05%	One to two drops, QID	Placebo	6 weeks	362
EFFICACY						
CAC No. 1	C-93-19	0.5%,0.1%, and 0.05%	One drop on each of two visits	Placebo	2 days - not sequential	240
CAC No. 2	C-94-90	0.005% and 0.05%	One drop on each of two visits	Placebo	2 days - not sequential	120

EMEDASTINE OPHTHALMIC SOLUTION CLINICAL STUDIES						
Study Type	Protocol No.	Concentration	Dosing	Control	Duration of Dosing	No. of Patients
CAC No. 3	C-95-71	0.05%	Two drops on each of two visits	LIVOSTIN (levocabastine HCl)	2 days - not sequential	97

All Other Emedastine Ophthalmic Solution Clinical Studies						
Study Type	Protocol No.	Concentration	Dosing	Control	Duration of Dosing	Projected No. of Patients
Seasonal AKC	C-94-86	0.05%	One to two drops, QID	2% cromolyn sodium	6 weeks	200 (discontinued after 66 patients were enrolled)*
Seasonal AKC	C-95-54	0.05%	One to two drops, BID	0.05% levocabastine	6 weeks	200

Case Report Forms for 57 patients have been received to date.

Reviewer's Comments: *Study C-94-86 was discontinued after 66 patients had been enrolled. Study C-95-54 was never begun and no patients have been enrolled.*

8 Clinical Studies

8.1 Indication # 1

8.1.1 Reviewer's Trial # 1

Sponsor's protocol # C93-19

8.1.1.1 Objective

Study objectives were to compare the safety and efficacy, onset and duration-of-action, and to determine the optimal concentration of Emedastine Ophthalmic Solution (0.05%, 0.10% and 0.50%) versus placebo in the treatment of allergen-mediated conjunctivitis using the conjunctival allergen challenge (CAC) test.

8.1.1.2 Design

The trial design was a randomized, triple-masked, placebo-controlled, parallel group, contralateral eye comparison study.

8.1.1.3 Protocol

On Visit 1, subjects received an ophthalmic examination and threshold dose causing a ≥2 responsiveness in ocular itching and redness. After approximately one week, on Visit 2, a confirmatory CAC was conducted. Two weeks later, on Visit 3, the onset-of-action of Emedastine Ophthalmic Solution was assessed by giving one of the 3 concentrations or placebo (vehicle) in one eye and placebo (vehicle) in the contralateral eye, 10 minutes before CAC. Two weeks later, on the final visit (Visit 4), the duration-of-action of Emedastine Ophthalmic Solution was assessed by giving one of the 3 concentrations or placebo (vehicle) in one and placebo (vehicle) in the contralateral eye, 4 hours before CAC. Visual acuity, ocular symptoms (itching) and slit-lamp (cornea, anterior chamber, iris, and redness) results were recorded 3, 10 and 20 minutes after the allergen was administered on Visits 2, 3 and 4. Criteria for evaluation were itching and the sum of the scores for regional redness.

8.1.1.3.1 Population

Healthy male and female subjects with a history of symptoms of a clinically active allergic conjunctivitis, who had a positive allergen diagnostic test and a successful baseline conjunctival challenge.

Investigator	#Enrolled	# Completed
Mark B. Abelson, M.D. Ophthalmic Research Associates 863 Turnpike Street, Suite 224 N. Andover, MA 01845	160	155
Lawrence Spitalny, M.D. Phoenix Eye Clinic 120 East Montecito Way Phoenix, AZ 85012	80	79

8.1.1.3.2 Endpoints

Itching (4-point scale) and Redness (12-point scale)

8.1.1.3.3 Statistical considerations

A paired t-test was used to compare itching and redness data of each concentration of Emedastine Ophthalmic Solution with contralateral placebo at each challenge and post-challenge time. For comparisons between the concentrations of Emedastine, the itching and redness raw score data were analyzed using an analysis of covariance model. Subject's contralateral placebo eye was used as covariate. The model contained terms for treatment, challenge, post-challenge time and variability contributed by repeated measures on subjects. The formal ANOVA model included treatment, challenge, post-challenge time, and interactions terms as fixed effects; the subject within treatment as a random effect; and placebo as a covariate.

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

Demographics

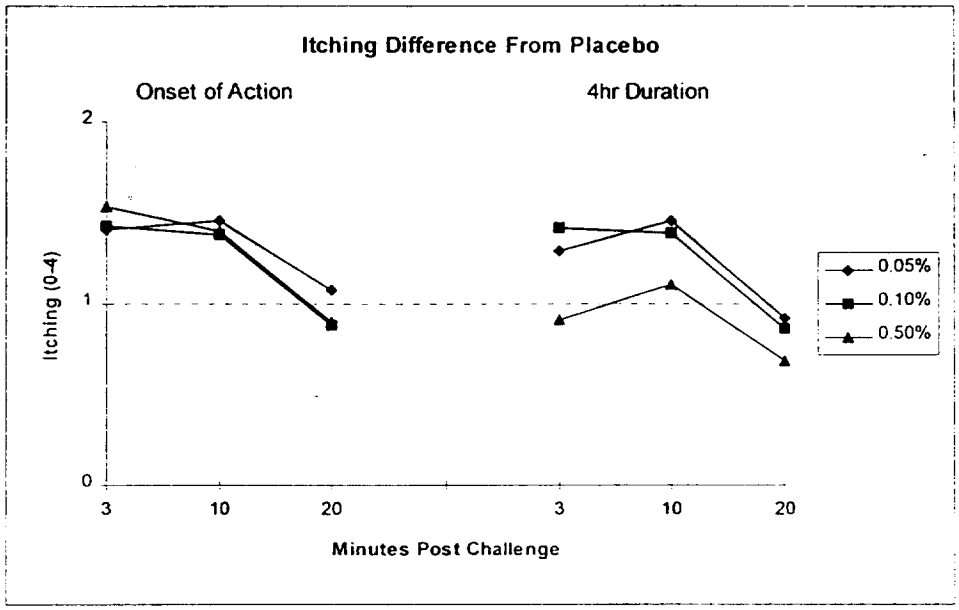
		Emedastine Solution				
		0.05%	0.10%	0.50%	Placebo	ALL
Age	MEAN	39	39	38	39	39
	STD	12	14	11	12	12
	N	60	60	60	60	240
	MIN	19	20	18	18	18
	MAX	70	69	67	69	70
Age						
13-64	N	58	57	58	58	231
> =65	N	2	3	2	2	9
Sex						
MALE	N	20	31	31	25	107
FEMALE	N	40	29	29	35	133
Race						
CAUCASIAN	N	58	59	58	60	235
BLACK	N	.	.	1	.	1
OTHER	N	2	1	1	.	4
Iris Color						
BROWN	N	20	25	20	21	86
HAZEL	N	15	11	9	18	53
GREEN	N	3	6	5	5	19
BLUE	N	22	18	26	16	82
Investigator						
1028	N	40	40	40	40	160
1814	N	20	20	20	20	80

Discontinued Subjects

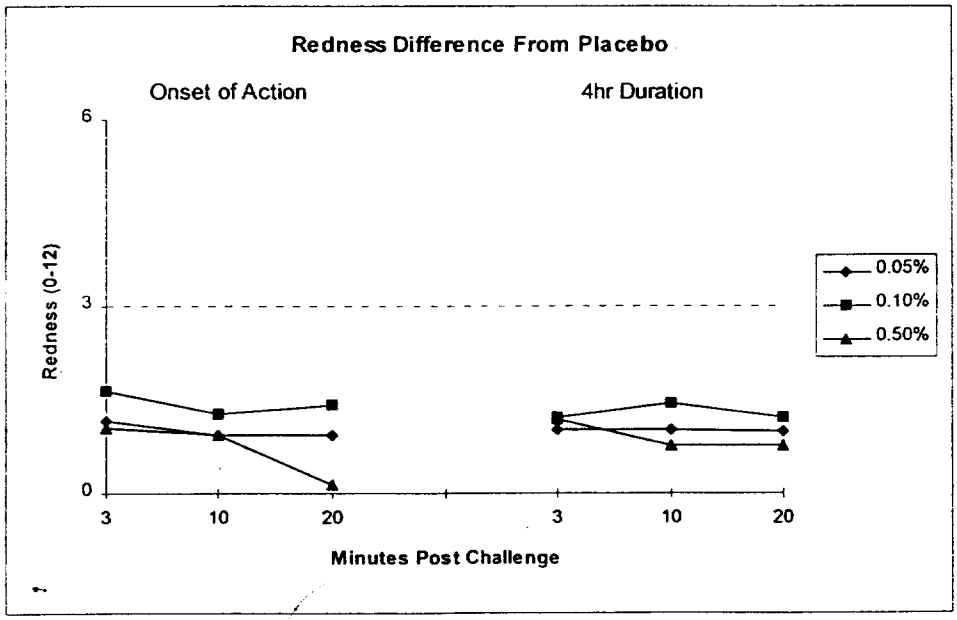
	Emedastine 0.05%	Emedastine 0.10%	Emedastine 0.50%	Placebo
Lost to Follow-up[1]	1	0	2	1
Other[2]	0	1	1	0
Total	1	1	3	1

[1] Subjects failed to return for Visit 4 exam.
[2] Subjects had > 1+ redness at Visit 4 baseline exam.

8.1.1.4.2 Efficacy endpoint outcomes



Itching differences from placebo were significant ($p<0.05$) at all time points for 0.05%, 0.10%, and 0.50% Emedastine Ophthalmic Solutions.



Redness differences from placebo were significant ($p<0.05$) at all time points for 0.05% and 0.10% Emedastine Ophthalmic Solutions. For 0.50% Emedastine Ophthalmic Solution, redness differences from placebo were significant at all time points except 20 minutes post onset challenge.

Reviewer's Comments: *This graph was copied directly from sponsor's CANDA*

ITCHING

		Difference from Contralateral Placebo Onset-of-Action (10-minute) Challenge		
		3 min	10 min	20 min
Emedastine 0.05%	**MEAN**	-1.41*	-1.46*	-1.08*
	STD	1.32	0.99	1.07
	N	60	60	60
Emedastine 0.10%	**MEAN**	-1.43*	-1.38*	-0.88*
	STD	1.10	1.23	1.02
	N	60	60	60
Emedastine 0.50%	**MEAN**	-1.53*	-1.40*	-0.90*
	STD	0.99	0.99	0.91
	N	60	60	60
Placebo	**MEAN**	-0.16	-0.10	-0.21
	STD	1.01	0.87	0.88
	N	60	60	60

*Indicates statistical significance ($p \leq 0.05$). Clinical significance = 1 unit.

REDNESS

		Difference from Contralateral Placebo Onset-of-Action (10-minute) Challenge		
		3 min	10 min	20 min
Emedastine 0.05%	**MEAN**	-1.17*	-0.93*	-0.94*
	STD	1.88	2.19	2.34
	N	60	60	60
Emedastine 0.10%	**MEAN**	-1.65*	-1.28*	-1.42*
	STD	2.15	2.30	2.33
	N	60	60	60
Emedastine 0.50%	**MEAN**	-1.04*	-0.94*	-0.14
	STD	2.32	2.03	2.25
	N	60	60	60
Placebo	**MEAN**	-0.08	-0.13	0.14
	STD	1.89	1.33	1.53
	N	60	60	60

Indicates statistical significance ($p \leq 0.05$). Clinical significance = 3 units.

Difference from contralateral placebo

Duration-of-Action (4-hour) Challenge

ITCHING

		3 min	10 min	20 min
Emedastine	**MEAN**	**-1.29***	**-1.46***	**-0.92***
0.05%	**STD**	**1.01**	**0.87**	**0.87**
	N	59	59	59
Emedastine	**MEAN**	**-1.42***	**-1.39***	**-0.86***
0.10%	**STD**	**1.04**	**1.00**	**1.03**
	N	59	59	59
Emedastine	**MEAN**	**-0.91***	**-1.11***	**-0.69***
0.50%	**STD**	**0.94**	**1.17**	**1.13**
	N	57	57	57
Placebo	**MEAN**	**0.06**	**0.08**	**0.06**
	STD	**0.89**	**0.90**	**0.66**
	N	59	59	59

*Indicates statistical significance ($p \leq 0.05$). Clinical significance = 1 unit.

REDNESS

Difference from contralateral placebo

Duration-of-Action (4-hour) Challenge

		3 min	10 min	20 min
Emedastine	**MEAN**	**-1.03***	**-1.02***	**-0.98***
0.05%	**STD**	**1.92**	**1.91**	**2.27**
	N	59	59	59
Emedastine	**MEAN**	**-1.22***	**-1.45***	**-1.23***
0.10%	**STD**	**2.26**	**2.43**	**2.42**
	N	59	59	59
Emedastine	**MEAN**	**-1.18***	**-0.77***	**-0.76***
0.50%	**STD**	**2.46**	**2.23**	**2.17**
	N	57	57	57
Placebo	**MEAN**	**0.01**	**0.25**	**0.36**
	STD	**1.68**	**1.31**	**1.43**
	N	59	59	59

*Indicates statistical significance ($p \leq 0.05$). Clinical significance = 3 units.

