

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-803

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-803

Original

NDA #20-803	Submission:	1/31/97
M.O. Review #1	Review completed:	8/11/97
	Revised printing:	1/27/98

Proposed Tradenames: Alrex or Altrin
Generic name: Loteprednol etabonate ophthalmic suspension, 0.2%

Chemical name: Chloromethyl-17 α -[(ethoxycarbonyl-oxy)-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 carboxylate

Sponsor: Pharmos Corporation
 2 Innovation Drive, Suite A
 Alachua, FL 32615

Pharmacologic Category: Steroid

Proposed Indication(s): Treatment of signs and symptoms of seasonal allergic conjunctivitis

Dosage Form and Route of Administration: Ophthalmic suspension for topical ocular administration

NDA Drug Classification: 1S

Related INDs:

Related NDAs: NDA 20-583 Loteprednol etabonate ophthalmic suspension, 0.5%
 NDA 20-841 Loteprednol etabonate ophthalmic suspension, 0.5%

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3 Material Reviewed

NDA 20-803 Volumes 1.1, 1.16-35

NDA 20-583 Studies by reference - See Medical Officer's Review (MOR)

4 Chemistry/Manufacturing Controls - see Chemistry Review

Raw Material	Quantity mg/mL	% label excess	Range
Loteprednol etabonate			
Povidone USP			
Benzalkonium Chloride.			
Edetate disodium			
Glycerin			
Tyloxapol			
Purified water	QS to 1 mL		
Sodium Hydroxide	Adjust pH		
Hydrochloric acid	Adjust pH		

Additional Specifications:

pH

Osmolality 250-310

Particle size

Sterility USP

Preservative efficacy USP

Reviewer's Comments:

- Issues related to water loss and the formation of "aggregate" material after storage of inverted containers will need to be resolved prior to approval.*
- The pH range in the NDA summary differs from other sections of the NDA. The range should be clarified.*

5 **Animal Pharmacology/Toxicology** - See Pharmacologist's Review
No additional issues identified.

6 **Clinical Background** *See MOR of NDA 20-583*

6.1 **Relevant human experience** No previous human experience.

6.3 **Foreign experience** No foreign marketing experience. No pending foreign applications.

6.4 **Human Pharmacology**
Pharmacokinetics & pharmacodynamics: *See MOR NDA 20-583*

7 **Description of Clinical Data Sources**

Review Number	Protocol	Indication	Design	Treatment Arms	Number in each arm	Age Range	% (♂/♀) B/W/D	Duration of treatment
1	143	Allergic Conjunctivitis	Parallel Double masked	Loteprednol Vehicle	66 67	23-73	(50/50) 0/64/39	42 days
2	144	Allergic Conjunctivitis	Parallel Double masked	Loteprednol Vehicle	67 68	19-74	(46/54) 0/67/32	42 days
3	141	Allergic Conjunctivitis	Paired eye Double masked	Loteprednol	60	19-85	(55/45) 0/97/3	28 days
4	145	Allergic Conjunctivitis	Paired eye Double masked	Lotepred 0.1% Lotepred 0.2% Lotepred 0.3% Lotepred 0.5%	28 31 29 27	19-86	(51/49) 0/99/1	28 days

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8 Clinical Studies**8.1 Indication # 1 Seasonal Allergic Conjunctivitis****8.1.1 Study #1 Protocol # 143**

Title: Safety and efficacy of loteprednol etabonate in the treatment of seasonal allergic conjunctivitis (QID dosing).

Objective: To evaluate the efficacy and safety of loteprednol etabonate 0.2% ophthalmic suspension in the treatment of signs and symptoms of environmental seasonal allergic conjunctivitis.

Study Design: A randomized, double-masked, placebo controlled, parallel group multicenter (3 sites) study.

Test Drug Schedule: All subjects received either loteprednol etabonate 0.2% ophthalmic suspension (LE), or placebo (vehicle) bilaterally, QID for 42 days.

Investigators:	Number of Patients Enrolled:
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Steven J. Dell, M.D.(#174) Eye Care Austin 1700 S. Mo-Pac Austin, TX 78746	34
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George M. Lowry, M.D.(#175) Vision Care 8123 Broadway San Antonio, TX 78209	60
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James A. Northcutt, M.D. (#178) Northcutt Eyecare Center 903 South W.W. White Rd. San Antonio, TX 78220	39
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Study Plan

This was a prospective, double masked, placebo controlled, multi center (3), study in patients with signs and symptoms of seasonal allergic conjunctivitis (SAC). Enrolled in the study were one hundred and thirty three (133) subjects, with a history of positive skin prick or RAST test, and at the time of enrollment, presenting with moderate to severe signs and symptoms of seasonal allergic conjunctivitis caused by mountain

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cedar pollen. Subjects were randomized to receive either loteprednol etabonate 0.2% ophthalmic suspension (LE) or placebo (vehicle), bilaterally, for 42 days.

Ocular safety evaluations included an external examination, slit lamp examination, tonometry and visual acuity taken prior to enrollment and at scheduled times during the study.

VISIT	Screen 1	2	3	4	5	6	Exit
(DAY)	-21 to 0	2/3	5-10	11-17	21-34	35-48	
PROCEDURE							
Informed Consent	x ^b						
Inclusion/Exclusion	x ^b						
Demographics, History	x ^b						
Medication History	x ^b						
Skin Test Results	x ^b						
Pregnancy Test	x ^a						x ^a
Visual Acuity	x ^b	x	x	x	x	x	
Ocular Signs & Symptoms	x ^{b,c}	x	x	x	x	x	
Intraocular Pressure	x ^b	x	x	x	x	x	
Undilated Fundus Exam	x ^b						x
Issue Medication	x ^b			x	x		
Issue Diary	x ^b						
Recover Diary			x	x	x		x
Investigator Global Assessment			x	x	x	x	
Recover Medications				x	x		x
Complete Exit Form							x
Dismiss Patient							x
Daily Environmental Allergen Counts ^d	x	x	x	x	x	x	x

^a Women of childbearing potential only.

^b Day -21 to Day-1 and Day 0 can be combined

^c Pre-treatment and 1 and 2 hours (\pm 10 min) post instillation of first drop

^d Daily Environmental Allergen Counts were required to be recorded until at least until 10 February 1996.

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Inclusion Criteria:

- Adults, at least 18 years of age, of either sex and any race.
- Experience itching (at least 4+), and redness (at least 2+) due to pollen at Visit 1.
- Documentation of a positive allergy test to mountain cedar pollen by skin test within 12 months or RAST test within 36 months.

Exclusion Criteria

- Pregnant or lactating females.
- Females of childbearing potential who were not using adequate birth control.
- Previous allergic hypersensitivity to corticosteroid, loteprednol etabonate or to any component of the study medication.
- Expected concurrent ocular therapy with a non-steroidal anti-inflammatory agent, mast cell stabilizer, antihistamine, decongestant or beta-blocker during the period of masked medication treatment.
- Use of the medications listed above within 48 hours prior to Visit 1 (Day 0).
- Therapy with systemic or topical (ocular) corticosteroids within two weeks prior to the start of the study.
- Any abnormality preventing reliable applanation tonometry in either eye.
- Intraocular pressure that is greater than 21 mm Hg in either eye or any type of glaucoma.
- History of intraocular or laser surgery within the past six months.
- Best corrected (by pinhole) distance visual acuity (Snellen) in either eye worse than or equal to 20/100.
- Anticipated travel for more than a 24 hour period greater than 50 miles outside of the San Antonio/Austin area.
- Presence of any ocular pathology other than acute, seasonal allergic conjunctivitis (i.e., excluded is vernal conjunctivitis, GPC, viral or bacterial conjunctivitis or perennial allergic conjunctivitis).
- History of any severe/serious ocular pathology or medical condition (including systemic allergic disorders such as asthma or rhinitis) that could result in the patient's inability to complete this study.
- Previous participation in this study.
- Participation in any study under an IND within the past 30 days.
- Unlikely to comply with the protocol instructions for any reason (e.g., confusion, infirmity, alcohol or drug abuse).
- Contact lens wear during the course of the study.

Masking

While the physical appearance of the study medications was different (i.e., loteprednol etabonate 0.2% ophthalmic suspensions - opaque, white suspension; placebo (vehicle) - clear solution), this study was considered a double masked evaluation. Medications were supplied in opaque plastic containers with opaque dropper tips. Subjects were admonished not to discuss their medication with others on the study or in specific detail with the Investigator. The Investigator did not dispense study medication to subjects. A third party at the Investigator's office who was not responsible for patient assessments was given the responsibility of dispensing study medication to the subject, instilling medication when necessary and instructing the subject in study medication use.

Efficacy Criteria

The primary efficacy variables were bulbar conjunctival injection (sign) and ocular itching (symptom). Other supportive efficacy variables were discomfort, foreign body sensation, burning/stinging, photophobia, tearing and discharge (symptoms) and palpebral conjunctival injection, chemosis and erythema (signs).

An Investigator Global Assessment of the Control of Signs and Symptoms of SAC was recorded at Visits 3, 4, 5 and 6 for Days 0 to 7, 0 to 14 (inclusive), 15 to 28 and 29 to 42, respectively. This was to be based on the two previous clinical evaluations and daily diary data over a 14 day (approximate) period, except for Visit 3 (7 days). The rating after 2 weeks (Visit 4) was considered a secondary efficacy parameter.

Most signs and symptoms were rated using a four point scale (0 - 3) where 0 = absent, 1 = mild, 2 = moderate and 3 = severe.

The Investigator Global Assessment used a 5 point scale (0-4) where 0=fully controlled, 1=reasonably controlled, 2=fairly controlled, 3=poorly controlled, 4=not controlled.

For selected parameters definitions were provided with the scales, as shown as follows:

Bulbar Conjunctival Injection

0	Absent	A normal, quiet eye; some subjects will exhibit rare vessels which are naturally prominent either by location or a large normal vessel diameter.
1	Mild	Slightly dilated blood vessels; color of vessels is typically pink; can be quadrant (i.e., quadrant specific).
2	Moderate	More apparent dilation of blood vessels; vessel color is more intense (redder); involves the vast majority of the vessel bed.
3	Severe	Numerous and obvious dilated blood vessels; in the absence of chemosis the color is deep red - in the presence of chemosis, the leaking interstitial fluid may make the color appear less red or even pinkish; is not quadrant.