Reviewer's Comments: *With respect to itching, all concentrations of Emedastine were clinically significant at the onset- challenge as compared to placebo. At the four-hour antigen challenge, both the 0.05% and 0.10% concentrations were clinically significant. Emedastine 0.05% and 0.10% concentrations begin to lose effectiveness after four hours. With respect to redness, clinical significance was not achieved by any concentration at any time-point, since a three-unit difference compared to placebo was necessary.*

8.1.1.4.3 Safety outcomes

Frequency and Incidence of Adverse Events

Coded Adverse Events	Emedastine 0.05% + Placebo N=60		Emedastine 0.10% + Placebo N=60		Emedastine 0.50% + Placebo N=60		Placebo N=60	
OCULAR	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Pruritus	1[c]	2	0		0		0	
Discomfort	0		1[d]	2	1[e]	2	0	
Decreased Visual Acuity	1	2	0		0		0	
Foreign Body Sensation	1	2	0		0		0	
Lid Edema	0		1	2	0		0	
NONOCULAR								
Body as a Whole Headache	8	13	5	8	11	18	4	7
Back Pain	1	2	1	2	0		0	
Cold Syndrome	0		3	5	2	3	3	5
Flu Syndrome	0		0		0		1	2

[c] Suspect Drug = Emedastine 0.05%
[d] Suspect Drug = Emedastine 0.10%
[e] Suspect Drug = Emedastine 0.50%

Reviewer's Comments: *Ocular adverse events including burning, stinging and pruritus each occurred in 2% of patients. During the study period, headache was reported in 18% of patients receiving Emedastine 0.50%; 13% of patients receiving Emedastine 0.05%; 8% of patients receiving Emedastine 0.1% and 7% of patients receiving placebo.*

8.1.1.5 Reviewer's Conclusions Regarding Efficacy Data

Emedastine 0.05% was clinically significant and superior overall to the 0.10% and 0.50% concentrations with respect to inhibiting itching as compared to placebo. At the four-hour 20 minute post-challenge time-point, Emedastine 0.05% did not achieve one full unit of improvement as compared to placebo. This indicates that the effectiveness of Emedastine 0.05% begins to decline at four hours.

With respect to redness, none of the three concentrations of Emedastine achieved clinical significance in this study.

8.1.2 **Reviewer's Trial # 2**

Sponser's protocol # C-94-90

8.1.2.1 **Objective**

Study objectives were to compare the safety and efficacy, onset and duration-of-action, and to confirm the optimal concentration of Emedastine Ophthalmic Solution (0.005% and 0.05%) versus placebo in the treatment of allergen-mediated conjunctivitis using the conjunctival allergen challenge (CAC) test.

8.1.2.2 **Design**

Randomized, triple-masked, placebo-controlled, parallel group, contralateral eye comparison study.

8.1.2.3 **Protocol**

One hundred twenty subjects who met the inclusion and exclusion criteria were randomly assigned to one of two treatment groups and received one of two concentrations of Emedastine Ophthalmic Solution (0.005% or 0.05%) in one eye and Emedastine vehicle (placebo) in the other eye. A conjunctival allergen challenge test was performed bilaterally 10 minutes after one of the two test concentrations were instilled in one eye and placebo was instilled in the contralateral eye. Itching and a slit-lamp examination of conjunctival redness were assessed and scored 3, 10, and 20 minutes after the allergen administration.

Subjects returned two weeks later to assess the duration-of-action of the test articles. Four hours prior to the CAC, one drop of one of the two concentrations of Emedastine Ophthalmic Solution was instilled in one eye and one drop of placebo in the other eye. Itching and slit-lamp examination of conjunctival redness were assessed and scored at 3, 10, and 20 minutes after the allergen administration. Subjects were closely monitored for adverse effects.

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Study Plan

Procedures	Visit 1		Visit 2 Minimum of 7 Days After Visit 1		Visit 3 Minimum of 14 Days After Visit 2		Visit 4 Minimum of 14 Days After Visit 3	
	Screening Challenge[1]		Confirmatory Challenge[2]		Onset-of-Action Challenge[3]		4-Hour Duration Challenge[4]	
	Pre CAC Titer	Post CAC Titer	Pre CAC	Post CAC 3, 10, 20 min	Pre CAC	Post CAC 3, 10, 20 min	Pre CAC	Post CAC 3, 10, 20 min
Informed Consent	X							
Medical History	X							
Pregnancy Test[5]	X							X
Visual Acuity	X		X		X		X	
Ocular Symptom: Itching	X	X	X	X	X	X	X	X
Slit Lamp: Cornea Ant. Chamber Iris	X		X		X		X	
Slit Lamp: Redness	X	X	X	X	X	X	X	X
Fundus Exam (Undilated)	X							
Diagnostic Test	X[5]							
CAC	X		X		X		X	
Instill Drug					X (10 min before CAC)		X (4 hrs before CAC)	
Exit Form								X

1. Determine allergen dose required to elicit redness and itching scores of ≥ 2 + OU.
2. Confirm allergen dose required to elicit redness and itching scores of ≥ 2 + OU.
3. Determine onset of drug action.
4. Determine duration of drug action.
5. If necessary

8.1.2.3.1 Population

Healthy male and female subjects with a history of symptoms of a clinically active allergic conjunctivitis, who had a positive allergen diagnostic test and a successful baseline conjunctival challenge.

Investigator

George M. Lowry, M.D.
Vision Care
8123 Broadway
San Antonio, TX 78209

8.1.2.3.2 Endpoints

Itching (4-point scale) and redness (12-point scale)

8.1.2.3.3 **Statistical Considerations**

A paired t-test was used to compare itching and redness data of each concentration of Emedastine Ophthalmic Solution with contralateral placebo at each challenge and post-challenge time. For comparisons between the two concentrations of Emedastine, the itching and redness raw score data were analyzed using an analysis of covariance model. Subject's contralateral placebo eye was used as covariate. The model contained terms for treatment, challenge, post-challenge time, and variability contributed by repeated measures on subjects. The formal ANOVA model included treatment, challenge, post-challenge time, and interactions terms as fixed effects; the subject within treatment as a random effect; and placebo as a covariate.

8.1.2.4 **Results**

8.1.2.4.1 **Populations enrolled/analyzed**

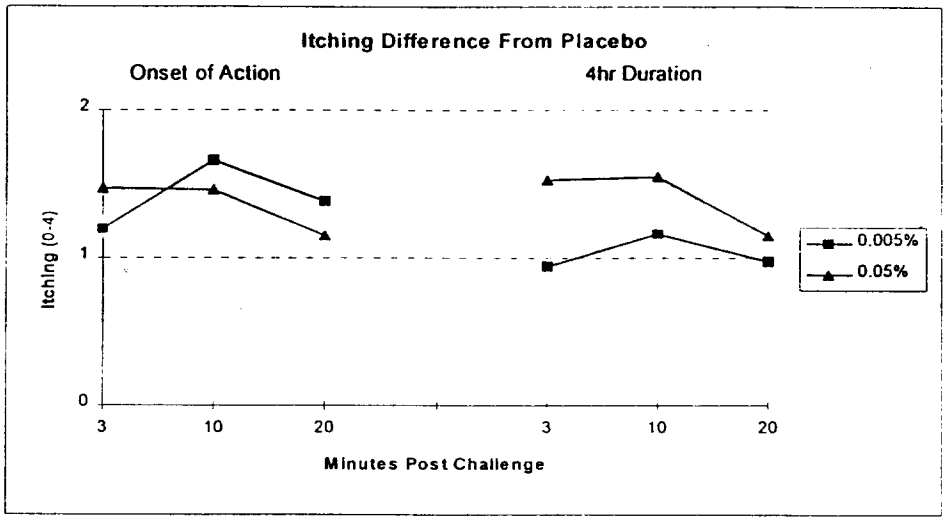
Demographics

		Emedastine 0.005%	Emedastine 0.05%	ALL
Age	MEAN	37	38	37
	STD	14	12	13
	N	60	60	120
	MIN	18	18	18
	MAX	72	73	73
Age				
13-64	N	56	56	112
>=65	N	4	4	8
Sex				
MALE	N	27	26	53
FEMALE	N	33	34	67
Race				
CAUCASIAN	N	34	32	66
BLACK	N	3	5	8
HISPANIC	N	23	23	46
Iris Color				
BROWN	N	37	38	75
HAZEL	N	8	5	13
GREEN	N	8	4	12
BLUE	N	7	13	20
Investigator				
1735	N	60	60	120

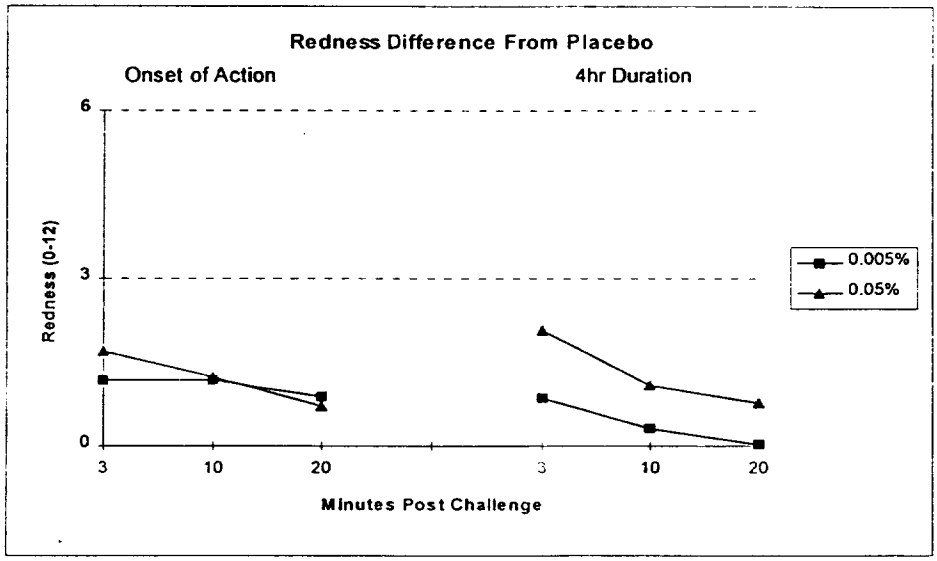
Discontinued Subjects

None

8.1.2.4.2 Efficacy endpoint outcomes



Itching differences from placebo were significant ($p<0.05$) at all time points for 0.05% and 0.005% Emedastine Ophthalmic Solutions.



Redness differences from placebo were significant ($p<0.05$) at all time points for 0.05% Emedastine Ophthalmic Solution. For 0.005% Emedastine Ophthalmic Solution, redness differences from placebo were significant at all time points except 10 and 20 minutes post duration challenge.

Reviewer's Comments: *This graph was copied directly from sponser's CANDA.*

ITCHING

		Difference from Contralateral Placebo Onset-of-Action (10-minute) Challenge		
		3 min	10min	20min
Emedastine 0.005%	MEAN	-1.20*	-1.66*	-1.38*
	STD	1.14	1.08	1.06
	N	60	60	60
Emedastine 0.05%	MEAN	-1.47*	-1.46*	-1.15*
	STD	0.95	1.10	0.95
	N	60	60	60

*Indicates statistical significance ($p \leq 0.05$). Clinical significance = 1 unit.

REDNESS

		Difference from Contralateral Placebo Onset-of-Action (10-minute) Challenge		
		3 min	10min	20min
Emedastine 0.005%	MEAN	-1.17*	-1.19*	-0.88*
	STD	1.49	1.81	1.70
	N	60	60	60
Emedastine 0.05%	MEAN	-1.68*	-1.24*	-0.72*
	STD	1.92	2.32	2.34
	N	60	60	60

*Indicates statistical significance ($p \leq 0.05$). Clinical significance = 3 units.

ITCHING		Difference from Contralateral Placebo Duration-of-Action (4-hour) Challenge		
		3 min	10min	20min
Emedastine	MEAN	-0.94*	-1.17*	-0.98*
0.005%	STD	1.27	1.28	1.02
	N	60	60	60
Emedastine	MEAN	-1.53*	-1.55*	-1.15*
0.05%	STD	1.01	1.10	1.04
	N	60	60	60

*Indicates statistical significance ($p \leq 0.05$).

REDNESS		Difference from Contralateral Placebo Duration-of-Action (4-hour) Challenge		
		3 min	10min	20min
Emedastine	MEAN	-0.85*	-0.31	-0.03
0.005%	STD	1.54	1.53	1.39
	N	60	60	60
Emedastine	MEAN	-2.06*	-1.08*	-0.78*
0.05%	STD	2.12	1.96	1.90
	N	60	60	60

*Indicates statistical significance ($p \leq 0.05$).

Reviewer's Comments: *Both concentrations of Emedastine (0.005% & 0.05%) were significant both statistically and clinically with respect to placebo in inhibiting itching at all time points.*

With respect to inhibition of redness, there were certain time points where each concentration of Emedastine was statistically significantly better than placebo, however, neither concentration reached clinical significance with respect to inhibiting redness as compared to placebo.

8.1.2.4.3 Safety Outcomes

Frequency and Incidence of Adverse Events

Coded Adverse Events	Emedastine 0.005% + Placebo N=60		Emedastine 0.05% + Placebo N=60	
OCULAR	**N**	**%**	**N**	**%**
None	0		0	
NONOCULAR				
Body as a Whole Headache	3	5	0	
Cold Syndrome	2	3	0	
Pain Chest	1	2	0	
Respiratory Rhinitis	3	5	0	
Bronchitis	1	2	0	

Adverse Events by Subject

Inv. No.	Subj. No.	Age	Sex	Treatment	Coded Adverse Event	Study Day	Intensity	Duration of Event	Outcome of Event
1735	1047	26	F	Emedastine 0.005% + Placebo	Headache	2	Moderate	2 Hours	Resolved
1735	1005	23	M	Emedastine 0.005% + Placebo	Rhinitis	OT	Mild	5 Days	Resolved
1735	1010	25	F	Emedastine 0.005% + Placebo	Rhinitis	OT	Moderate	12 Days	Resolved
1735	1012	32	F	Emedastine 0.005% + Placebo	Rhinitis	OT	Mild	3 Days	Resolved
1735	1010	25	F	Emedastine 0.005% + Placebo	Headache	OT	Moderate	12 Days	Resolved
1735	1048	40	F	Emedastine 0.005% + Placebo	Headache	OT	Mild	14 Days	Resolved
1735	1065	67	M	Emedastine 0.005% + Placebo	Cold Syndrome	OT	Mild	6 Days	Resolved
1735	1093	23	M	Emedastine 0.005% + Placebo	Cold Syndrome	OT	Mild	5 Days	Resolved
1735	1075	30	F	Emedastine 0.005% + Placebo	Pain Chest	OT	Mild	4 Hours	Resolved
1735	1038	22	F	Emedastine 0.005% + Placebo	Bronchitis	OT	Moderate	10 Days	Resolved

Reviewer's Comments: *There were no ocular related adverse events reported in this study. There was one subject reporting headache on therapy. The remainder of the adverse events occurred off therapy.*

8.1.2.5 Reviewer's Conclusions Regarding Efficacy Data

While both the 0.05% and the 0.005% concentrations of Emedastine were statistically and clinically significantly superior to placebo in inhibiting itching, the 0.05% concentration was superior to the 0.005% concentration, particularly in the 4-hour duration-of-action challenge.

Neither concentration reached clinical significance over placebo with respect to the inhibition of redness.

8.1.3 Reviewer's Trial # 3
Sponser's Protocol # C-95-71

8.1.3.1 Objective

To compare the efficacy and safety of Emedastine Ophthalmic Solution 0.05% versus Levocabastine Ophthalmic Suspension 0.05% in the treatment of allergen-mediated conjunctivitis using the provocation challenge test.

8.1.3.2 Design

Triple-masked, randomized, active-controlled, and contralateral eye comparison study

8.1.3.3 Protocol

Ninety-seven (97) normal, healthy male and female subjects with a history of symptoms of a clinically active allergic conjunctivitis, who had a positive allergen diagnostic test and a successful baseline conjunctival challenge were enrolled. Sixty-four (64) subjects received Emedastine Ophthalmic Solution 0.05% in one eye and Levocabastine Ophthalmic Suspension 0.05% in the other eye. To preserve masking, a small (n=33) group of subjects received either Emedastine Ophthalmic Solution 0.05% or Levocabastine Ophthalmic Suspension 0.05% in one eye and placebo (Emedastine Ophthalmic Vehicle) in the other eye. Six subjects participated in a previous Emedastine CAC study (Protocol C-93-19). These six subjects (4 in the Emedastine/Levocabastine group and 2 in the Levocabastine/placebo group) were considered not evaluable for the efficacy analysis, but were included in the intent-to-treat analysis of the efficacy data.

On Visit 1, subjects received an ophthalmic examination (visual acuity, ocular symptoms of itching, slit-lamp examination of the cornea, anterior chamber, iris, and redness, and fundus examination) and the allergen (grasses, weeds, or animal dander) and threshold dose causing a ≥ 2 responsiveness in ocular itching and redness (defined as the CAC) identified. After approximately one week, on Visit 2, a confirmatory CAC was conducted. Two weeks later, on Visit 3, subjects received two drops of Emedastine Ophthalmic Solution 0.05% in one eye and two drops of Levocabastine Ophthalmic Suspension 0.05% in the other eye; a parallel masking control group of 33 subjects received two drops of Emedastine Ophthalmic Vehicle (placebo) in one eye and two drops of either Emedastine Ophthalmic Solution 0.05% or Levocabastine Ophthalmic Suspension 0.05% in the other eye, 10 minutes before CAC. Two weeks later, on the final visit (Visit 4), subjects received two drops of Emedastine Ophthalmic Solution 0.05% in one eye and two drops of Levocabastine Ophthalmic Suspension 0.05% in the other eye; a parallel masking control group of 33 subjects received two drops of Emedastine Ophthalmic Vehicle (placebo) in one eye and two drops of either Emedastine Ophthalmic Solution 0.05% or Levocabastine Ophthalmic Suspension 0.05% in the other eye, 2 hours before CAC. Visual acuity, ocular symptoms (itching) and slit-lamp (cornea, anterior chamber, iris, and redness) results were recorded 3, 5 and 10 minutes after the allergen was administered on Visits 2, 3 and 4. Criteria for evaluation were itching and conjunctival redness.

Study Plan

Procedures	Visit 1		Visit 2 Minimum of 3 Days After Visit 1		Visit 3 Minimum of 14 Days After Visit 2		Visit 4 Minimum of 14 Days After Visit 3	
	Screening Challenge[1]		Confirmatory Challenge[2]		Onset-of-Action Challenge		2 Hour Challenge	
	Pre CAC Titer	Post CAC Titer	Pre CAC	Post CAC 3, 5, 10 min	Pre CAC	Post CAC 3, 5, 10 min	Pre CAC	Post CAC 3, 5, 10 min
Informed Consent	X							
Medical History	X							
Pregnancy Test[3]	X							X
Visual Acuity	X		X		X		X	
Ocular Symptom: Itching	X	X	X	X	X	X	X	X
Slit Lamp: Cornea Ant. Chamber Iris	X		X		X		X	
Slit Lamp: Redness	X	X	X	X	X	X	X	X
Fundus Exam (Undilated)	X							
Diagnostic Test	X[3]							
CAC	X		X		X		X	
Assign Randomization Number					X			
Instill Drug					X (10 min before CAC)		X (2 hr before CAC)	
Post-Drug Comfort Exam					X (Immediately after drug)		X (Immediately after drug)	
Photograph Each Eye						X (After 10 min. evaluation)		X (After 10 min evaluation)
Exit Form								X

1. Determine allergen dose required to elicit redness and itching scores of ≥ 2.0 OU.
2. Confirm allergen dose required to elicit redness and itching scores of ≥ 2.0 OU.
3. If necessary

Reviewer's Comments: *It is unclear how the group of 33 patients added in Amendment 1 of this protocol ensured adequate masking of the comparison between Emedastine and Levocabastine in the main study contingent. The data on these patients were not included in the original submission, but were sent in at the request of the FDA .The sponser did not complete statistical analyses on these data.*

8.1.3.3.1 **Population**

Normal, healthy male and female volunteers,currently not using topical or systemic medications, with a history of symptoms of a clinically active allergic conjunctivitis, who had a positive allergen diagnostic test and a successful baseline challenge

Investigator

Peter A. Netland, M.D., Ph.D
Andover Eye Associates
555 Turnpike Street
North Andover, MA 01845

8.1.3.3.2 **Endpoints**

Itching (4-point scale), conjunctival redness (4-point scale)

8.1.3.3.3 **Statistical Considerations**

Paired t-test for comparisons between Emedastine and Levocabastine

8.1.3.4 Results

8.1.3.4.1 **Populations enrolled/analyzed**

Demographics

		Emedastine/ Levocabastine	Emedastine/ Placebo	Levocabastine/ Placebo	Total
Age	MEAN	36	34	36	35
	STD	11	8	12	10
	N	64	16	17	97
	MIN	18	19	20	18
	MAX	62	45	66	66
Age					
13-64	N	64	16	16	96
> = 65	N	.	.	1	1
Sex					
MALE	N	27	7	9	43
FEMALE	N	37	9	8	54
Race					
CAUCASIAN	N	61	15	17	93
BLACK	N	1	1	.	2
OTHER	N	2	.	.	2
Iris Color					
BROWN	N	26	7	5	38
HAZEL	N	10	4	6	20
GREEN	N	7	.	1	8
BLUE	N	21	5	5	31
Investigator					
1960	N	64	16	17	97

Discontinued Subjects:

Patient Number/Age/Sex	Treatment	Adverse Event	Causality Assessment
# 174/30/F	Emedastine 0.05% + Placebo	keratopathy	not related

8.1.3.4.2 Efficacy endpoint outcomes

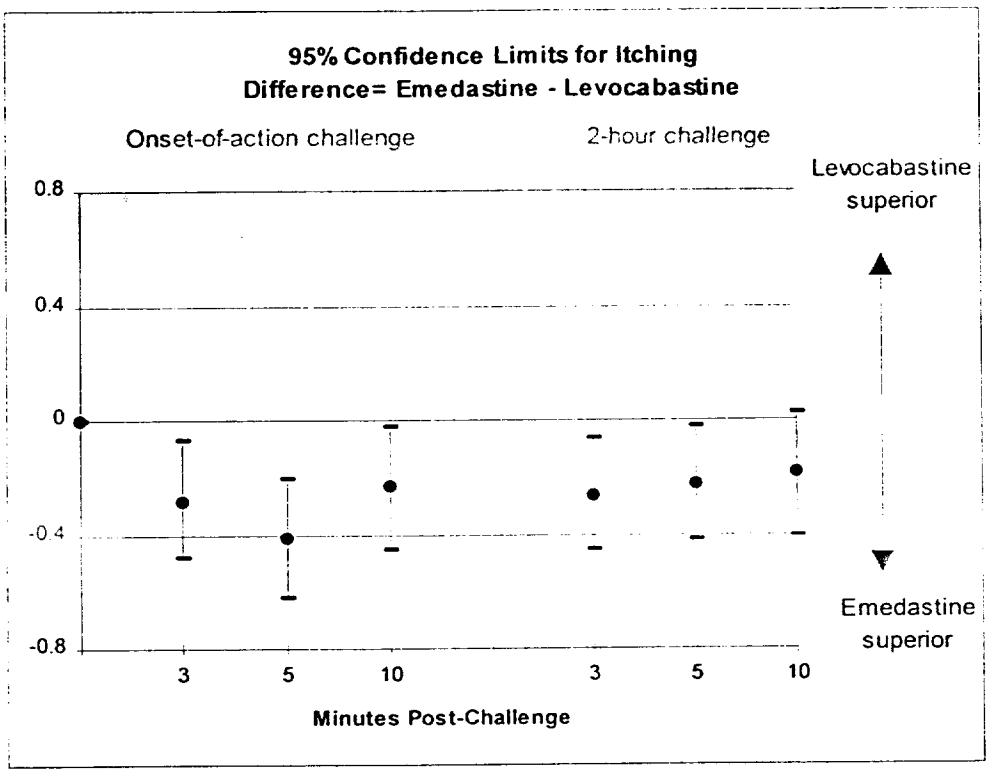
Mean Scores for Itching and Conjunctival Redness (Efficacy Data Set)

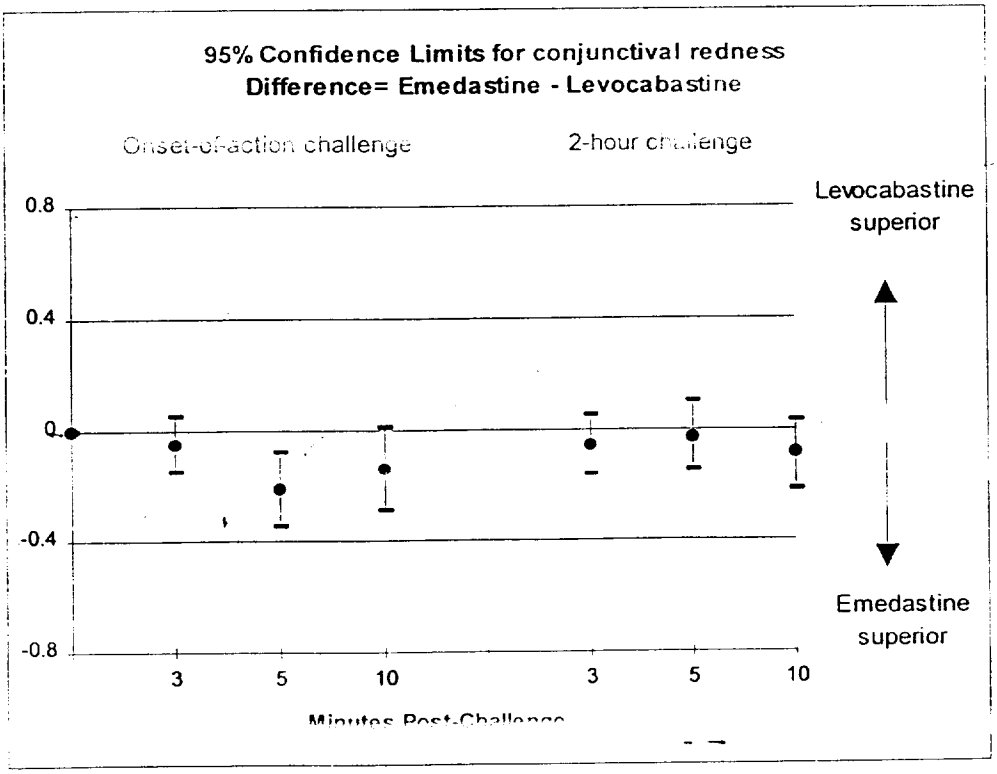
ITCHING	N=60	Onset-of-action challenge			Two-hour challenge		
		3min	5min	10min	3min	5min	10min
Emedastine 0.05%	MEAN	0.88	0.90	0.90	0.56	0.64	0.68
	STD	0.97	0.96	0.94	0.81	0.80	0.81
Levocabastine 0.05%	MEAN	1.15	1.31	1.13	0.82	0.86	0.87
	STD	0.94	0.93	0.88	0.79	0.85	0.92
Emed-Levo	MEAN	-0.28*	-0.41*	-0.23*	-0.26*	-0.22*	-0.18[T]
	STD	0.78	0.82	0.84	0.75	0.78	0.82

CONJUNCTIVAL REDNESS	N=60	Onset-of-action challenge			Two-hour challenge		
		3min	5min	10min	3min	5min	10min
Emedastine 0.05%	MEAN	0.79	1.05	1.29	0.86	1.19	1.48
	STD	0.62	0.61	0.68	0.60	0.67	0.77
Levocabastine 0.05%	MEAN	0.84	1.26	1.43	0.92	1.22	1.57
	STD	0.60	0.71	0.72	0.58	0.72	0.80
Emed-Levo	MEAN	-0.05	-0.21*	-0.14	-0.06	-0.03	-0.09
	STD	0.40	0.51	0.59	0.40	0.50	0.48

* $p < 0.05$
T: $0.05 \leq p \leq 0.10$

Ocular Itching and Redness - Emedastine Ophthalmic Solution 0.05% Versus Levocabastine Ophthalmic Suspension 0.05%





Reviewer's Comments: *The following comments refer to the main study contingent of Protocol C-95-71. According to the summary statistics on the sponser-defined efficacy data set, (not the 64 subject intent-to-treat data set), with respect to the inhibition of itching, Emedastine 0.05% is statistically significantly superior to Levocabastine 0.05%, but not enough to warrant a claim of clinical superiority. Additionally, the comparison of the two drugs was for two hours instead of the usual four hours. With respect to inhibiting redness, there was only one time-point where Emedastine 0.05% reached statistical significance over Levocabastine 0.05% (5 min. post onset-of-action challenge), but this was not clinically significant. In this study, the two drugs were shown to be essentially equivalent in the inhibition of redness. This is clearly demonstrated by the fact that, with the exception of one, all the 95% confidence intervals for the difference in conjunctival redness between the two drugs include zero.*

The following data and comments refer to the masking control group of patients in Protocol C-95-71.