Itching:

A sensation of the need to scratch or rub the eyelids or the periorbital area.

0	Absent	No desire to scratch or rub area.
1	Trace	Rare need to scratch or rub area but sensation is not completely absent.
2	Mild	Occasional need to scratch or rub area.
3	Moderate	Frequent need to scratch or rub area.
4	Severe	Constant need to scratch or rub area.

<u>Discharge:</u>		Involves the lash margin and adjacent eyelids and include crusts, collarettes, scaling, etc.
0	Absent	No abnormal discharge.
1	Mild	Small amount of mucopurulent or purulent discharge noted in the lower cul-de-sac. No true matting of eyelids upon awakening in the morning.
2	Moderate	Moderate amount of mucopurulent or purulent discharge is noted in the lower cul-de-sac. Frank matting together of eyelids in the morning upon awakening.
3	Severe	Profuse amount of mucopurulent or purulent discharge noted in the lower cul-de-sac and in the marginal tear strip.

Photophobia: Abnormal ocular or periocular discomfort, pain or sensitivity upon exposure to light.

0	Absent	Absence of positive sensation
1	Mild	Very minimal light intolerance which may require some degree of sunglass protection to eliminate the symptom, notice primarily in sunlight.
2	Moderate	Infrequent or intermittent discomfort in the globe associated with exposure to room light or sunlight which is only partially relieved by dark glasses or subdued light. The symptoms still persist to some degree even with sunglasses.
3	Severe	Constant or nearly constant exquisite pain in the eye that is not relieved by sunglasses and is only relieved by total occlusion of the eye. This total occlusion can be achieved with an eye patch or by closing the eyes. This sensation is so significant that frequently bed rest and occasionally systemic sedation is required to relieve this severe grade of symptom.

Safety Criteria

Ocular safety examinations included an external examination, slit lamp examination, funduscopy, applanation tonometry and visual acuity, taken prior to enrollment and at scheduled times during the study. Systemic safety evaluation was obtained by subject comment with physician follow-up. Safety parameters were tabulated to identify those showing a difference in incidence rate between treatment groups.

Allergen Counts

During the study all investigators were required to record local environmental allergen counts from the time of the first screening visit until all patients had completed the study.

The study was carried out during the mountain cedar pollen season in South Central Texas (December 1995 to February 1996). For safety evaluation some patients continued taking the test article beyond the active pollen season. The final on-study patient day was 9 March 1996.

Concurrent Therapy

The following systemic medications were allowed to be used concurrently: NSAID's, oral birth control pills, estrogen replacement, thyroid preparations, insulin, hypoglycemic agents and anti-microbials for non-ocular conditions. The following nasal and ocular rescue medications could be used as needed to control **EXCESSIVE** nasal and ocular allergic symptoms: phenylephrine hydrochloride nasal solution (Neo-Synephrine®, Dristan®, etc.) and cromolyn sodium nasal solution (Nasal crom®) could be used at the onset of nasal allergic symptoms. The only allowed ocular rescue medication was artificial tears. Those individuals receiving immunotherapy (allergy shots) should have been on a stable regimen prior to the last allergy season and must have no unusual changes to their dosing regimen during the period of masked medication and within two (2) days prior to the Enrollment exam. Patients receiving concurrent medication during the study that was prohibited were to be discontinued from the study as a protocol violation. Patients requiring additional ocular medication other than the masked study medication or artificial tears during the study were to be discontinued from the study as a protocol violation or a treatment failure and placed on appropriate medication. Specifically excluded were: ocular steroids, ocular non-steroidal anti-inflammatory agents, and ocular mast cell stabilizers; systemic steroids, systemic antihistamines and systemic decongestants. All concurrent drug use was to be documented in the Case Report Form.

The target sample size was 64 evaluable patients per treatment group (total = 128 patients). There were 133 patients randomized to treatment out of 387 patients screened. Sixty six were assigned to receive LE and 67 were assigned to receive placebo. The first patient was enrolled on 19 December 1995 and the last patient visit occurred on 9 March 1996. Patients who discontinued treatment before Visit 6 (Day 42) were considered to have not completed the study. One hundred twenty six (126) patients completed treatment through Visit 6, and thus, the study. Four (4) patients (2 on LE; 2 on placebo) were discontinued due to a medical event, one patient was lost to follow-up (placebo), and two patients (both on placebo) due to reasons unrelated to the study as shown below:

- | | | | |
|---|--------------------|--------|--|
| ● | 174-3004 (Placebo) | Day 16 | Terminated: Severe itching |
| ● | 174-3014 (Placebo) | Day 7 | Discontinued: Protocol violation (Patient used Alka-Seltzer Plus®) |
| ● | 174-3019 (Placebo) | Day 22 | Discontinued: Needed to travel |
| ● | 175-3084 (LE) | Day 7 | Terminated: Elevated IOP, O.U. |
| ● | 175-3093 (LE) | Day 31 | Terminated: Acute pharyngeal reaction, headache |
| ● | 175-3097 (Placebo) | Day 1 | Terminated: Viral conjunctivitis |
| ● | 178-3170 (Placebo) | Day 0 | Discontinued: Lost to follow-up |

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There was one patient with no on-treatment evaluation (178:3170, placebo). This patient was not included in the intent to treat analysis. For the intent to treat analysis, all patient data for Visit 2 (Day 2/3), Visit 3 (Day 7) and Visit 4 (Day 28) were included in the primary intent to treat analysis without regard to whether the visits were in the day range specified in the protocol.

A threshold pollen count of $100/m^3$ was set *a priori* in the study protocol. Pollen counts by date for each of the two cities with investigational sites are shown. For the efficacy analysis, no visits within the first two weeks were disqualified due to evaluations after the allergy season. For visits 5 and 6 (four and six weeks), only visits which were in the defined allergy season were used in the intent-to-treat efficacy analysis.

The pollen count in Austin (Investigator 174) was over $100/m^3$ after 11 December 1995 and the first patient entered the study on 21 December 1995. The pollen count in San Antonio (Investigators 175 and 178) was over $100/m^3$ after 14 December 1995 and the first patient entered on 19 December 1995. All patients had itching and bulbar injection of sufficient severity to qualify.

After 28 January 1996 in Austin and 9 February 1996 in San Antonio pollen counts were mostly under $100/m^3$ and these dates were determined to be the end of the mountain cedar season prior to unmasking the study. There were 3 patients with Visits 3 and 4 after the season and 12 patients with Visit 4 afterwards.

	Austin	San Antonio
Investigator(s)	174	175, 178
Pollen > $100/m^3$	12 December 1995	15 December 1995
First patient enrolled	21 December 1995	19 December 1995
Last patient enrolled	25 January 1996	27 January 1996
Pollen < $100/m^3$	28 January 1996	9 February 1996

A valid visit for a patient required that the patient had to take study medication within 48 hours. There were 2 scheduled visits that occurred more than 48 hours after the last dose; these were Visit 6 evaluations that occurred after the end of the mountain cedar season. A tighter criterion was applied for a per protocol valid visit. Study medication had to be taken within 4 hours of the visit, disallowed medications were not to be taken prior to the visit and the visit had to be within the day range specified in the protocol.

One LE and two placebo patients exceeded the four hour limit at their final visit, but these visits were after the end of the mountain cedar season. Disallowed medications were taken by 2 LE and 2 placebo patients. One placebo patient (174:3014) was dropped because of this deviation from the protocol; one (175:3093) was discontinued at an unscheduled visit after being instructed to begin treatment with a disallowed medication. The LE patient (174:3016) and the placebo patient (178:3189) continued in the study after their deviations. There were 3 LE patients and 1 placebo patient who were off-schedule for visits that occurred after the end of the mountain cedar season. There were 1 LE (178:3182) and 2 placebo patients (175:3116 and 178:3184) who were off schedule during the season for Visit 3, 4 and 2, respectively.

It was anticipated that the mountain cedar season would end before Visits 5 (Day 28) and Visit 6 (Day 42) for many patients. These visits were not to be included in the intent to treat statistical analysis of Visit 5 or 6. The per protocol criteria disallowed any visit after the end of the mountain cedar season.

There was 1 placebo patient (175:3097) who developed viral conjunctivitis on Day 1 in the right eye. The ratings for the left eye were used in the intent to treat analysis, but failed to meet the criteria of an on-schedule visit for per protocol. There were 2 additional missed visits (LE 174:3009 Visit 3 and placebo 174:3025 Visit 2).