C-95-71: Emedastine vs Levocabastine CAC study

Emedastine vs Placebo (Efficacy Data Set)

ITCHING		Onset-of-Action Challenge			Two-hour Challenge		
		3min	5min	10min	3min	5min	10min
Emedastine 0.05%	MEAN	0.81	0.81	0.66	0.20	0.10	0.20
	STD	0.93	1.00	0.75	0.53	0.28	0.37
	N	16	16	16	15	15	15
Placebo	MEAN	2.06	2.00	1.94	1.87	1.73	1.37
	STD	1.00	0.88	0.93	1.11	0.86	1.01
	N	16	16	16	15	15	15
Emed-Placebo	MEAN	-1.25	-1.19	-1.28	-1.67	-1.63	-1.17
	STD	1.40	1.09	1.14	1.21	0.92	0.84
	N	16	16	16	15	15	15

Reviewer's Comments: *With respect to itching, Emedastine 0.05% is clinically superior to placebo.*

C-95-71: Emedastine vs Levocabastine CAC study

Levocabastine vs Placebo (Intent To Treat Data Set)

ITCHING		Onset-of-Action Challenge			Two-hour Challenge		
		3min	5min	10min	3min	5min	10min
Levocabastine 0.05%	MEAN	1.21	1.15	0.76	0.79	0.56	0.71
	STD	1.15	1.10	1.05	0.92	0.86	0.94
	N	17	17	17	17	17	17
Placebo	MEAN	2.21	2.38	2.15	1.68	1.71	1.53
	STD	1.02	0.80	0.96	0.75	0.95	1.04
	N	17	17	17	17	17	17
Levo-Placebo	MEAN	-1.00	-1.24	-1.38	-0.88	-1.15	-0.82
	STD	1.37	1.15	1.15	0.93	1.04	0.93
	N	17	17	17	17	17	17

Reviewer's Comments: *With respect to itching, Levocabastine 0.05% was clinically superior to placebo except at the 3 and 10 minute time-points in the two-hour challenge.*

Study C-95-71

Mean Differences Between Emedastine /Placebo and Levocabastine/Placebo
In Total and Conjunctival Redness

time point	0	3	5	10	cac0	3	5	10	2hr0	3	5	10
					Total Redness							
Emed.average	1.22	5.25	7.09	7.84	1.22	2.47	3.34	4.22	1.63	3.5	4.3	5.67
Placebo average	1.41	5.61	6.88	7.5	1.34	3.81	4.97	5.56	1.91	4.23	5.67	6.63
Emed-Placebo	-0.19	-0.36	0.21	0.34	-0.12	-1.34	-1.63	-1.34	-0.28	-0.73	-1.37	-0.96
					Conjunctival Redness							
Emed.average	0.47	1.66	2.22	2.38	0.34	0.84	1.06	1.31	0.53	1.07	1.23	1.67
Placebo average	0.5	1.88	2.16	2.31	0.41	1.16	1.47	1.47	0.59	1.23	1.77	1.97
Emed-Placebo	-0.03	-0.22	0.06	0.07	-0.07	-0.32	-0.41	-0.16	-0.06	-0.16	-0.54	-0.3
					Total Redness							
Levo.average	1.47	4.76	6.56	7.29	1.41	3.21	4.09	4.94	1.38	2.76	3.53	4.68
Placebo average	1.5	4.59	6.59	7.26	1.41	4.38	5.88	6.97	1.38	4.35	5.74	6.68
Levo-Placebo	-0.03	0.17	-0.03	0.03	0	-1.17	-1.79	-2.03	0	-1.59	-2.21	-2
					Conjunctival Redness							
Levo.average	0.53	1.47	2.06	2.32	0.5	0.97	1.29	1.5	0.38	0.82	1.03	1.32
Placebo average	0.59	1.5	2.12	2.26	0.44	1.35	1.88	2.15	0.44	1.24	1.66	2
Levo-Placebo	-0.06	-0.03	-0.06	0.06	0.06	-0.38	-0.59	-0.65	-0.06	-0.42	-0.63	-0.68

C-95-71
Conjunctival Redness for All Eyes

		Onset-of-action challenge			Two-hour challenge		
		3min	5min	10min	3min	5min	10min
Emedastine avg.	N=76	.80	1.05	1.29	.90	1.20	1.52
Levocabastine avg.	N=77	.88	1.25	1.41	.86	1.14	1.48
Placebo avg.	N=33	1.26	1.68	1.82	1.24	1.71	1.98

Intent-to-treat data set used for Levocabastine

Reviewer's Comments: *With respect to conjunctival redness, although both Emedastine and Levocabastine are numerically superior to placebo, neither one reaches clinical significance (≥ 1-unit difference) over placebo in inhibiting redness. With respect to total redness, again, both Emedastine and Levocabastine are numerically superior to placebo, but neither reaches clinical significance (≥ 3-unit difference) over placebo in inhibiting redness. When the actual raw mean score differences are compared, Emedastine is numerically superior to Levocabastine at each of the three onset-of-action challenge points, but Levocabastine is numerically superior to Emedastine at each of the three two-hour challenge points. The differences are not great enough to be of clinical significance with respect to the inhibition of redness.*

8.1.3.4.3 Safety outcomes

Frequency and Incidence of Adverse Events

Coded Adverse Events	Emedastine 0.05% + Levocabastine 0.05% N=64		Emedastine 0.05% + Placebo N=16		Levocabastine 0.05% + Placebo N=17	
	N	%	N	%	N	%
Ocular						
Discomfort	5[c,e]	8	1[d]	6	0	
Pruritus	0		1[f]	6	0	
Keratopathy	0		1	6	0	
Nonocular						
Body as a Whole Headache	7	11	0		0	
Cold Syndrome	2	3	0		0	
Flu Syndrome	1	2	0		0	
Surgical/Medical Procedure	1	2	0		0	
Hemic & Lymphatic Lymphadenopathy	1	2	0		0	
Respiratory Bronchitis	2	3	0		0	
Rhinitis	1	2	1	6	0	
Pharyngitis	1	2	0		0	
Cough Increased	0		0		1	6

[c] Suspect Drug was Levocabastine 0.05% Ophthalmic Suspension 0.05% in 3 patients
[d] Suspect Drugs were Emedastine Ophthalmic Solution 0.05% and Placebo in 1 patient
[e] Suspect Drugs were Emedastine Ophthalmic Solution 0.05% and Levocabastine Ophthalmic Suspension 0.05% in 2 patients
[f] Suspect Drug was Emedastine Ophthalmic Solution 0.05% in 1 patient

Reviewer's Comments:*The most common ocular related adverse event in this study was ocular discomfort (stinging or burning) occurring in 6 of 97 subjects (6%). The suspect drug was Levocabastine Ophthalmic Suspension 0.05% in 3 subjects (3%); either Levocabastine Ophthalmic Suspension 0.05% or Emedastine Ophthalmic Solution 0.05% in 2 subjects (2%) and either Emedastine Ophthalmic Solution 0.05% or placebo in 1 subject (1%). Therefore, the largest possible percentage of burning and stinging attributable to Emedastine Ophthalmic Solution 0.05% in this study was 3% The most common adverse event reported as non-related was headache occurring in 7 of the 64 subjects in the Emedastine 0.05% and Levocabastine 0.05% group. One subject experienced keratopathy in the Emedastine 0.05% + placebo group and was discontinued from the study.*

8.1.3.5 Reviewer's Conclusions Regarding Efficacy Data

Emedastine 0.05% and Levocabastine 0.05% are clinically superior to placebo in inhibiting itching. There is no evidence to support clinical superiority of Emedastine 0.05% over Levocabastine 0.05% with respect to itching. With respect to the inhibition of redness, Emedastine 0.05% and Levocabastine 0.05% are clinically equivalent.

Although the sample sizes were small in the masking control groups, there is no evidence to support that either Emedastine 0.05% or Levocabastine 0.05% are clinically superior to placebo with respect to inhibition of redness.

8.1.4 **Reviewer's Trial # 4**
Sponser's Protocol # C-94-93

8.1.4.1 **Objectives**

1.To evaluate the ocular safety of Emedastine Ophthalmic Solution 0.05% in normal healthy volunteers

2.To determine the safety of Emedastine Ophthalmic Solution 0.05% following topical ocular administration four times daily for 42 days

8.1.4.2 **Design**

Randomized, placebo-controlled, triple-masked, parallel groups study

8.1.4.3 **Protocol**

Each of the 362 subjects was randomly assigned to instill one to two drops of Emedastine Ophthalmic Solution 0.05% or placebo (vehicle) four times daily in each eye for 42 days. Evaluations of visual acuity, ocular signs andsymptoms and intraocular pressure (IOP) were conducted on Day 0 (prior to dosing and approximately 30 minutes after dosing), Day 7 (± 2), 14 (±2), 42 and 36-72 hours after Day 42. Dilated fundus examinations were conducted on Days 0 (prior to dosing) and 42. All subjects completed a diary in which they recorded each time they dosed during the 42-day treatment period.

8.1.4.3.1 **Population**

Healthy subjects of any race, males and nonpregnant females, ages 3 years and older, asymptomatic and free of any concomitant topical or systemic treatment which would interfere with results.

Investigators	**# Enrolled**	**#Completed**
Mark B. Abelson, M.D./No.1028 Ophthalmic Research Associates 863 Turnpike Street, Suite 224 N.Andover, MA 01845	100	94
Gregg J. Berdy, M.D./No. 1335 465 North Bew Ballas Road, Suite 386 Creve Coeur, MO 63141	40	40
Robert A. Laibovitz, M.D./No. 943 Eye Research Associates 3307 Northland Drive, Suite 470 Austin, TX 78731	100	100
David G. Schulman, M.D./No. 1710 Eye Care 999 East Basse Road, Suite 116 San Antonio, TX 78209	122	97

Study Plan

Emedastine LONG TERM Safety Study Plan						
Procedures	Visit 1 Baseline	Visit 2 Day 7 ± 2	Visit 3 Day 14 ± 2	Visit 4 (Telephone) Day 28 ± 2	Visit 5 Day 42	Visit 6 Day 42 + 36-72 hr
Medical History, Informed Consent	X					
Pregnancy Test	X				X	
Pulse & Blood Pressure	X				X	X
Visual Acuity/ IOP/ Slit-lamp	X	X	X		X	X
Dilated Fundus Exam	X				X	
Dispense Medication	X(2)	X(2)	X(4)			
Initial Medication Dose	X					
Thirty Minute Post Dose Follow-up Exam	X					
Dispense Subject Compliance Diary*	X					
Check concurrent drugs/AEs	X	X	X	X	X	
Monitor Subject Diary/Transcribe to CRF		X	X		X	
Recover Medication					X	
Recover Subject Diary					X	
Exit Form						X

8.1.4.3.2 Endpoints

Safety parameters: IOP, pulse, diastolic blood pressure, systolic blood pressure, visual acuity

8.1.4.3.3 Statistical Considerations

Paired t-test for changes from baseline in intraocular pressure (IOP), pulse, diastolic blood pressure, visual acuity

8.1.4.4 Results

8.1.4.4.1 Populations enrolled/analyzed

Demographics

		Emedastine	Placebo	Total
Age	MEAN	30	29	30
	STD	17	16	17
	N	242	120	362
	MIN	3	3	3
	MAX	79	66	79
Age				
3 - 6	N	23	9	32
3 - 16	N	67	33	100
> 16	N	175	87	262
Sex				
MALE	N	98	50	148
FEMALE	N	144	70	214
Race				
CAUC.	N	180	84	264
HISPANIC	N	38	21	59
BLACK	N	23	15	38
ASIAN	N	1	.	1
Iris Color				
BROWN	N	122	51	173
HAZEL	N	37	29	66
GREEN	N	22	9	31
BLUE	N	59	30	89
GREY	N	2	1	3
Investigator				
943	N	67	33	100
1028	N	67	33	100
1335	N	27	13	40
1710	N	81	41	122

Discontinued Subjects

Reason for Discontinuation (Number of Subjects)	Emedastine (N = 242) Number of Subjects (%) SUBJECT NUMBERS	Placebo (N = 120) Number of Subjects (%) SUBJECT NUMBERS
Adverse Events (4)	2 (1%) 4090, 4095	2 (2%) 4072, 4084
Protocol Violations (14)	8 (3%) 1026, 1053, 1095, 1097, 1102, 1112, 1115, 1120	6 (5%) 1006, 1054, 1075, 1084, 1098, 1125
Noncompliance (5)	5 (2%) 1032, 1067, 1121, 4023, 4073	0
Personal Reasons/ Subject Decision (4)	3 (1%) 1038, 1062, 1068	1 (1%) 1029
Lost to Follow-up (3)	1 (<1%) 1108	2 (2%) 1065, 1100
Missed last visit (1)	0	1 (<1%) 1119

APPEARS THIS WAY
ON ORIGINAL

8.1.4.4.2 Safety Outcomes

Frequency of Adverse Events

Coded Adverse Events	Emedastine Ophthalmic Solution 0.05% N=242		Placebo (Emedastine Ophthalmic Vehicle) N=120	
OCULAR	N	%	N	%
Discomfort	7	3	4	4
Hyperemia	7	3	4	3
Dry Eye	6	3	2	2
Corneal Staining	4	2	2	2
Pruritus	7	3	2	2
Blurred Vision	2	1	3	3
Foreign Body Sensation	2	1	1	1
Infiltrate	1	<1	1	1
Tearing	2	1	2	2
Irritation	1	<1	0	
Keratitis	3	1	0	
Conjunctivitis	1	<1	1	1
Lid Edema	1	<1	1	1
Conjunctival Edema	1	<1	0	
Accidental Injury	1	<1		
Lid Margin Crusting	1	<1	0	
Photophobia	1	<1	0	
Hordeolum	0		2	2
Eye Disorder	0		1	1
Decreased Vision	0		1	1

Frequency of Adverse Events Cont'd

NONOCULAR				
Body as a Whole Headache	36	15	24	20
Asthenia	1	<1	0	
Respiratory Rhinitis	10	4	5	4
Skin and Appendages Dermatitis	2	1	0	
Special Senses Taste Perversion	1	<1	0	
Cold Syndrome	9	4	7	6
Pain	9	4	3	3
Infection	6	3	4	3
Back Pain	6	3	0	
Flu Syndrome	4	2	2	2
Surgical/Medical Procedure	3	1	2	2
Accidental Injury	1	<1	3	3
Abdominal Pain	1	<1	1	1
Neck Pain	1	<1	1	1
Neck Rigidity	1	<1	0	
Fever	0		2	2
Cardiovascular Migraine	1	<1	0	
Digestive Gastroenteritis	2	1	0	
Constipation	1	<1	0	
Diarrhea	1	<1	0	
Tooth Caries	1	<1	0	
Hemic and Lymphatic Ecchymosis	0		1	1
Metabolic and Nutritional Diabetes Mellitus	0		1	1

Frequency of Adverse Events Cont'd

Musculoskeletal Myalgia	1	<1	0	
Tendon Disorder	1	<1	0	
Spasm	0		1	1
Nervous Hypesthesia	1	<1	0	
Insomnia	1	<1	0	
Neuritis	1	<1	0	
Somnolence	0		1	1
Respiratory Rhinitis	10	4	4	3
Sinusitis	4	2	0	
Pharyngitis	3	1	0	
Asthma	3	1	0	
Increased Cough	1	<1	2	2
Bronchitis	1	<1	0	
Laryngitis	1	<1	0	
Lung Disorder	1	<1	0	
Pneumonia	1	<1	0	
Skin and Appendages Dermatitis	1	<1	2	2
Skin Discoloration	1	<1	0	
Contact Dermatitis	0		1	1
Special Senses Tinnitus	1	<1	0	
Otitis Media	0		1	1
Urogenital Dysmenorrhea	5	2	2	2
Cystitis	1	<1	0	

Reviewer's Comments: *The most common ocular adverse events reported in this safety study were: discomfort (stinging and burning); hyperemia; dry eye; pruritus; all occurring in approximately 3% of patients receiving Emedastine Ophthalmic Solution 0.5%. Other ocular adverse events which occurred in less than 3% of patients included corneal staining; blurred vision; foreign body sensation; tearing; and keratitis. The most commonly reported non-ocular*

adverse event reported in this study was headache which occurred in 15% of patients receiving Emedastine 0.5% and in 20% of patients receiving placebo (vehicle). Other non-ocular adverse events reported include: rhinitis occurring in 4% of patients receiving Emedastine; back pain occurring in 3% of patients receiving Emedastine and sinusitis occurring in 2% of patients receiving Emedastine.

Intraocular Pressure

Mean Change in Intraocular Pressure (IOP)

Treatment	Mean by Visit						Mean Change			
	Baseline		Day 42		Day 44		Baseline Compared to Day 42[a]		Baseline Compared to Day 44[b]	
	N	IOP (mm Hg) ± SD	N	IOP (mm Hg) ± SD	N	IOP (mm Hg) ± SD	N	IOP (mm Hg) ± SD	N	IOP (mm Hg) ± SD
Emedastine N=242	242	15.9±2.6	225	15.4±2.4	223	15.1±2.5	225	-0.47±2.09	223	-0.83±2.34
Placebo N=120	120	15.7±2.7	111	15.1±2.4	108	14.7±2.5	111	-0.48±2.24	108	-0.80±2.36

[a] p = 0.9653 (Two-sample t-test for comparison between treatments)
[b] p = 0.9106 (Two-sample t-test for comparison between treatments)
For comparison between treatments refer to Appendix I, page 88

Reviewer's Comments: *There was no statistically or clinically significant difference in mean change in IOP between the Emedastine and placebo treatment groups.*

Pulse

Mean Change From Baseline in Pulse

Treatment	Mean by Visit						Mean Change from Baseline			
	Baseline		Day 42		Day 44		Baseline Compared to Day 42[a]		Baseline Compared to Day 44[b]	
	N	Pulse (BPM) ± SD	N	Pulse (BPM) ± SD	N	Pulse (BPM) ± SD	N	Pulse (BPM) ± SD	N	Pulse (BPM) ± SD
Emedastine N=242	242	78.4±13.4	225	78.6±12.7	223	77.1±11.6	225	-0.12±11.27	223	-1.78±12.69
Placebo N=120	120	77.3±13.1	111	75.8±12.0	108	77.2±11.4	111	-2.23±9.69	108	-0.86±12.11

BPM = Beats per minute
[a] p = 0.0937 (Two-sample t-test for comparison between treatments)
[b] p = 0.5331 (Two-sample t-test for comparison between treatments)

Reviewer's Comments: *There was no clinically or statistically significant in mean change in pulse between the two treatment groups.*

Blood Pressure

Mean Change From Baseline in Mean Arterial Pressure (MAP)

Treatment	Mean by Visit						Mean Change from Baseline			
	Baseline		Day 42		Day 44		Baseline Compared to Day 42*		Baseline Compared to Day 44*	
	N	MAP (mm Hg) ± SD	N	MAP (mm Hg) ± SD	N	MAP (mm Hg) ± SD	N	MAP (mm Hg) ± SD	N	MAP (mm Hg) ± SD
Emedastine 0.05% N=242	242	87.26±15.31	225	87.57±13.62	223	87.42±13.63	225	0.10±9.67	223	-0.13±9.93
Placebo N=120	120	85.19±13.65	111	84.80±11.19	108	85.92±12.23	111	0.22±9.68	108	1.44±9.34

* p = 0.9160 (Two-sample t-test for comparison between treatments)
* p = 0.1709 (Two-sample t-test for comparison between treatments)
For comparison between treatments refer to Appendix I, page 88

Reviewer's Comments: *There was no clinically or statistically significant difference in mean change from baseline in mean arterial pressure between treatment groups.*

Dilated Fundus Examination

Dilated fundus examinations (retina/macula/choroid, vitreous, lens, optic nerve, disc pallor) were performed at Visit Day 0 predosing (baseline), Visit Day 42, and unscheduled visits. One adult subject (No. 3015) receiving placebo experienced clinically significant worsening from baseline in retina/macula/choroid and vitreous (Appendix II, page 129). This subject was found to have a retinal hole OS during the Visit Day 42 dilated fundus examination. It was concluded that the retinal hole was probably present at baseline but was not detected during the baseline exam. No subject wearing contact lenses experienced clinically significant worsening from baseline in dilated fundus parameters. No clinically significant differences in dilated fundus parameters were noted between Emedastine Ophthalmic Solution 0.05% and placebo with or without contact lenses. Dilated Fundus Examinations in Children: No subjects 3 to 16 years of age receiving Emedastine Ophthalmic Solution 0.05% or placebo experienced a clinically significant worsening from baseline in dilated fundus parameters.

Visual Acuity
Maximum Change in Visual Acuity at Final Visit (Visit Day 44) Off-Therapy

		2 line Increase		1 line Increase		No Change		1 line Decrease		2 line Decrease	
Treatment	Lens	N	%	N	%	N	%	N	%	N	%
Emedastine	None N=229	6	2.6	26	11.4	171	74.7	25	10.9	1	0.4
	RGP N=4	0	0	0	0	4	100.0	0	0	0	0
	SOFT N=9	0	0	2	22.2	7	77.7	0	0	0	0
Placebo	None N=116	9	7.8	9	7.8	86	74.1	10	8.6	2	1.7
	SOFT N=4	0	0	0	0	4	100.0	0	0	0	0

No patients reported greater than a 2 line change (increase or decrease) in visual acuity.

Reviewer's Comments: *No statistically or clinically significant differences in visual acuity were observed between treatment groups.*

Pupil Diameter
Mean Change in Pupil Diameter

Treatment	Predosing	Postdosing	Postdosing compared to Predosing*
	Mean Pupil Diameter (mm) ± STD	Mean Pupil Diameter (mm) ± STD	Mean Pupil Diameter (mm) ± STD
Emedastine 0.05% (N=20)	4.350 ± 0.587	4.325 ± 0.545	-0.025 ± 0.380
Placebo (N=20)	4.300 ± 0.677	4.300 ± 0.715	0.000 ± 0.397

*p-value for comparison of change in pupil diameter from baseline between treatments = 0.840 (based on two-sample t-test)

Reviewer's Comments: *No statistically or clinically significant differences in pupil diameter were observed between treatment groups.*

8.1.4.5 Reviewer's Conclusions Regarding Safety Data

No clinically significant decrease in visual acuity, increase in IOP, change in pulse or mean arterial pressure, or change in pupil size was observed in subjects receiving Emedastine Ophthalmic Solution 0.05% or placebo.

Significant adverse events reported were stinging/burning, hyperemia, dry eye, and pruritus. Significant non-ocular events were headache, rhinitis and sinusitis.

9 Reviewer's Overview of Efficacy

Emedastine Ophthalmic Solution 0.05% is efficacious in the temporary relief of itching associated with seasonal allergic conjunctivitis. There is no evidence to support clinical superiority over Levocabastine or placebo in the relief of redness.

10 Reviewer's Overview of Safety

Significant adverse events reported were ocular discomfort (burning/stinging), hyperemia, dry eye, pruritus, headache, rhinitis and sinusitis.

Four-Month Safety Update Report-March 1996 through June 1996(submitted 7/22/96)

The frequency and type of adverse events from completed and on-going clinical studies reported in this update are similar to those previously reported in the NDA submission and do not necessitate any changes in the previous conclusions.

5 pages

PURGED

(Draft Labeling)

Medical Officer's Review of NDA 20-706
Amendment

NDA # 20-706
Review #2

Submission date:	10/24/97
Received date:	10/27/97
Review date:	12/ 2/97
Revised date:	12/ 9/97

Proposed Trade name: Emadine

Generic name: Emedastine difumarate ophthalmic solution, (0.05%)

Chemical name: 1H-Benzimidazole,1-(2-ethoxyethyl)-2(hexahydro-4-methyl-1,4-diazepin-1-yl), (E)-2-butenedioate (1:2)

Sponsor: Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Pharmacologic Category: Histamine H_1 antagonist

Proposed Indication(s): Prevention, immediate relief and treatment of the signs and symptoms of allergic conjunctivitis.

Dosage Form and Route of Administration: Topical, ophthalmic solution

NDA Drug Classification: 1-S

Related Reviews: Medical Officer's Review (Ludwig) dated 8/30/96.

Related Drugs: Livostin™ NDA 20-219 Approved

2 Table of Contents

3 Material Reviewed

NDA Volumes 6.1-6.4

4 Chemistry/Manufacturing Controls - See Chemist's Review.

5 Animal Pharmacology/Toxicology - See Original MOR.

6 Clinical Background

6.1 Relevant human experience - See Original MOR.

6.4 Human Pharmacology, pharmacokinetics, pharmacodynamics

Normal volunteers were dosed with 0.01, 0.05, 0.1 and 0.5% Emedastine Ophthalmic Solution BID to both eyes for 15 days (10 subjects per dose group). Plasma samples were collected immediately prior to the morning dose and at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 hours postdose on Days 1 and 15. Emedastine plasma levels were low, generally <0.3 ng/mL with the highest concentration reported being 1.55 ng/mL from a 30 minute, Day 15 sample in the 0.5% dose group. The 0.5% dose group showed modest accumulation with mean C_{max} increasing from 0.64 ± 0.18 ng/mL on Day 1 to 0.94 ± 0.33 ng/mL on Day 15. The corresponding $AUC_{0\text{-}8\ hour}$ values were 3.77 ± 1.26 and 5.31 ± 1.41 ng.hour/mL, respectively. Mean $t_{1/2}$ values on both Day 1 and Day 15 were approximately 10 hours.

6.6 Proposed Directions for Use

The recommended dose in patients 3 years old or greater is one drop in each affected eye twice daily.

7 Description of Clinical Data

EMEDASTINE OPHTHALMIC SOLUTION CLINICAL STUDIES						
Study Type	**Protocol No.**	**Concentration**	**Dosing**	**Control**	**Duration of Dosing**	**No. of Patients**
Comfort Study No. 1	C-93-12	0.5%,0.1%, 0.05%, and 0.01%	Single drop	ACULAR Placebo	1 drop	30
Comfort Study No. 2	C-95-13	0.05%	Single drop, one eye	ACULAR LIVOSTIN	1 drop	30
Comfort Study No. 3	C-95-35	0.05%	Single drop, one eye	ACULAR LIVOSTIN	1 drop	30
Pupil Diameter Study	C-95-11	0.05%	Single drop	Placebo	1 drop	40
Multidose Safety	C-93-16	0.5%,0.1%, 0.05%, and 0.01%	Two drops BID, both eyes	None	15 days	40
Long Term Safety	C-94-93	0.05%	One to two drops, QID	Placebo	6 weeks	362
CAC No. 1	C-93-19	0.5%,0.1%, and 0.05%	One drop on each of two visits	Placebo	2 days - not sequential	240
CAC No. 2	C-94-90	0.005% and 0.05%	One drop on each of two visits	Placebo	2 days - not sequential	120
CAC No. 3	C-95-71	0.05%	Two drops on each of two visits	LIVOSTIN	2 days - not sequential	97
Seasonal AKC	C-94-86	0.05%	One to two drops, QID	2% cromolyn sodium	6 weeks	200 (discontinued after 66 patients were enrolled)*
Seasonal AKC	C-95-54	0.05%	One to two drops, BID	0.05% levocabastine	6 weeks	200

Reviewer's Comments: *See MOR #1 for a review of the majority of these studies. Only protocol C-95-54 has been submitted in this amendment.*

8 Clinical Studies

8.1 Indication # 1

8.1.5 Reviewer's Trial # 5 Sponsor's protocol # C-95-54

8.1.5.1 Objective

The objective of this study is to determine the efficacy and safety of Emedastine 0.05% Ophthalmic Solution administered BID versus Levocabastine 0.05% Ophthalmic Suspension administered BID in the treatment of moderate to severe seasonal allergic conjunctivitis.