**APPEARS THIS WAY
ON ORIGINAL**

Pollen Counts

WEEK BEGINNING	CITY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
11DEC95	AUSTIN	47	1720	4005	3750	3250	325	300
	SAN ANTONIO	0	0	20	0	990	14100	1590
18DEC95	AUSTIN	188	287	105	253	1700	355	25
	SAN ANTONIO	1870	2330	830	100	70	50	90
25DEC95	AUSTIN	70	1800	4515	8000	1145	2020	3010
	SAN ANTONIO	50	160	40	16500	7250		
01JAN96	AUSTIN	3002	2960	1150	3885	3650	3240	1950
	SAN ANTONIO	50000	18100	1420	700	200	12200	13480
08JAN96	AUSTIN	1980	1460	2085	1500	2350	2100	2025
	SAN ANTONIO	25200	650	5400	29000	21500	50000	44000
15JAN96	AUSTIN	2285	1950	1900	2400	1435	1645	3545
	SAN ANTONIO	11400	50000	6500	19000	5220	810	3200
22JAN96	AUSTIN	875	1520	1655	425	330	600	180
	SAN ANTONIO	360	8000	4220	200	150	500	370
29JAN96	AUSTIN	45	40	25	80	20	20	40
	SAN ANTONIO	260	100	970	160	0	50	0
05FEB96	AUSTIN	135	25	260	45	20	25	18
	SAN ANTONIO	0	1220	1570	250	200	0	0
12FEB96	AUSTIN	18	0	0	0	0	0	0
	SAN ANTONIO	0	0	0	60	320	0	0

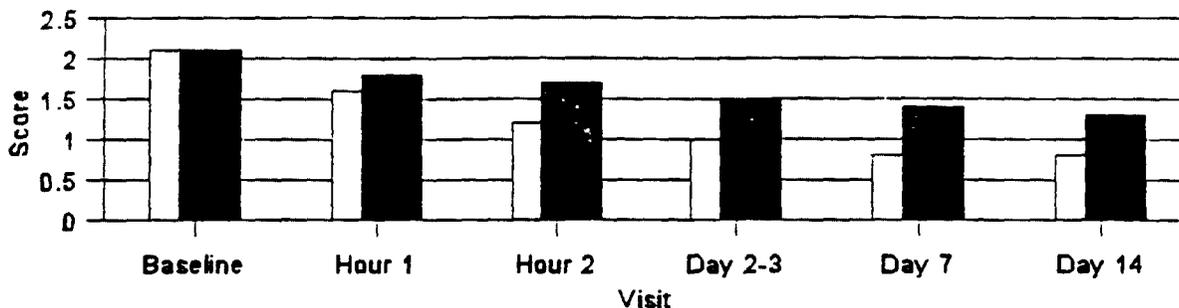
**APPEARS THIS WAY
ON ORIGINAL**

Treatment	Randomized	Completed Study	Reason: Study Incomplete			
			Lack of Efficacy	Adverse Event	Lost to Follow-up	Other Unrelated
LE	66	64 (97%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)
Placebo	67	62 (93%)	0 (0%)	2 (3%)	1 (1%)	2 (3%)

		LOTEPREDNOL	PLACEBO	INV 174	INV 175	INV 178
AGE	N	66	67	34	60	39
	MEAN	40.6	41.5	41.6	42.1	39.0
	MIN					
	MAX					
GENDER						
MALE	N %	33 50%	32 48%	14 41%	30 50%	21 54%
FEMALE	N %	33 50%	35 52%	20 59%	30 50%	18 46%
		HO:LE=PL p=0.863		HO:INV EQUAL p=0.543		
RACE						
CAUCASIAN	N %	42 64%	41 61%	30 88%	40 67%	13 33%
HISPANIC	N %	22 33%	19 28%	2 6%	18 30%	21 54%
OTHER	N %	2 3%	7 10%	2 6%	2 3%	5 13%
		HO:LE=PL p=0.223		HO:INV EQUAL p=0.001		
IRIS						
LIGHT	N %	29 44%	26 39%	19 56%	24 40%	12 31%
DARK	N %	37 56%	41 61%	15 44%	36 60%	27 69%
		HO:LE=PL p=0.599		HO:INV EQUAL p=0.090		
CITY						
AUSTIN	N %	16 24%	18 27%	34 100%	0 0%	0 0%
SAN ANTONIO	N %	50 76%	49 73%	0 0%	60 100%	39 100%
		HO:LE=PL p=0.843		HO:INV EQUAL p=0.001		
BASELINE POLLEN						
	N	64	66	34	58	38
	MEAN	10843.0	11164.5	2154.1	12185.5	17126.6
	SD	16573.6	16056.8	1010.3	16284.0	19966.3
	MIN					
	MAX					
0-500	N %	16 25%	15 23%	4 12%	16 28%	11 29%
501-1000	N %	9 14%	9 14%	0 0%	14 24%	4 11%
1001-5000	N %	18 28%	19 29%	30 88%	4 7%	3 8%
5001-15000	N %	5 8%	5 8%	0 0%	5 9%	5 13%
>15000	N %	16 25%	18 27%	0 0%	19 33%	15 39%
		HO:LE=PL p=0.723		HO:INV EQUAL p=0.396		

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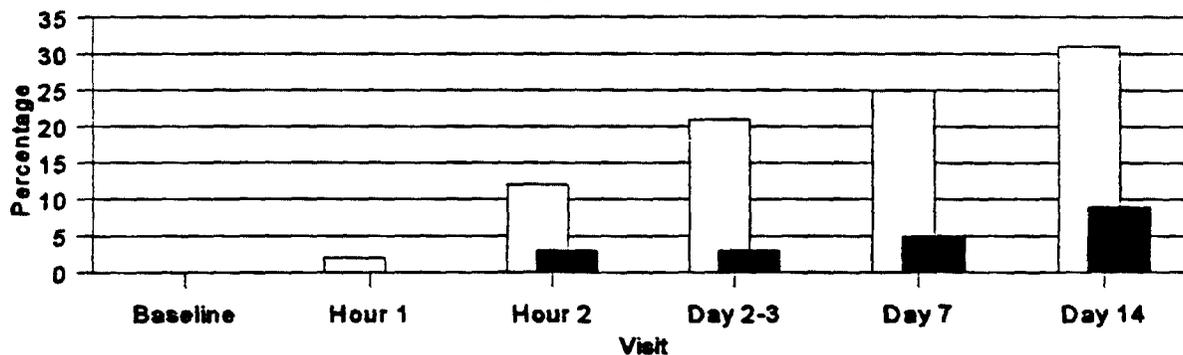
Bulbar Injection



□ Loteprednol ■ Vehicle

Loteprednol	2.1	1.6	1.2	1.0	0.8	0.8
Vehicle	2.1	1.8	1.7	1.5	1.4	1.3

Bulbar Injection Resolved



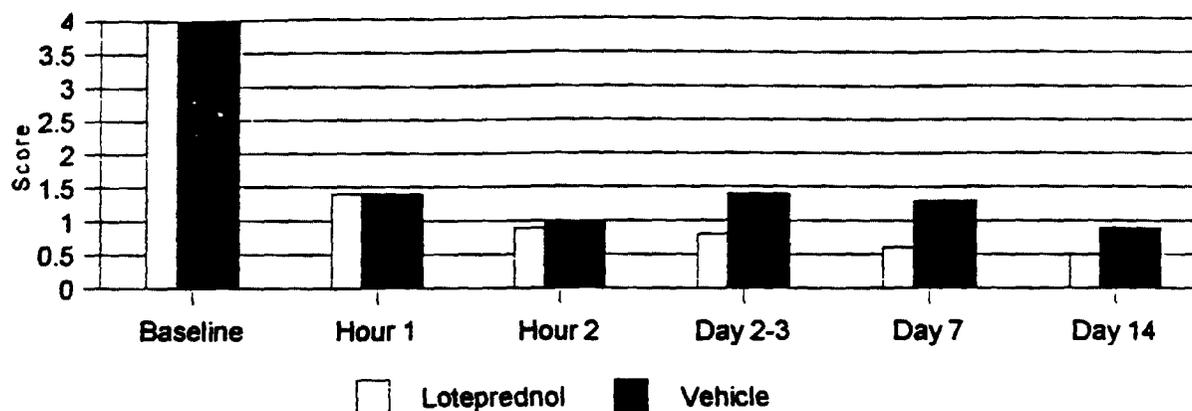
□ Loteprednol ■ Vehicle

Loteprednol	0	2	12	21	25	31
Vehicle	0	0	3	3	6	9

Reviewer's Comments:

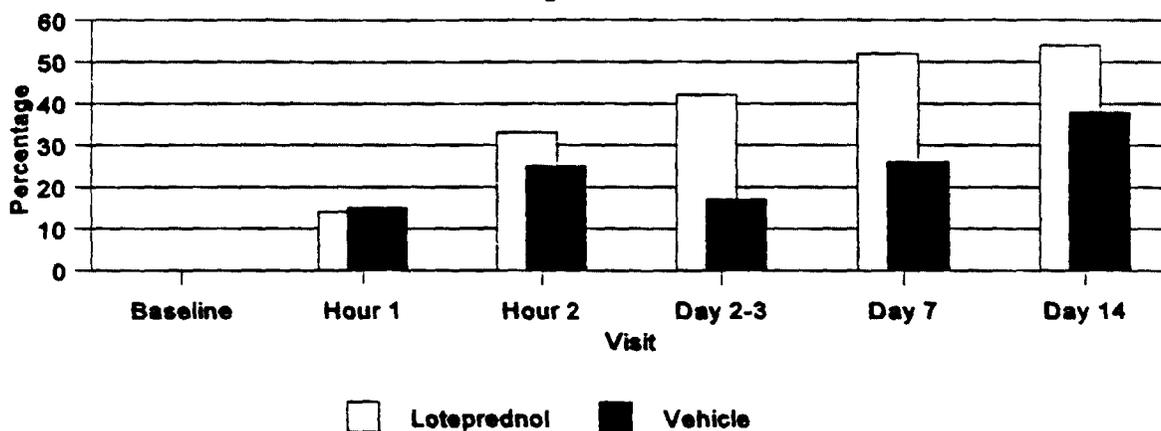
A higher percentage of patients in the loteprednol group had resolution of redness compared to the vehicle group. The means scores are not impressively different.

Itching



Loteprednol	4	1.4	0.9	0.8	0.6	0.5
Vehicle	4	1.4	1	1.4	1.3	0.9

Itching Resolved



Loteprednol	0	14	33	42	52	54
Vehicle	0	15	25	17	28	38

Reviewer's Comments:

A higher percentage of patients in the loteprednol group had resolution of itching compared to the vehicle group. The means scores are not impressively different.

Bulbar Injection

LOTEPREDNOL (LE)	OBSERVED RATINGS: MEAN OF EYES ((00+05)/2)							
	BASELINE	VISIT 1 (DAY 0)		VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
		HOURL 1	HOURL 2	DAY 2-3	DAY 7	DAY 14	DAY 28	DAY 42
DISTRIBUTION								
0: ABSENT	0 0%	1 2%	8 12%	14 21%	16 25%	20 31%	6 22%	1 13%
0.5-1: MILD	0 0%	20 30%	36 55%	35 53%	40 62%	36 55%	17 63%	5 63%
1.5-2: MODERATE	56 85%	40 61%	20 30%	17 26%	9 14%	9 14%	4 15%	2 25%
2.5-3: SEVERE	10 15%	5 8%	2 3%	0 0%	0 0%	0 0%	0 0%	0 0%
N	66	66	66	66	65	65	27	8
MEAN	2.1	1.6	1.2	1.0	0.8	0.8	0.9	1.1
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.2
MIN. MAX								
MEDIAN	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0

PLACEBO (PL)	N %	N %	N %	N %	N %	N %	N %	N %
DISTRIBUTION								
0: ABSENT	0 0%	0 0%	2 3%	2 3%	3 5%	6 9%	2 8%	0 0%
0.5-1: MILD	0 0%	13 19%	15 22%	26 40%	28 43%	33 52%	7 27%	4 50%
1.5-2: MODERATE	54 81%	40 72%	40 72%	34 52%	33 51%	23 36%	16 62%	3 38%
2.5-3: SEVERE	13 19%	6 9%	2 3%	3 5%	1 2%	2 3%	1 4%	1 13%
N	67	67	67	65	65	64	26	8
MEAN	2.1	1.8	1.7	1.5	1.4	1.3	1.5	1.6
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.2
MIN. MAX								
MEDIAN	2.0	2.0	2.0	1.5	1.5	1.0	1.5	1.5

LOTEPREDNOL (LE)	CHANGE FROM BASELINE (OBSERVED - BASELINE [a])							
		HOURL 1	HOURL 2	DAY 2-3	DAY 7	DAY 14	DAY 28	DAY 42
FREQUENCY DISTRIBUTION								
IMPROVED								
-3	1 2%	1 2%	1 2%	1 2%	1 2%	1 2%	0 0%	0 0%
-2.5 - -2	0 0%	0 0%	0 12%	13 20%	17 26%	20 31%	6 22%	1 13%
-1.5 - -1	22 33%	35 53%	35 53%	39 60%	36 55%	17 63%	5 63%	
UNCHANGED -0.5 - 0.5	43 65%	21 32%	17 26%	8 12%	8 12%	4 15%	2 25%	
1.5 - 1	0 0%	1 2%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
WORSENEED 2.5 - 2	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
N	66	66	66	66	65	65	27	8
MEAN	2.1	-0.5	-0.9	-1.1	-1.3	-1.3	-1.2	-0.9
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.2
MIN. MAX								
MEDIAN	2.0	-0.5	-1.0	-1.0	-1.0	-1.0	-1.0	-1.0

PLACEBO (PL)	N %	N %	N %	N %	N %	N %	N %	N %
FREQUENCY DISTRIBUTION								
IMPROVED								
-3	0 0%	0 0%	0 0%	2 3%	1 2%	0 0%	0 0%	0 0%
-2.5 - -2	1 1%	3 4%	5 8%	3 5%	8 13%	4 15%	0 0%	0 0%
-1.5 - -1	17 25%	20 30%	29 45%	32 49%	33 52%	8 31%	4 50%	
UNCHANGED -0.5 - 0.5	49 73%	44 66%	30 46%	27 42%	21 33%	14 54%	4 50%	
1.5 - 1	0 0%	0 0%	1 2%	1 2%	1 2%	0 0%	0 0%	0 0%
WORSENEED 2.5 - 2	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
N	67	67	67	65	65	64	26	8
MEAN	2.1	-0.3	-0.4	-0.7	-0.7	-0.9	-0.7	-0.5
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.2
MIN. MAX								
MEDIAN	2.0	0.0	0.0	-1.0	-1.0	-1.0	-0.5	-0.5

UNIVARIATE ANALYSES	BASELINE	HOURL 1	HOURL 2	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
INVEST p-VALUE[c]	0.792							
TRT p-VALUE[d]	0.280	0.274	0.000	0.001	0.000	0.006	0.030	0.135
TREATMENT EFFECT[e]	0.0	0.0	-0.5	-0.5	-0.5	-0.5	-0.5	0.0
95% CONF LIMITS	0.0, 0.0	0.0, 0.0	-1.0, -0.5	-0.5, 0.0	-1.0, -0.5	-0.5, 0.0	-1.0, 0.0	-1.0, 0.0

[a] OBSERVED RATINGS ARE THE MEAN OF BOTH EYES AT THE VISIT; CHANGE FROM BASELINE IS OBSERVED RATING - BASELINE RATINGS; THUS, IMPROVEMENT IS A NEGATIVE NUMBER

[b] REPEATED MEASURES ANALYSIS OF COVARIANCE WITH AN ESTIMATE OF OVERALL TREATMENT EFFECT (LE-PL); NEGATIVE TREATMENT EFFECTS INDICATE LOTEPREDNOL FAVORED OVER PLACEBO

[c] COCHRAN-MANTEL-HAENSZEL TEST FOR EQUALITY OF RDM (INVESTIGATOR) MEAN RANKS AT BASELINE

[d] COCHRAN-MANTEL-HAENSZEL TEST FOR EQUALITY OF RDM (TREATMENT) MEAN RANKS CONTROLLING FOR INVESTIGATOR

[e] LARGE SAMPLE ESTIMATE OF THE MEDIAN DIFFERENCE BETWEEN TREATMENT GROUPS (LE-PL) AND ITS CONFIDENCE LIMITS

Reviewer's Comments:

Visits 5 and 6 do not have sufficient numbers of patients for evaluations of efficacy.

Itching

	OBSERVED RATINGS: MEAN OF EYES ((OD+OS)/2)								
	VISIT 1 (DAY 0)		VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 28	VISIT 6 DAY 42		
	BASELINE	HOUR 1						HOUR 2	N %
LOTEPREDNOL (LE)									
DISTRIBUTION									
0:ABSENT	0 0%	9 14%	22 33%	28 42%	34 52%	35 54%	20 74%	6 75%	
0.5-1:TRACE	0 0%	28 42%	29 44%	28 42%	23 35%	25 38%	3 11%	2 25%	
1.5-2:MILD	0 0%	20 30%	12 18%	7 11%	7 11%	3 5%	3 11%	0 0%	
2.5-3:MODERATE	0 0%	7 11%	3 5%	2 3%	1 2%	2 3%	1 4%	0 0%	
3.5-4:SEVERE	66100%	2 3%	0 0%	1 2%	0 0%	0 0%	0 0%	0 0%	
N	66	66	66	66	65	65	27	8	
MEAN	4.0	1.4	0.9	0.8	0.6	0.5	0.4	0.3	
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.2	0.2	
MIN. MAX									
MEDIAN	4.0	1.0	1.0	1.0	0.0	0.0	0.0	0.0	

	OBSERVED RATINGS: MEAN OF EYES ((OD+OS)/2)								
	VISIT 1 (DAY 0)		VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 28	VISIT 6 DAY 42		
	BASELINE	HOUR 1						HOUR 2	N %
PLACEBO (PL)									
DISTRIBUTION									
0:ABSENT	0 0%	10 15%	17 25%	11 17%	17 26%	24 38%	18 69%	8 100%	
0.5-1:TRACE	0 0%	30 45%	29 43%	22 34%	24 37%	25 39%	2 8%	0 0%	
1.5-2:MILD	0 0%	16 24%	19 28%	22 34%	13 20%	10 16%	4 15%	0 0%	
2.5-3:MODERATE	0 0%	11 16%	2 3%	9 14%	8 12%	4 6%	2 8%	0 0%	
3.5-4:SEVERE	67100%	0 0%	0 0%	1 2%	3 5%	1 2%	0 0%	0 0%	
N	67	67	67	65	65	64	26	8	
MEAN	4.0	1.4	1.0	1.4	1.3	0.9	0.6	0.0	
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.2	0.0	
MIN. MAX									
MEDIAN	4.0	1.0	1.0	1.0	1.0	1.0	0.0	0.0	

	CHANGE FROM BASELINE (OBSERVED - BASELINE [a])								
	VISIT 1 (DAY 0)		VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 28	VISIT 6 DAY 42		
	HOUR 1	HOUR 2						N %	N %
LOTEPREDNOL (LE)									
FREQUENCY DISTRIBUTION									
IMPROVED -4	9 14%	22 33%	28 42%	34 52%	35 54%	20 74%	6 75%		
-3.5 - -3	28 42%	29 44%	28 42%	23 35%	25 38%	3 11%	2 25%		
-2.5 - -2	20 30%	12 18%	7 11%	7 11%	3 5%	3 11%	0 0%		
-1.5 - -1	7 11%	3 5%	2 3%	1 2%	2 3%	1 4%	0 0%		
UNCHANGED -0.5 - 0.5	2 3%	0 0%	1 2%	0 0%	0 0%	0 0%	0 0%		
N	66	66	66	65	65	65	27	8	
MEAN	4.0	-2.6	-3.1	-3.2	-3.4	-3.5	-3.6	-3.8	
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.2	0.2	
MIN. MAX									
MEDIAN	4.0	-3.0	-3.0	-3.0	-4.0	-4.0	-4.0	-4.0	

	CHANGE FROM BASELINE (OBSERVED - BASELINE [a])								
	VISIT 1 (DAY 0)		VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 28	VISIT 6 DAY 42		
	HOUR 1	HOUR 2						N %	N %
PLACEBO (PL)									
FREQUENCY DISTRIBUTION									
IMPROVED -4	10 15%	17 25%	11 17%	17 26%	24 38%	18 69%	8 100%		
-3.5 - -3	30 45%	29 43%	22 34%	24 37%	25 39%	2 8%	0 0%		
-2.5 - -2	16 24%	19 28%	22 34%	13 20%	10 16%	4 15%	0 0%		
-1.5 - -1	11 16%	2 3%	9 14%	8 12%	4 6%	2 8%	0 0%		
UNCHANGED -0.5 - 0.5	0 0%	0 0%	1 2%	3 5%	1 2%	0 0%	0 0%		
N	67	67	65	65	64	26	8		
MEAN	4.0	-2.6	-3.0	-2.6	-2.7	-3.1	-3.4	-4.0	
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.2	0.0	
MIN. MAX									
MEDIAN	4.0	-3.0	-3.0	-3.0	-3.0	-3.0	-4.0	-4.0	