8.1.5.2 Design

Randomized, controlled, parallel group, triple-masked comparison of Emedastine 0.05% versus Levocabastine 0.05% with a minimum of 172 evaluable patients (Approximately 200 patients to be enrolled).

Dosage: Emedastine 0.05% and Levocabastine 0.05% were administered BID (approximately at 8.00 a.m. and 8.00 p.m) for 42 days.

8.1.5.3 Protocol

	Screening	Day 0	Day 3 ±1	Day 7 ±2	Day 14±2	Day 30±3	Day 42±3	7 to 10 Days Off Therapy
1-week wash-out	X							
Pregnancy Test (if applicable)	X							X
Inclusion/Exclusion Criteria		X						
Visual Acuity		X	X	X	X	X	X	X
Pupil Diameter		X	X	X	X	X	X	X
Slit Lamp (Signs and Symptoms)		X	X	X	X	X	X	X
Physician's Global Assessment			X	X	X	X	X	X
IOP - Goldmann Applanation Tonometry		X					X	
Fundus Exam		X					X	
Adverse Events			X	X	X	X	X	X
Diary No. 1 Distributed		X						
Diary No. 1 Returned					X			
Diary No. 2 Distributed						X		
Medication Dispensed		X						
Last Day Medication Instilled							X	
Diary No. 2/All Medication Returned							X	
Complete Exit Form								X

8.1.5.3.1 Population

Inclusion Criteria

1. At least (and including) 4+ itching and 2+ conjunctival hyperemia (redness) in both eyes (redness was based on a standard photograph scale supplied to the investigator).

2. History of allergic conjunctivitis for at least one allergy season and a positive skin test (within the past 12 months) to at least one common pollen indigenous to the area at the time of the study.

3. Patients (or their guardians) must have been willing and able to make four daily entries in a diary for the first 14 days of treatment and for the last 12 days of treatment

4. Signed an informed consent form

5. Willing to avoid disallowed medications for at least one week before the study start and during the study period

6. Four (4) years of age and over

Exclusion Criteria

1. Any ocular disease or disorder other than allergic conjunctivitis

2. Known hypersensitivity to any component of test and control articles, including BAC

3. Concomitant medications, systemic and topical, which may interfere with the evaluation of response to therapy; e.g., steroids (hydrocortisone, betamethasone, etc.), nonsteroidal anti-inflammatories, aspirin, anticholinergics, immunosuppressives, mast cell inhibitors (Cromolyn sodium, Lodoxamide, etc.), antihistamines other than the test and control medications object of this investigation and topical ocular vasoconstrictors. All these medications were to be discontinued at least one week before enrollment and for the duration of the study. Allowed: paracetamol for pain and pseudoephedrine hydrochloride (i.e., Sudafed) WITHOUT antihistamine for congestion.

4. Ocular surgery within the last 3 months

5. Wearing of contact lenses less than three days before beginning of the study, or during the course of the study

6. History of ocular hypertension (≥ 21 mmHg) or glaucoma

7. History of retinal detachment, diabetic retinopathy, or any retinal disease which may be progressive during the time course of the study

8. History or evidence of nasolacrimal drainage system malfunction

9. Participation in any other investigational study within one month before entry into this study, or concomitantly with this study

10. Pregnancy or lactation

11. Use of inadequate birth control methods (This applies to females of childbearing potential only.) Adequate birth control=birth control pills, IUD, tubal section or ligation, hysterectomy, and abstinence

	Investigator	Emedastine	Levocabastine
736	D. L. Easty, M.D.,Univ of Bristol, BRISTOL (UK)	10	10
764	A. Secchi, M.D., Univ of Padua, PADUA (Italy)	10	10
768	Ph. Verin, M.D., Centre Jean Abadie, BORDEAUX (France)	30	30
1713	T. R. Carmichael, M.D., New Redruth, ALBERTON 1450 (South Africa)	0	1
1836	R. Brancato, M.D., Hospital San Raffaele, Univ. of Milan, MILAN (Italy)	8	8
1843	G. Ciprandi, M.D., Univ. of Genoa, GENOA (Italy)	10	10
1942	D. J. Coster, M.D., BEDFORD PARK SA 5042 (Australia)	5	4
1947	A. J. G. Apel, M.D., Fig Tree Pocket, BRISBANE (Australia)	2	2
1953	B. T. Kent-Smith, M.D., RANDBURG 2125 (South Africa)	0	1
1955	C. J. Harrisberg, M.D., SANDTON 2146 (South Africa)	6	8
1962	M. T. Coroneo, M.D., RANDWICK NSW 2031 (Australia)	2	1
1967	M. Knorr, M.D., University Eye Hospital, TÜBINGEN (Germany)	2	2
1983	Montserrat Molina, M.D., HOSPITALET DE LLOBREGAT (Spain)	0	0
1984	P. Abrantes, M.D., Hospital de San José, 1150 LISBON (Portugal)	0	1
1995	Ph. Partouche, M.D., 31 Course Vitton, 69006 Lyon (France)	10	9
1996	C. Estivin-Ebrardt, M.D., TOURS (France)	4	6
1997	G. Nemeth-Wasmer, M.D., 2 Place du 2 Fevrier, COLMAR (France)	10	9
1998	G. Leoz, M.D., Clínica Puerta de Hierro, 28035 MADRID (Spain)	0	0

8.1.5.3.2 Endpoints

Itching

Patients were asked, "How often during the last three days did your eyes itch enough that you wanted to rub them?" The term "wanted" was used instead of "did" since interviews with patients have indicated that women who wear makeup will not rub their eyes since rubbing would ruin their makeup.

0	=	None	-	Did not occur
1	=	Rarely	-	Once
2	=	Occasionally	-	At Least Once On Two days
3	=	Frequently	-	At Least Once Every Day
4	=	Very Frequently	-	Two or More Times Every Day

(Redness) Injection Reference photographs were provided.

0	=	Baseline; no dilatation of vessels; only 1-2 naturally prominent scleral vessels which remain relatively constant in size and prominence over a smooth white sclera.
0.5	=	Very fine pink vessels become evident in a delicate web-like pattern; may be in one or more quadrants (medial, lateral, upper, lower).
1.0	=	Vessels are still pink and thin, vessel caliber has not increased; still appears like a delicate web-like pattern, but is more diffuse and appears in more quadrants than 0.5.
1.5	=	Fine pink vessels with some pale red vessels; caliber of vessels is definitively increased; a deeper color and wider caliber than 1.0; can be quadratic.
2.0	=	Color overall is more red than pink; caliber of vessels has increased so that the vessels have lost their delicate web-like pattern; more diffuse than 1.5.
2.5	=	Vessels are definitely red; vessel caliber is increased even further; a deeper color or a more diffuse pattern, spreading out towards the limbus, distinguishes this from a 2.0.
3.0	=	Vessels are red, and are in all quadrants and around the limbus; vessels are very dilated; although it is a thoroughly diffuse pattern, distinct white sclera shows through around the vessels and in the background.
3.5	=	The same as 3.0 but more diffuse; distinguishable from a 3.0 by the significantly less white sclera showing through around the vessels; a 3.5 has very little sclera showing through.
4.0	=	Beefy, tomato red vessels; very dilated and leaky; total involvement of all quadrants and straight through to the limbus 360°; background limbus does not show through white but has turned a pink color from vessel leakage and swelling; distinguishable from a 3.5 by the lack of any white sclera.

Chemosis

0	=	None
0.5	=	Detectable only by slit lamp beam; slight separation of conjunctiva from sclera.
1.0	=	Detectable only by slit lamp beam; definite separation of conjunctiva from sclera.
1.5	=	Detectable with pen light illumination; localized microchemosis.
2.0	=	Visible in normal room light; more diffuse edema.
2.5	=	Conjunctiva elevated to and at the limbus; very diffuse.
3.0	=	Conjunctival pillowing at the limbus; very diffuse and noticeable.
3.5	=	Large pocket of fluid localized anywhere in conjunctiva.
4.0	=	Severe overall ballooning of conjunctiva.

Eyelid swelling

0	=	None
0.5	=	Any detectable change in lids
1.0	=	Edema in one quadrant of lids
1.5	=	Edema in two quadrants of lids
2.0	=	Definite alteration in lid folds
2.5	=	Loss of lid folds
3.0	=	Edema to lash margin
3.5	=	Ptosis
4.0	=	Lid closure

Physician's Global Assessment

0	=	Clinical Cure
1	=	Satisfactory Clinical Response
2	=	Slight Clinical Improvement
3	=	Unchanged
4	=	Slightly Clinically Worse
5	=	Significantly Clinically Worse

Patient Assessment of Redness and Itching (Daily Diary)

	NONE									SEVERE
Morning***	0	1	2	3	4	5	6	7	8	9
Noon	0	1	2	3	4	5	6	7	8	9
Afternoon	0	1	2	3	4	5	6	7	8	9
Evening***	0	1	2	3	4	5	6	7	8	9

***Before Using Drops

8.1.5.3.3 Statistical considerations

The statistical objective of this protocol is to demonstrate equivalence between Emedastine and Levocabastine.

Comparisons between treatments will be performed using analysis of variance. The two treatments will be compared for equivalency. If the 95% Confidence Interval is ≤ 0.5 unit for itching and redness, the two treatments will be declared equivalent.

Based on two-sample t-test with 90% power and two-sided alpha = 0.05, eighty-six (86) evaluable patients per treatment group will be needed to detect differences between treatments greater than 0.5 unit in itching and redness, with standard deviation 1.

8.1.5.4 Results

8.1.5.4.1 Populations enrolled/analyzed - Demographics

		Emedastine	Levocabastine	p-value
Age	Mean	30.10	30.66	0.795
	Std	14.55	17.28	
	Min	4.00	5.00	
	Max	71.00	76.00	
Age group				0.360
4-6	N	6	5	
7-16	N	14	17	
17-64	N	87	83	
> = 65	N	2	7	
Gender				0.385
Male	N	56	51	
Female	N	53	61	
Race				0.369
Caucasian	N	94	99	
Black	N	8	9	
Asian	N	3	.	
Other	N	4	4	
Iris Color				0.718
Brown	N	48	47	
Hazel	N	22	20	
Green	N	12	11	
Blue	N	20	29	
Gray	N	7	5	

Distribution of Pediatric Patients By Age (Years)

Age (Years)	Emedastine (N)	Levocabastine (N)
4	2	0
5	2	1
6	2	4
7	2	2
8	1	5
9	2	1
10	2	1
11	1	3
12	1	3
13	2	1
14	2	1
15	0	0
16	1	0

Discontinued Subjects

Reason Discontinued	Emedastine	Levocabastine
Adverse Event	3	0
Lost to follow-up	6	4
Patient decision	3	2
Noncompliance	3	2
Treatment failure	3	5
Other	2	3
Total	**20**	**16**

Discontinued Patients by Investigator

Treatment	Inv	Pat	Last Visit	Reason Discontinued	Exit Form Comments
Emedastine	736	1212	Day 30	Noncompliance	Patient used all study medication by 7-6-97 despite being instructed on proper usage, and was withdrawn at visit Day 30.
Emedastine	736	1217	Day 14	Adverse event	At visit Day 14 patient was found to have bacterial conjunctivitis and was withdrawn from the study.
Emedastine	764	501	Day 14	Adverse event	Patient complained about rhinitis that needed addition therapy
Emedastine	764	511	Day 30	Treatment failure	Symptoms were slightly better, but clinical signs are worse
Emedastine	764	515	Day 14	Patient decision	Although patient obtained a clinical positive response still did not want continue the study. and this decision was not related with the adverse event reported by the patient.
Emedastine	768	942	Day 14	Adverse event	Mother anxious: "if drop sting give me another prescription" - ok. Nedocromil x3 per Day topically.
Emedastine	1836	604	Day 7	Treatment failure	No comments on exit form
Emedastine	1843	409	Day 30	Lost to follow-up	Patient was contacted on 11-7-96. but she was absent.
Emedastine	1843	419	Day 7	Noncompliance	Patient's mother had a very negative feeling about study drug medication: she gave to her child a not allowed concomitant treatment and stopped without any reason the study drug before the visit
Emedastine	1942	701	Day 7	Treatment failure	No comments on exit form
Emedastine	1942	706	Day 14	Lost to follow-up	No comments on exit form
Emedastine	1955	309	Day 0	Lost to follow-up	Patient never returned after Day 0 even though contacted on +/- Day 3 gave diary results telephonically - lost to follow up after initial assessment - therefore not to be used.
Emedastine	1955	310	History	No study medication	Patient never returned - lost to follow up.
Emedastine	1955	314	Day 0	Lost to follow-up	Never returned after first visit - no success with follow up contacts
Emedastine	1962	1101	Day 42	Patient decision	Patient did not wish to return
Emedastine	1962	1102	Day 7	Prohibited medication	Patient used budesonide
Emedastine	1967	1303	Day 42	Lost to follow-up	No comments on exit form
Emedastine	1995	1401	Day 14	Lost to follow-up	No comments on exit form
Emedastine	1996	1506	Day 3	Sponsor decision	End of recruitment period
Emedastine	1997	1603	Day 7	Patient decision	Visits schedule not compatible with the patient's profession
Emedastine	1997	1610	Follow-up	Patient decision	Patient feels cured - study drug stopped 4 Days before Day 42 visit.
Levocabastine	736	1208	Day 0	Patient decision	He didn't notice any significant changes while taking the medication. Patient did not bring diary #1 back.
Levocabastine	736	1213	Day 30	Noncompliance	Patient used all bottles of study drug before visit Day 30 despite being instructed on proper usage instructions..