TREATMENT EFFECT	-0.02	-0.62
95% CONF LIMITS	-0.29, 0.24	-0.86, -0.37
SUPPORTIVE		
UNIVARIATE ANALYSES		
TRT p-VALUE[c]	0.590	0.304
TREATMENT EFFECT[d]	0.0	0.0
95% CONF LIMITS	0.0, 0.0	-1.0, -0.5
	0.0, 0.0	-1.0, 0.0
	0.0, 0.0	-0.5, 0.0
	0.0, 0.0	0.0, 0.0
	0.0, 0.0	0.0, 1.0

[a] OBSERVED RATINGS ARE THE MEAN OF BOTH EYES AT THE VISIT. BASELINE ITCHING WAS SEVERE (4) FOR ALL PATIENTS. CHANGE FROM BASELINE IS OBSERVED RATING - 4; THUS, IMPROVEMENT IS A NEGATIVE NUMBER
 [b] REPEATED MEASURES ANALYSIS OF VARIANCE WITH AN ESTIMATE OF OVERALL TREATMENT EFFECT (LE-PL); NEGATIVE TREATMENT EFFECTS INDICATE LOTE PREDNOL FAVORED OVER PLACEBO.
 [c] COCHRAN-MANTEL-HAENSZEL TEST FOR EQUALITY OF ROW (TREATMENT) MEAN RANKS CONTROLLING FOR INVESTIGATOR
 [d] LARGE SAMPLE ESTIMATE OF THE MEDIAN DIFFERENCE BETWEEN TREATMENT GROUPS (LE-PL) AND ITS CONFIDENCE LIMITS

Reviewer's Comments:

Visits 5 and 6 do not have sufficient numbers of patients for evaluations of efficacy.

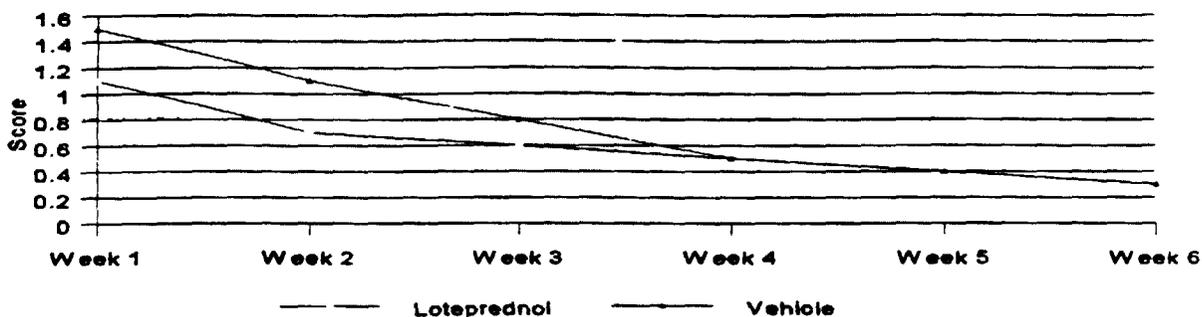
			Patients with zero rating (sign or symptom no longer present)				
			Visit 1	Visit 2	Visit 3	Visit 4	
Measure:	Treatment	N	Hour 1	Hour 2	Day 2/3	Day 7	Day 14
Discomfort:	LE	65	14%	35%	43%	47%	66%
	Placebo	66	17%	27%	22%	41%	52%
Foreign body sensation:	LE	50	40%	48%	57%	68%	84%
	Placebo	62	35%	52%	43%	60%	61%
Burning/Stinging:	LE	64	33%	36%	53%	60%	68%
	Placebo	67	30%	33%	38%	43%	53%
Photophobia:	LE	56	48%	52%	64%	64%	65%
	Placebo	53	43%	49%	52%	55%	54%
Tearing:	LE	64	41%	50%	61%	67%	70%
	Placebo	64	34%	44%	42%	58%	57%
Discharge:	LE	52	58%	71%	63%	63%	63%
	Placebo	44	80%	80%	56%	67%	71%
Palpebral injection:	LE	66	2%	9%	23%	25%	29%
	Placebo	67	0%	3%	6%	8%	13%
Chemosis:	LE	63	10%	16%	33%	35%	35%
	Placebo	60	2%	5%	24%	22%	22%
Erythema:	LE	61	13%	25%	49%	51%	45%
	Placebo	59	10%	17%	28%	28%	36%

N is the intent-to-treat sample size of patients with the sign or symptom present at baseline.

Reviewer's Comments:

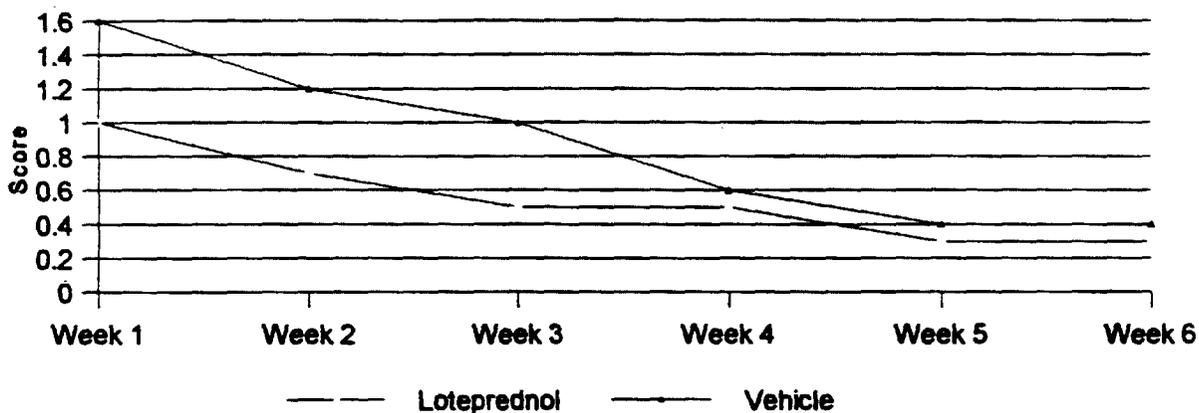
With the exception of the measure of Discharge, the loteprednol group almost always had a higher percentage of patients with resolved signs and symptoms.

Itching - Morning Diary



Loteprednol	1.1	0.7	0.5	0.5	0.4	0.3
Vehicle	1.6	1.1	0.8	0.6	0.4	0.3

Itching - Evening Diary



Loteprednol	1	0.7	0.5	0.5	0.3	0.3
Vehicle	1.6	1.2	1	0.6	0.4	0.4

Reviewer's Comments:

The graphs show overall improvement from baseline in both groups and little difference between groups.

Intraocular Pressure Elevations

Treatment	Elevation in IOP (mm Hg)	Number of patients			
		Day 7	Day 14	Day 28	Day 42
LE	> 15	0	0	0	0
	10-15	0	0	0	0
	6-9	6	6	8	4
	< 6	59	59	57	60
Placebo	> 15	0	0	0	0
	10-15	0	0	0	0
	6-9	0	4	1	1
	< 6	65	60	61	61

The distributions (above and below) displayed are the changes in IOP in the eye with the greatest increase from baseline in IOP

	BASELINE	OBSERVED			
		VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 28	VISIT 6 DAY 42
LOTEPREDNOL					
DISTRIBUTION	N %	N %	N %	N %	N %
< 20 MM HG	66 100%	58 89%	59 91%	58 89%	57 89%
20 - 25 MM HG	0 0%	6 9%	6 9%	7 11%	7 11%
26 - 31 MM HG	0 0%	1 2%	0 0%	0 0%	0 0%
> 31 MM HG	0 0%	0 0%	0 0%	0 0%	0 0%
N	66	65	65	65	64
MEAN	14.6	16.1	15.8	16.1	15.7
STANDARD ERROR	0.3	0.4	0.4	0.4	0.4
MIN. MAX					
MEDIAN	14.5	16.0	16.0	16.0	15.0
PLACEBO (PL)					
< 20 MM HG	65 97%	64 98%	63 98%	59 95%	58 94%
20 - 25 MM HG	2 3%	1 2%	1 2%	3 5%	4 6%
26 - 31 MM HG	0 0%	0 0%	0 0%	0 0%	0 0%
> 31 MM HG	0 0%	0 0%	0 0%	0 0%	0 0%
N	67	65	64	62	62
MEAN	14.4	14.5	14.7	15.0	15.1
STANDARD ERROR	0.3	0.4	0.4	0.4	0.4
MIN. MAX					
MEDIAN	14.0	14.0	15.0	14.5	15.3

Reviewer's Comments:

Elevations in IOP were seen more frequently in the loteprednol group.

Adverse Experiences: (>2%)

SPECIAL SENSES	PATIENTS AT RISK	PATIENTS REPORTING EVENT AT LEAST ONCE		TOTAL NUMBER OF EVENTS	SEVERITY OF EVENTS		
					MILD	MODERATE	SEVERE
BODY AS A WHOLE -Any Event							
LOTEPREDNOL	66	21	32%	24	12	9	3
PLACEBO	67	20	30%	23	16	7	0
CHEMOSIS (EYE/CONJ)							
LOTEPREDNOL	66	11	17%	14	13	1	0
PLACEBO	67	15	22%	17	16	1	0
ITCHING, EYE (EYE/GEN)							
LOTEPREDNOL	66	10	15%	10	9	1	0
PLACEBO	67	25	37%	28	19	7	2
HEADACHE (HEAD)							
LOTEPREDNOL	66	10	15%	11	5	4	2
PLACEBO	67	10	15%	10	9	1	0
ERYTHEMA, EYELIDS (EYE/APP)							
LOTEPREDNOL	66	7	11%	7	7	0	0
PLACEBO	67	6	9%	7	4	3	0
FLU SYNDROME (GEN)							
LOTEPREDNOL	66	6	9%	6	1	4	1
PLACEBO	67	0	0%	0	0	0	0
BURNING/STINGING, EYE, NOT ON INSTILLATION (EYE/GEN)							
LOTEPREDNOL	66	6	9%	6	5	1	0
PLACEBO	67	6	9%	9	3	3	3
DISCHARGE, EYE (EYE/GEN)							
LOTEPREDNOL	66	6	9%	6	6	0	0
PLACEBO	67	17	25%	20	17	1	2
EPIPHORA (EYE/APP)							
LOTEPREDNOL	66	5	8%	5	4	0	1
PLACEBO	67	14	21%	14	7	6	1
FOREIGN BODY SENSATION (EYE/GEN)							
LOTEPREDNOL	66	5	8%	5	4	1	0
PLACEBO	67	11	16%	12	8	2	2
DRY EYES (EYE/GEN)							
LOTEPREDNOL	66	4	6%	5	3	2	0
PLACEBO	67	2	3%	2	1	1	0
DISCOMFORT, EYE (EYE/GEN)							
LOTEPREDNOL	66	4	6%	4	4	0	0
PLACEBO	67	3	4%	3	2	0	1
INJECTION (EYE/CON)							
LOTEPREDNOL	66	3	5%	3	2	1	0
PLACEBO	67	16	24%	18	12	4	2
BURN/STING, EYE, ON INSTILLATION (EYE/GEN)							
LOTEPREDNOL	66	3	5%	3	2	1	0
PLACEBO	67	4	6%	4	2	1	0

NDA 20-803: loteprednol etabonate ophthalmic suspension, 0.2%

EYE PAIN (EYE/GEN)							
LOTEPREDNOL	66	3	5%	3	3	0	0
PLACEBO	67	1	1%	1	1	0	0
ALLERGIC REACTION (GEN)							
LOTEPREDNOL	66	2	3%	2	2	0	0
PAIN (GEN)							
LOTEPREDNOL	66	2	3%	2	2	0	0
PLACEBO	67	1	1%	1	0	1	0
INFECTION, EAR, NOS (EAR/GEN)							
LOTEPREDNOL	66	2	3%	2	0	2	0
PLACEBO	67	0	0%	0	0	0	0

Reviewer's Summary of Safety and Efficacy

Marginal efficacy has been demonstrated in the resolution of itching and redness. Adverse experiences in this limited study (42 days) were generally confined to mild to moderate ocular events. There was an increased chance of increased IOP during use.

8.1.2 Study #2 Protocol: 144

Title: Safety and efficacy of loteprednol etabonate in the treatment of seasonal allergic conjunctivitis (QID) dosing.

Objective: To evaluate the efficacy and safety of loteprednol etabonate 0.2% ophthalmic suspension in the treatment of signs and symptoms of environmental seasonal allergic conjunctivitis.

Study Design: A randomized, double-masked, placebo controlled, parallel group multicenter (4 sites) study.

Population: There were 135 adult patients, exhibiting signs and symptoms of environmental seasonal allergic conjunctivitis, coincident with elevated levels of an airborne pollen to which they had a demonstrated skin prick or RAST reaction.

Test Drug Schedule: Same as Study #2 (Protocol #143)

Investigators:	Number of Patients Enrolled
Richard B. Briggs, M.D. (#181) Brackenridge Professional Building 1313 Red River, Suite 206 Austin, TX 78701	30
Larry L. Lothringer, M.D. (#179) The Center for Corrective Eye Surgery 303 East Quincy San Antonio, TX 78215	36
Jay M. Rubin, M.D. (#180) Eye Physicians 999 E. Basse Road San Antonio, TX 78220	32
David G. Shulman, M.D. (#176) Eye Clinic 999 E. Basse Road, Suite 116 San Antonio, TX 78220	37

Study Plan: Same as Study #2
Inclusion Criteria: Same as Study #2
Exclusion Criteria: Same as Study #2
Masking: Same as Study #2
Efficacy Criteria: Same as Study #2
Concurrent Therapy: Same as Study #2

Patient Disposition:

The target sample size was 64 evaluable patients per treatment group (total = 128 patients). There were 135 patients randomized to treatment out of 480 patients screened. Sixty seven were assigned to receive LE and 68 were assigned to receive placebo. The first patient was enrolled on 18 December 1995 and the last patient visit occurred on 9 March 1996. Patients who discontinued treatment before Visit 6 (Day 42) were considered to have not completed the study. One hundred twenty eight (128) patients completed treatment through Visit 6. Three (3) patients (1 on LE; 2 on placebo) were discontinued due to a medical event, 3 (1 on LE; 2 on placebo) were lost to follow-up and 1 patient (LE) due to reasons unrelated to the study as shown below:

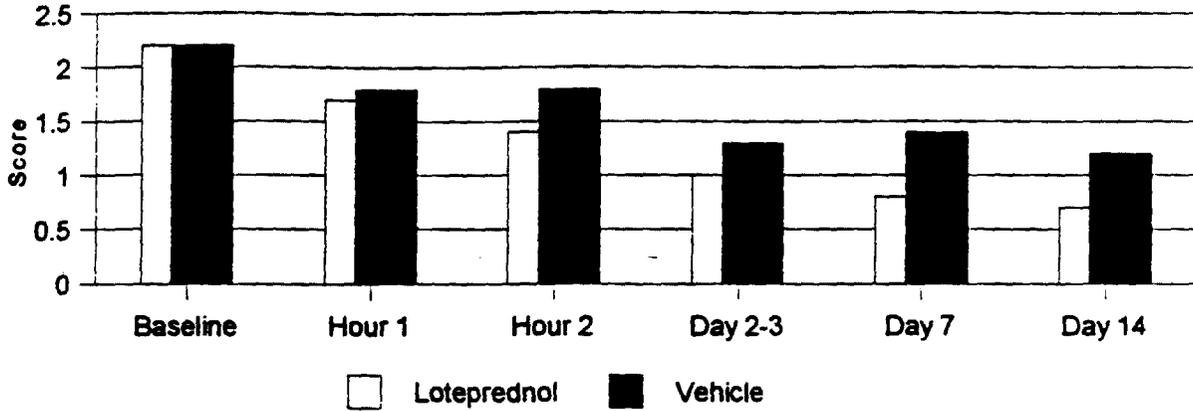
- 176:4013 (placebo) Day 0 Lost to follow-up
- 176:4016 (placebo) Day 14 Increased IOP
- 179:4081 (LE) Day 2 Diagnosed with ovarian tumor - scheduled for surgery
- 179:4100 (LE) Day 0 Lost to follow-up
- 180:4135 (placebo) Day 6 Eye spasm (OD) upon instillation
- 180:4158 (LE) Day 7 Hospitalized following motor vehicle accident
- 180:4159 (placebo) Day 28 Lost to follow-up

	Austin	San Antonio
Investigator(s)	181	176, 179,180
Pollen > 100/m ³	12 December 1995	15 December 1995
First patient enrolled	18 December 1995	18 December 1995
Last patient enrolled	26 January 1996	27 January 1996
Pollen < 100/m ³	28 January 1996	9 February 1996

WEEK BEGINNING	CITY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
11DEC95	AUSTIN	47	1720	4005	3750	3250	325	300
	SAN ANTONIO	0	0	20	0	990	14100	1590
18DEC95	AUSTIN	188	287	105	253	1700	355	25
	SAN ANTONIO	1870	2330	830	100	70	50	90
25DEC95	AUSTIN	70	1800	4515	8000	1145	2020	3010
	SAN ANTONIO	50	160	40	16500	7250		
01JAN96	AUSTIN	3002	2960	1150	3885	3650	3240	1950
	SAN ANTONIO	50000	18100	1420	700	200	12200	13480
08JAN96	AUSTIN	1980	1460	2085	1500	2350	2100	2025
	SAN ANTONIO	25200	650	5400	29000	21500	50000	44000
15JAN96	AUSTIN	2285	1950	1900	2400	1435	1645	3545
	SAN ANTONIO	11400	50000	6500	19000	5220	810	3200
22JAN96	AUSTIN	875	1520	1655	425	330	600	180
	SAN ANTONIO	360	8000	4220	200	150	500	370
29JAN96	AUSTIN	45	40	25	80	20	20	40
	SAN ANTONIO	260	100	970	160	0	50	0
05FEB96	AUSTIN	135	25	260	45	20	25	18
	SAN ANTONIO	0	1220	1570	250	200	0	0
12FEB96	AUSTIN	18	0	0	0	0	0	0
	SAN ANTONIO	0	0	0	60	320	0	0