Levocabastine	736	1219	Follow-up	Noncompliance	Patient ran out of study medication 24 hours before Day 30 visit, study medication was then supplied to patient on Day 33, 12-7-97 so patient was off treatment for 3 Days in total, new medication number was 1221.
Levocabastine	768	941	Day 14	Treatment failure	No comments on exit form
Levocabastine	1713	101	Day 7	Treatment failure	Allergic conjunctivitis too severe for successful treatment without steroid medication
Levocabastine	1843	401	Day 30	Patient decision	Patient had an improvement and decided not to continue the study.
Levocabastine	1843	410	Day 7	Patient decision	Patient's mother contacted by phone, decided not to continue study any more.
Levocabastine	1942	705	Day 14	Lost to follow-up	No comments on exit form
Levocabastine	1955	301	Day 30	Lost to follow-up	No comments on exit form
Levocabastine	1955	305	Day 7	Lost to follow-up	Repeated attempts to contact. Patient did not return even though said she would - decided on 1/3/96 lost to follow up
Levocabastine	1955	307	Day 3	Lost to follow-up	Lost to follow up. Did not return diary
Levocabastine	1962	1103	Day 7	Treatment failure	Did not feel medication was sufficient. This patient did not perform a pregnancy test as they were sure they weren't pregnant as they were on the pill.
Levocabastine	1996	1507	Day 3	Sponsor's decision	End of study.
Levocabastine	1997	1601	Day 14	Treatment failure	No comments on exit form
Levocabastine	1997	1611	Day 7	Treatment failure	No comments on exit form
Levocabastine	1997	1619	Day 3	Other	Skin test not very positive (performed on 9/5/97); patient did not have pollin allergy last year (1996)

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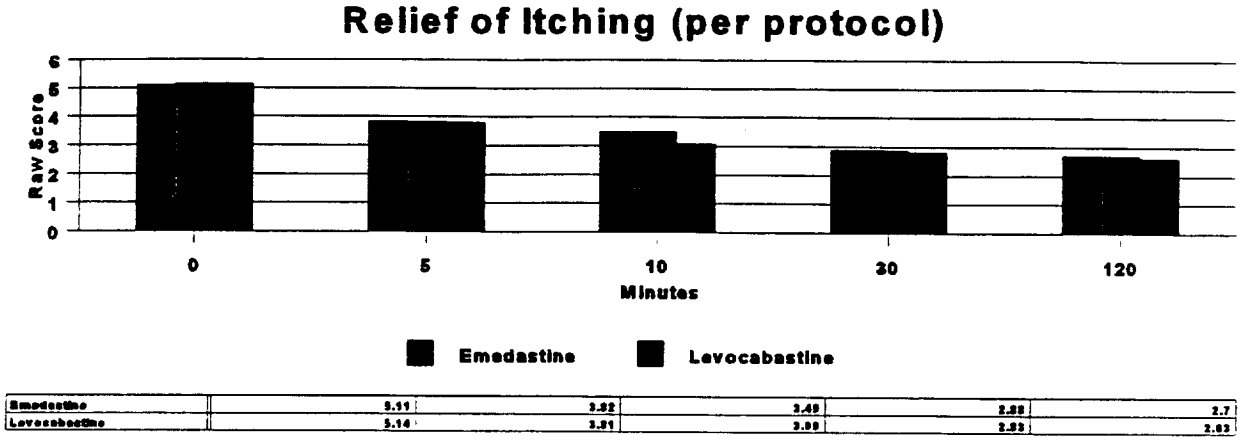
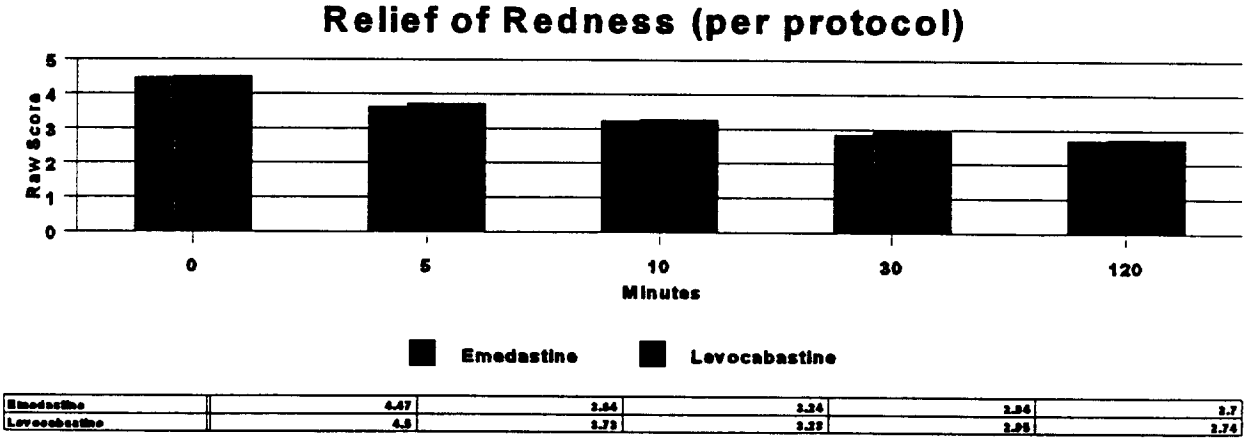
ON ORIGINAL

8.1.5.4.2 Efficacy endpoint outcomes

Immediate Drug Effect



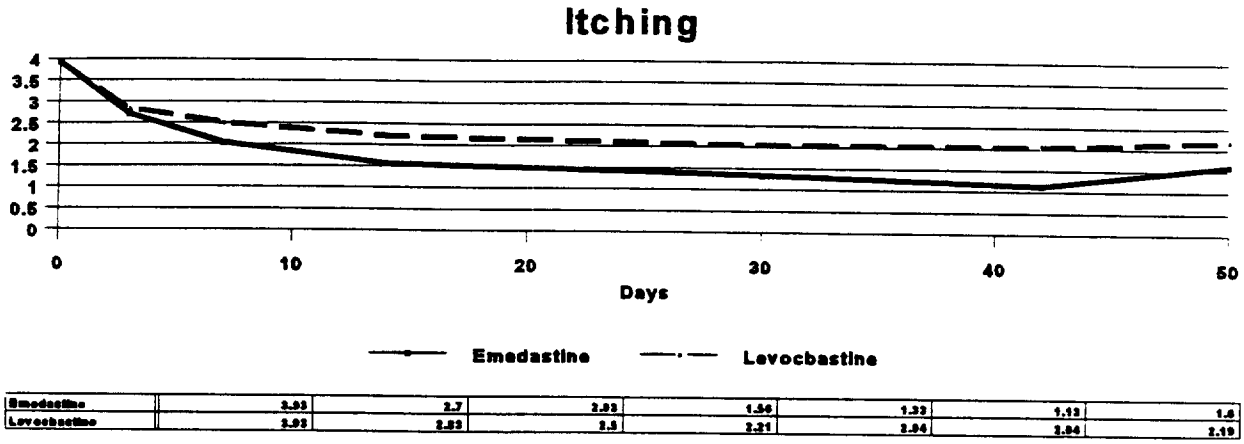
Emedastine	5.11	3.92	3.49	2.88	2.7
Levocabastine	5.14	3.91	3.99	2.93	2.83



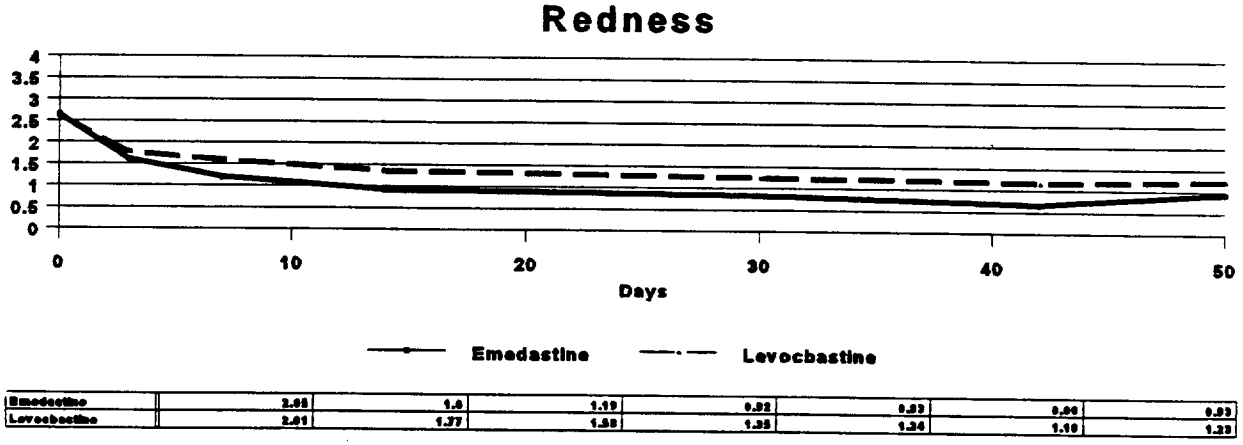
Emedastine	4.47	3.64	3.24	2.86	2.7
Levocabastine	4.9	3.73	3.33	2.95	2.74

Reviewer's Comments: *There is no significant difference between groups during the first two hours.*

Physician Office - Observed Signs and Symptoms



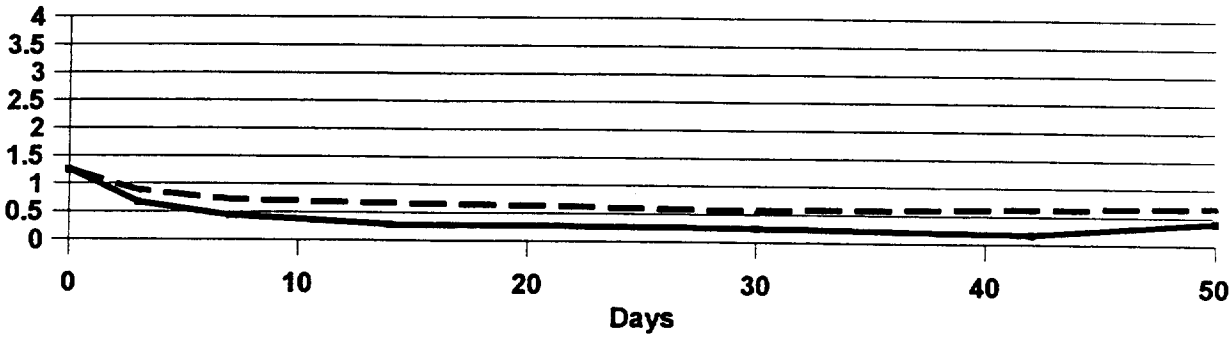
Emedastine	2.93	2.7	2.33	1.56	1.33	1.13	1.0
Levocbastine	2.93	2.83	2.5	2.21	2.04	2.04	2.19



Emedastine	2.08	1.6	1.19	0.92	0.83	0.86	0.93
Levocbastine	2.01	1.77	1.58	1.35	1.24	1.16	1.23

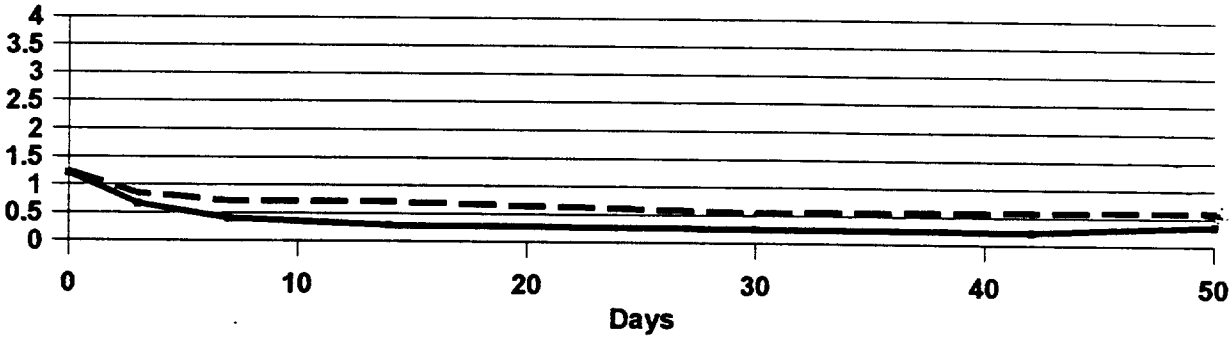
Reviewer's Comments: *The differences are statistically significant after day 7 in favor of emedastine.*

Chemosis



Emedastine	1.25	0.67	0.44	0.29	0.25	0.17	0.4
Levocbastine	1.26	0.89	0.73	0.67	0.57	0.62	0.67

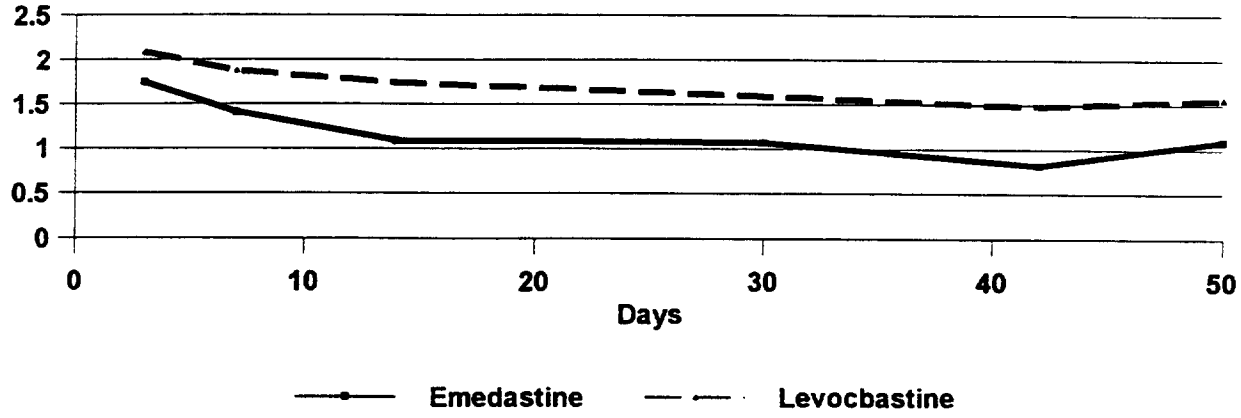
Eyelid Swelling



Emedastine	1.21	0.67	0.4	0.29	0.26	0.23	0.36
Levocbastine	1.24	0.86	0.72	0.71	0.56	0.59	0.62