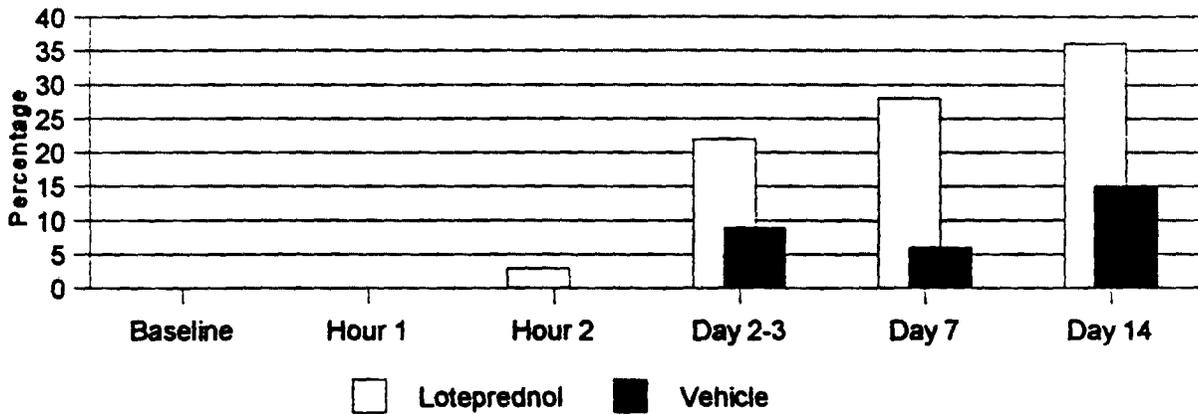
		LOTEPREDNOL	PLACEBO	INV 176	INV 179	INV 180	INV 181
AGE							
	N	67	68	37	36	32	30
	MEAN	39.2	38.2	39.5	39.2	37.2	38.8
	SD	10.5	9.3	11.0	7.9	11.1	9.7
	MIN						
	MAX						
GENDER							
	N %	31 46%	31 46%	18 49%	15 42%	16 50%	13 43%
MALE	N %	31 46%	31 46%	18 49%	15 42%	16 50%	13 43%
FEMALE	N %	36 54%	37 54%	19 51%	21 58%	16 50%	17 57%
		HO:LE=PL p=1.000		HO:INV EQUAL p=0.881			
RACE							
	N %	45 67%	41 60%	23 62%	15 42%	24 75%	24 80%
CAUCASIAN	N %	45 67%	41 60%	23 62%	15 42%	24 75%	24 80%
HISPANIC	N %	17 25%	25 37%	12 32%	18 50%	7 22%	5 17%
OTHER	N %	5 7%	2 3%	2 5%	3 8%	1 3%	1 3%
		HO:LE=PL p=0.224		HO:INV EQUAL p=0.046			
IRIS							
	N %	31 46%	28 41%	17 46%	9 25%	19 59%	14 47%
LIGHT	N %	31 46%	28 41%	17 46%	9 25%	19 59%	14 47%
DARK	N %	36 54%	40 59%	20 54%	27 75%	13 41%	16 53%
		HO:LE=PL p=0.605		HO:INV EQUAL p=0.037			
CITY							
	N %	15 22%	15 22%	0 0%	0 0%	0 0%	30 100%
AUSTIN	N %	15 22%	15 22%	0 0%	0 0%	0 0%	30 100%
SAN ANTONIO	N %	52 78%	53 78%	37 100%	36 100%	32 100%	0 0%
		HO:LE=PL p=1.000		HO:INV EQUAL p=0.001			
BASELINE POLLEN							
	N	66	68	37	36	31	30
	MEAN	11756.2	12119.5	12256.5	7271.9	26651.6	1951.9
	SD	15430.5	16010.3	16613.6	7979.4	18227.5	1058.9
	MIN						
	MAX						
0-500	N %	8 12%	10 15%	7 19%	7 19%	0 0%	4 13%
501-1000	N %	8 12%	8 12%	10 27%	1 3%	4 13%	1 3%
1001-5000	N %	17 26%	17 25%	0 0%	9 25%	0 0%	25 83%
5001-15000	N %	14 21%	14 21%	8 22%	13 36%	7 23%	0 0%
>15000	N %	19 29%	19 28%	12 32%	6 17%	20 65%	0 0%
		HO:LE=PL p=0.762		HO:INV EQUAL p=0.001			

Bulbar Injection



Loteprednol	2.2	1.7	1.4	1	0.8	0.7
Vehicle	2.2	1.8	1.8	1.3	1.4	1.2

Resolution of Injection

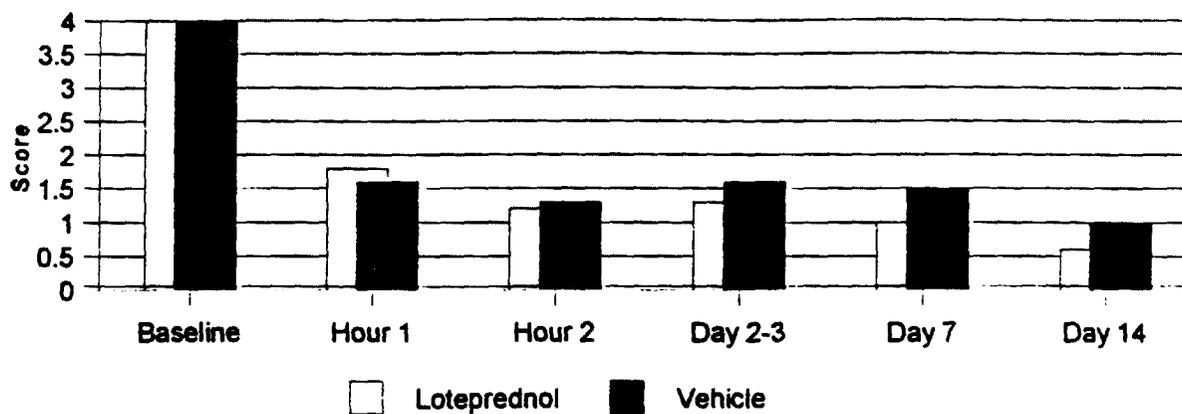


Loteprednol	0	0	3	22	28	36
Vehicle	0	0	0	9	6	15

Reviewer's Comments:

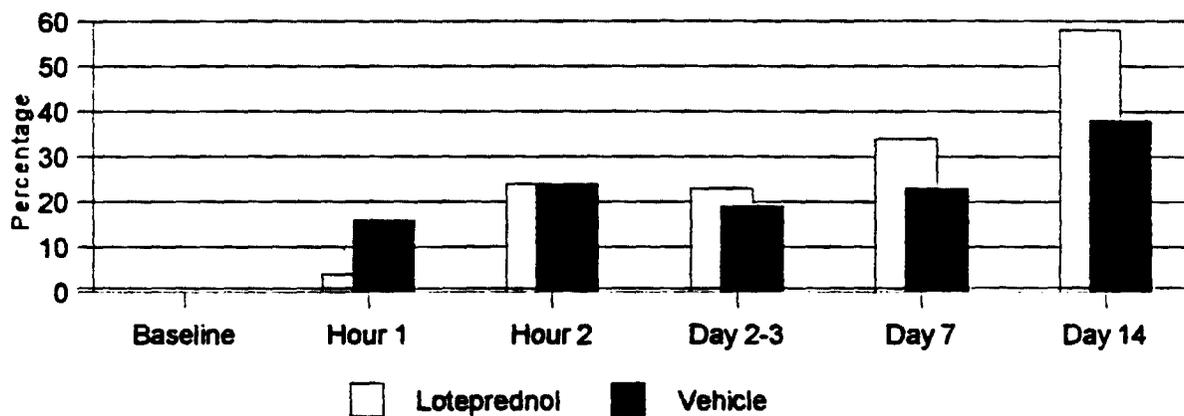
A higher percentage of patients in the loteprednol group had resolution of redness compared to the vehicle group. The means scores are not impressively different.

Itching



Loteprednol	4	1.8	1.2	1.3	1	0.6
Vehicle	4	1.6	1.3	1.6	1.5	1

Resolution of Itching



Loteprednol	0	4	24	23	34	58
Vehicle	0	16	24	19	23	38

Reviewer's Comments:

A significantly higher percentage of patients in the loteprednol group had resolution of itching compared to the vehicle group. The means scores are not impressively different.

Bulbar Injection	OBSERVED RATINGS, MEAN OF EYES (OD+OS)/2											
	VISIT 1 (DAY 0)		VISIT 2		VISIT 3		VISIT 4		VISIT 5		VISIT 6	
	BASELINE	HOUR 1	HOUR 2	DAY 2-3	DAY 7	DAY 14	DAY 28	DAY 42				
LOTEPREDNOL (LE)												
DISTRIBUTION	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0: ABSENT	0 0%	0 0%	2 3%	14 22%	18 28%	23 36%	6 26%	2 40%	0 0%	0 0%	0 0%	0 0%
0.5-1: MILD	0 0%	19 28%	33 49%	34 52%	40 62%	32 50%	15 65%	3 60%	0 0%	0 0%	0 0%	0 0%
1.5-2: MODERATE	48 72%	39 58%	24 36%	16 25%	7 11%	9 14%	2 9%	0 0%	0 0%	0 0%	0 0%	0 0%
2.5-3: SEVERE	19 28%	9 13%	8 12%	1 2%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
N	67	67	67	65	65	64	23	5				
MEAN	2.2	1.7	1.4	1.0	0.8	0.7	0.7	0.4				
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.2				
MIN. MAX												
MEDIAN	2.0	2.0	1.0	1.0	1.0	1.0	1.0	0.5				
PLACEBO (PL)												
DISTRIBUTION	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0: ABSENT	0 0%	0 0%	0 0%	6 9%	4 6%	10 15%	2 10%	0 0%	0 0%	0 0%	0 0%	0 0%
0.5-1: MILD	0 0%	18 26%	20 29%	32 48%	33 50%	30 45%	10 50%	31 100%	0 0%	0 0%	0 0%	0 0%
1.5-2: MODERATE	51 75%	40 59%	36 53%	26 39%	21 32%	22 33%	8 40%	0 0%	0 0%	0 0%	0 0%	0 0%
2.5-3: SEVERE	17 25%	10 15%	12 18%	3 4%	8 12%	4 6%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
N	68	68	68	67	66	66	20	3				
MEAN	2.2	1.8	1.8	1.3	1.4	1.2	1.2	1.0				
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.0				
MIN. MAX												
MEDIAN	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0				