Reviewer's Comments: *There were statistically significant differences after day 7 between groups in favor of emedastine.*

Physician's Impression



Emedastine		1.75	1.41	1.09	1.07	0.82	1.09
Levocbastine		2.09	1.88	1.74	1.59	1.48	1.56

Reviewer's Comments: *There was a statistically significant difference between groups in favor of emedastine.*

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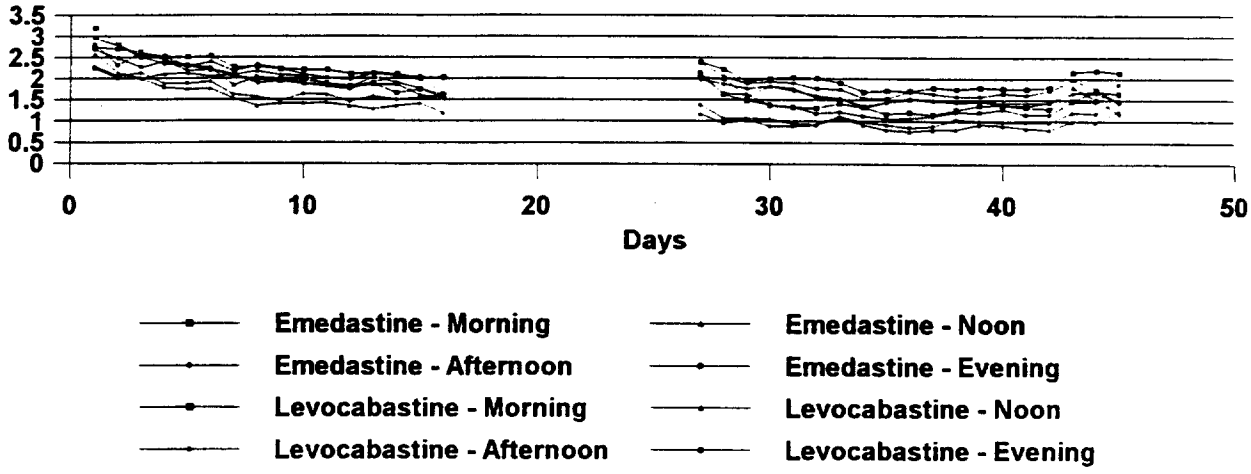
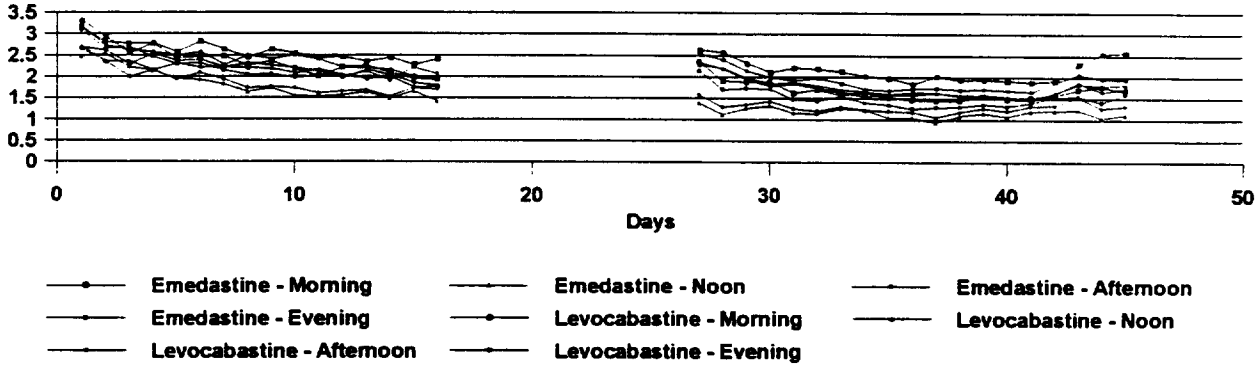
Diary

Itching - Diary Data (Intent to Treat)

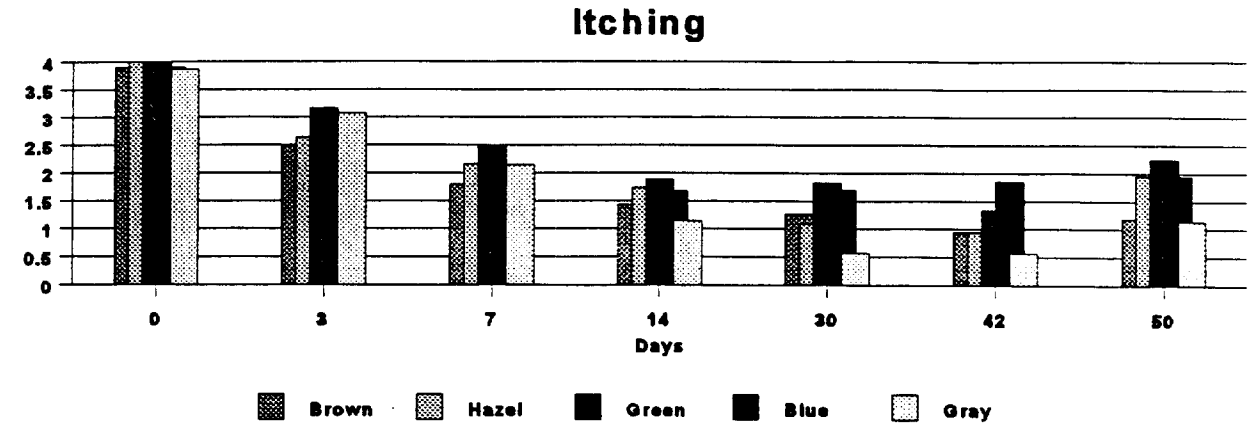


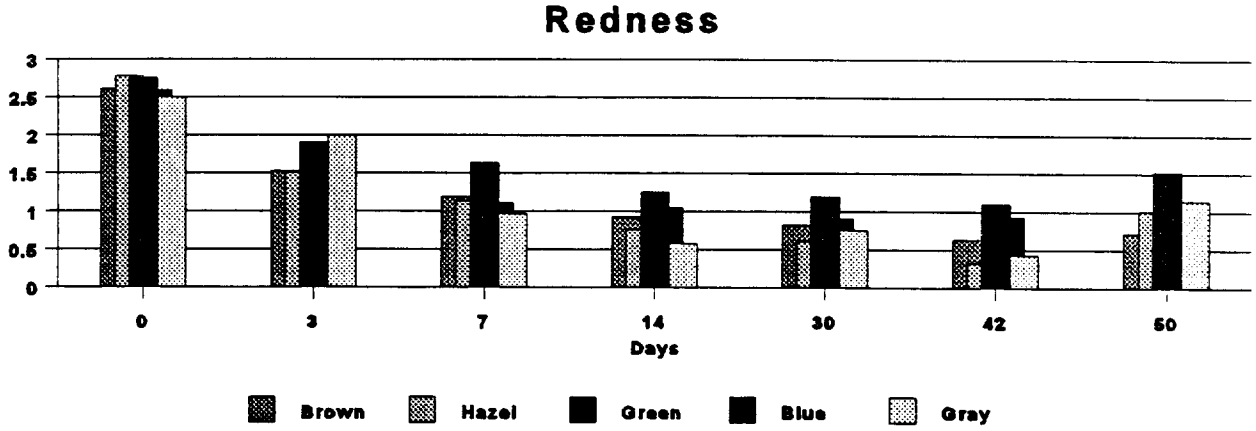
Redness - Diary Data (Intent to Treat)



Reviewer's Comments: *There is a general, although marginal superiority of emedastine over levocabastine in the daily diary reports.*

Iris Color





Reviewer's comments: *There are no clinically significant differences.*

8.1.5.4.3 Safety outcomes

Visual Acuity

Treatment	Total	No Change or Improvement		One Line Decrease		Two Line Decrease		Greater Than a Two Line Decrease	
	N	N	%	N	%	N	%	N	%
Emedastine 0.05%	107	103	96.3	4	3.7	0		0	
Levocabastine 0.05%	111	107	96.4	3	2.7	0		1	0.9

Reviewer's Comments: *Visual acuity should have been reported as the number of eyes with 1, 2 and greater than 2 lines of* ***both*** *improvement and decrease from baseline.*

Frequency and Incidence of Adverse Events

	Emedastine 0.05% N=109		Levocabastine 0.05% N=112	
	N	%	N	%
Ocular				
Discomfort	9	8.3	12	10.7
Blurred Vision	4	3.7	1	0.9
Lid Edema	3	2.8		
Pruritus	2	1.8	3	2.7
Dry Eye	2	1.8		
Conjunctivitis	2	1.8		
Hordeolum	2	1.8		
Tearing	2	1.8	1	0.9
Eye Fatigue	1	0.9		
Corneal Infiltrate	1	0.9		
Foreign Body Sensation	1	0.9		
Hyperemia	1	0.9		
Lid Margin Crusting	1	0.9		
Decreased Visual Acuity	1	0.9		

	Emedastine 0.05% N=109		Levocabastine 0.05% N=112	
	N	%	N	%
Non-ocular				
Body as a Whole				
Headache	2	1.8	2	1.8
Back Pain	2	1.8		
Allergy	1	0.9	1	0.9
Cold Syndrome	1	0.9	1	0.9
Accidental Injury	1	0.9	1	0.9
Flu Syndrome	1	0.9		
Infection	1	0.9		
Surgical/Medical Procedure	1	0.9		
Cardiovascular				
Hypertension			1	0.9
Migraine	2	1.8		
Digestive				
Gastroenteritis			1	0.9
Nervous				
Anxiety			1	0.9
Hypesthesia			1	0.9
Neuralgia	1	0.9		
Respiratory				
Asthma			2	1.8
Pharyngitis			1	0.9
Rhinitis	3	2.8	3	2.7
Increased Cough	1	0.9		
Skin and Appendages				
Eczema			1	0.9

9 Summary Efficacy Conclusions

The allergen challenge studies (C-94-90 and C-95-71) demonstrated emedastine's efficacy with respect to the relief of itching for a 4 hour period. The environmental study (C-95-54) demonstrated emedastine's efficacy with respect to the relief of redness.

10 Summary of Safety

The most frequently reported adverse experiences were: abnormal dreams, asthenia, blurred vision, burning or stinging, corneal infiltrates, corneal staining, dermatitis, discomfort, dry eye, foreign body sensation, headaches, hyperemia, keratitis, pruritus, rhinitis, sinusitis, taste perversion and tearing.

Overall Frequency and Incidence of Adverse Events for Emedastine
(C-94-93, C-95-54)

Coded Adverse Events	N=351	
	N	%
Ocular		
Discomfort	16	4.6
Pruritus	9	2.6
Dry Eye	8*	2.3
Hyperemia	8	2.3
Blurred Vision	6*	1.7
Corneal Staining	4*	1.1
Tearing	4	1.1
Lid Edema	4	1.1
Foreign Body Sensation	3*	0.9
Keratitis	3	0.9
Conjunctivitis	3	0.9
Infiltrate	2	0.6
Lid Margin Crusting	2	0.6
Hordeolum	2	0.6
Irritation	1	0.3
Eye Fatigue	1	0.3
Conjunctival Edema	1	0.3
Accidental Injury	1	0.3
Photophobia	1*	0.3
Decreased Visual Acuity	1	0.3

Coded Adverse Events	N=351	
	N	%
Nonocular		
Body as a Whole		
Headache	38[a]	10.8
Cold Syndrome	10	2.8
Pain	9	2.6
Back Pain	8	2.3
Infection	7	2.0
Flu Syndrome	5	1.4
Surgical/Medical Procedure	4	1.1
Accidental Injury	2	0.6
Asthenia	1	0.3
Abdominal Pain	1	0.3
Neck Pain	1	0.3
Neck Rigidity	1	0.3
Allergy	1	0.3
Cardiovascular		
Migraine	3	0.9
Digestive		
Gastroenteritis	2	0.6
Constipation	1	0.3
Diarrhea	1	0.3
Tooth Caries	1	0.3
Musculoskeletal		
Myalgia	1	0.3
Tendon Disorder	1	0.3
Nervous		
Hypesthesia	1	0.3
Insomnia	1	0.3
Neuritis	1	0.3
Neuralgia	1	0.3
Respiratory		
Rhinitis	13	3.7
Sinusitis	4	1.1
Pharyngitis	3	0.9
Asthma	3	0.9
Increased Cough	2	0.6
Bronchitis	1	0.3
Laryngitis	1	0.3
Lung Disorder	1	0.3
Pneumonia	1	0.3
Skin and Appendages		
Dermatitis	2	0.6
Skin Discoloration	1	0.3
Special Senses		
Taste Perversion	1	0.3
Tinnitus	1	0.3
Urogenital		
Dysmenorrhea	5	1.4
Cystitis	1	0.3

[a] Event occurred in one subject wearing soft contact lenses
[b] Event occurred in one subject wearing rigid gas permeable contact lenses

6 pages

PURGED

Draft Labeling

13 Recommendations

1. With the revisions identified in this review, NDA 20-706, Emadine (emedastine difumarate ophthalmic solution) 0.05% is recommended for approval for the temporary relief of signs and symptoms of allergic conjunctivitis.

2. The applicant should submit a revised analysis of the visual acuity results. Visual acuity should have been reported as the number of eyes with 1, 2 and greater than 2 lines of **both** improvement and decrease from baseline.

/s/ 12/9/97

Wiley A. Chambers, M.D.

cc: Original NDA 20-706
HFD-550
HFD-550/PM/LoBianco
HFD-830/CHEM/Lin
HFD-805/MICRO/Vincent
HFD-550/PHARM/Yang
HFD-550/MO/Ludwig
HFD-550/MO/Chambers