LOTEPREDNOL (LE)	CHANGE FROM BASELINE (OBSERVED - BASELINE [a])											
	VISIT 1 (DAY 0)		VISIT 2		VISIT 3		VISIT 4		VISIT 5		VISIT 6	
	HOUR 1	HOUR 2	DAY 2-3	DAY 7	DAY 14	DAY 28	DAY 42					
FREQUENCY DISTRIBUTION												
IMPROVED	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
-2.5 - -2	0 0%	0 0%	2 3%	3 5%	5 8%	2 9%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
-1.5 - -1	27 40%	38 57%	31 48%	36 55%	30 47%	11 48%	2 40%	0 0%	0 0%	0 0%	0 0%	0 0%
UNCHANGED -0.5 - 0.5	40 60%	25 37%	12 18%	4 6%	6 9%	1 4%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1.5 - 1	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
WORSENE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
2.5 - 2	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
N	67	67	65	65	64	23	5					
MEAN	2.2	-0.5	-0.8	-1.3	-1.5	-1.5	-1.7	-1.8				
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.2	0.2				
MIN. MAX												
MEDIAN	2.0	-0.5	-1.0	-1.0	-1.5	-1.5	-1.5	-2.0				
PLACEBO (PL)												
FREQUENCY DISTRIBUTION												
IMPROVED	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
-2.5 - -2	0 0%	0 0%	1 1%	1 2%	1 2%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
-1.5 - -1	22 32%	23 34%	34 51%	39 59%	28 42%	14 70%	31 100%	0 0%	0 0%	0 0%	0 0%	0 0%
UNCHANGED -0.5 - 0.5	46 68%	45 66%	24 36%	20 30%	22 33%	4 20%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1.5 - 1	0 0%	0 0%	0 0%	2 3%	1 2%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
WORSENE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
2.5 - 2	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
N	68	68	67	66	66	20	3					
MEAN	2.2	-0.4	-0.4	-0.9	-0.8	-1.0	-1.1	-1.0				
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.0				
MIN. MAX												
MEDIAN	2.0	0.0	0.0	-1.0	-1.0	-1.0	-1.0	-1.0				
TREATMENT EFFECT		-0.29		-0.52								
95% CONF LIMITS		-0.43, -0.14		-0.67, -0.38								
INVEST p-VALUE[c]	0.001											
TRT p-VALUE[d]	0.822	0.054	0.000	0.001	0.000	0.000	0.010	0.087				
TREATMENT EFFECT[e]	0.0	0.0	-0.5	-0.5	-0.5	-0.5	-0.5	-1.0				
95% CONF LIMITS	0.0, 0.0	0.0, 0.0	-0.5, 0.0	-0.5, 0.0	-1.0, -0.5	-1.0, 0.0	-1.0, 0.0	-1.5, 0.0				

[a] OBSERVED RATINGS ARE THE MEAN OF BOTH EYES AT THE VISIT; CHANGE FROM BASELINE IS OBSERVED RATING - BASELINE RATING. THUS, IMPROVEMENT IS A NEGATIVE NUMBER

Reviewer's Comments:

Visits 5 and 6 do not have sufficient numbers of patients for evaluations of efficacy.

itching	OBSERVED RATINGS MEAN OF EYES (OD+OS)/2							
	VISIT 1 (DAY 0)		HOUR 2	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 28	VISIT 6 DAY 42
BASELINE	HOUR 1	N %						
LOTEPREDNOL (LE)								
DISTRIBUTION	N %	N %	N %	N %	N %	N %	N %	N %
0: ABSENT	0 0%	3 4%	16 24%	15 23%	22 34%	37 58%	14 61%	1 20%
0.5-1: TRACE	0 0%	19 28%	24 36%	20 31%	21 32%	18 28%	6 26%	3 60%
1.5-2: MILD	0 0%	25 37%	20 30%	23 35%	17 26%	8 13%	3 13%	1 20%
2.5-3: MODERATE	0 0%	18 27%	4 6%	7 11%	5 8%	1 2%	0 0%	0 0%
3.5-4: SEVERE	67 100%	2 3%	3 4%	0 0%	0 0%	0 0%	0 0%	0 0%
N	67	67	67	65	65	64	23	5
MEAN	4.0	1.8	1.2	1.3	1.0	0.6	0.5	1.0
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1
MIN. MAX								
MEDIAN	4.0	2.0	1.0	1.0	1.0	0.0	0.0	1.0
PLACEBO (PL)								
DISTRIBUTION	N %	N %	N %	N %	N %	N %	N %	N %
0: ABSENT	0 0%	11 16%	16 24%	13 19%	15 23%	25 38%	11 55%	2 67%
0.5-1: TRACE	0 0%	21 31%	23 34%	18 27%	17 26%	19 29%	5 25%	1 33%
1.5-2: MILD	0 0%	21 31%	20 29%	19 28%	20 30%	17 26%	3 15%	0 0%
2.5-3: MODERATE	0 0%	11 16%	8 12%	14 21%	12 18%	4 6%	1 5%	0 0%
3.5-4: SEVERE	68 100%	4 6%	1 1%	3 4%	2 3%	1 2%	0 0%	0 0%
N	68	68	68	67	66	66	20	3
MEAN	4.0	1.6	1.3	1.6	1.5	1.0	0.7	0.3
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1
MIN. MAX								
MEDIAN	4.0	1.0	1.0	2.0	1.8	1.0	0.0	0.0
CHANGE FROM BASELINE (OBSERVED - BASELINE (a))								
LOTEPREDNOL (LE)	VISIT 1 (DAY 0)		HOUR 2	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 28	VISIT 6 DAY 42
	HOUR 1	N %						
FREQUENCY DISTRIBUTION	N %	N %	N %	N %	N %	N %	N %	N %
IMPROVED -4	3 4%	16 24%	15 23%	22 34%	37 58%	14 61%	1 20%	
-3.5 - -3	19 28%	24 36%	20 31%	21 32%	18 28%	6 26%	3 60%	
-2.5 - -2	25 37%	20 30%	23 35%	17 26%	8 13%	3 13%	1 20%	
-1.5 - -1	18 27%	4 6%	7 11%	5 8%	1 2%	0 0%	0 0%	
UNCHANGED -0.5 - 0.5	2 3%	3 4%	0 0%	0 0%	0 0%	0 0%	0 0%	
N	67	67	67	65	65	64	23	5
MEAN	4.0	-2.2	-2.8	-2.7	-3.0	-3.4	-3.5	-3.0
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1
MIN. MAX								
MEDIAN	4.0	-2.0	-3.0	-3.0	-3.0	-4.0	-4.0	-3.0
PLACEBO (PL)								
FREQUENCY DISTRIBUTION	N %	N %	N %	N %	N %	N %	N %	N %
IMPROVED -4	11 16%	16 24%	13 19%	15 23%	25 38%	11 55%	2 67%	
-3.5 - -3	21 31%	23 34%	18 27%	17 26%	19 29%	5 25%	1 33%	
-2.5 - -2	21 31%	20 29%	19 28%	20 30%	17 26%	3 15%	0 0%	
-1.5 - -1	11 16%	8 12%	14 21%	12 18%	4 6%	1 5%	0 0%	
UNCHANGED -0.5 - 0.5	4 6%	1 1%	3 4%	2 3%	1 2%	0 0%	0 0%	
N	68	68	68	67	66	66	20	3
MEAN	4.0	-2.4	-2.7	-2.4	-2.5	-3.0	-3.3	-3.7
STANDARD ERROR	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1
MIN. MAX								
MEDIAN	4.0	-2.0	-3.0	-2.0	-2.3	-3.0	-4.0	-4.0
TREATMENT EFFECT		0.09		-0.40				
95% CONF LIMITS		-0.23, 0.40		-0.69, -0.11				
UNIVARIATE ANALYSES		HOUR 1	HOUR 2	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
TRT P-VALUE(c)	=	0.072	0.527	0.140	0.014	0.004	0.799	0.157
TREATMENT EFFECT(d)		0.0	0.0	0.0	-0.5	0.0	0.0	1.0
95% CONF LIMITS		0.0, 0.5	0.0, 0.0	-1.0, 0.0	-1.0, 0.0	-1.0, 0.0	0.0, 0.0	0.0, 2.0

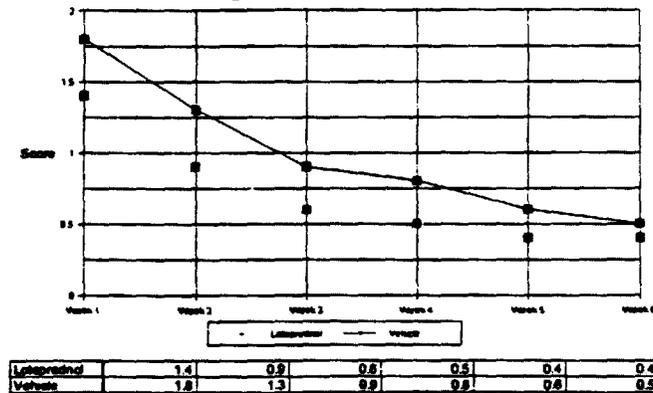
(a) OBSERVED RATINGS ARE THE MEAN OF BOTH EYES AT THE VISIT. BASELINE ITCHING WAS SEVERE (4) FOR ALL PATIENTS.

CHANGE FROM BASELINE IS OBSERVED RATING - 4; THUS, IMPROVEMENT IS A NEGATIVE NUMBER

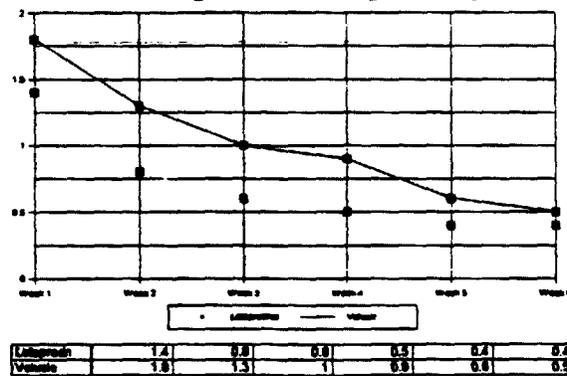
Reviewer's Comments:

Visits 5 and 6 do not have sufficient numbers of patients for evaluations of efficacy.

Itching - Morning Diary



Itching - Evening Diary



Reviewer's Comments:

The graphs show overall improvement from baseline in both groups and little difference between groups.

Measure:	Treatment	N	Patients with zero rating (sign or symptom no longer present)				
			Visit 1 Hour 1	Visit 1 Hour 2	Visit 2 Day 2/3	Visit 3 Day 7	Visit 4 Day 14
Discomfort:	LE	65	7%	21%	30%	48%	63%
	Placebo	66	13%	24%	24%	32%	48%
Foreign body sensation:	LE	61	24%	38%	54%	54%	72%
	Placebo	63	30%	39%	43%	44%	53%
Burning/Stinging:	LE	64	18%	32%	47%	56%	63%
	Placebo	66	30%	28%	33%	42%	54%
Photophobia:	LE	53	29%	40%	51%	57%	63%
	Placebo	56	25%	36%	39%	40%	56%
Tearing:	LE	63	20%	42%	56%	60%	81%
	Placebo	62	30%	37%	50%	49%	66%
Discharge:	LE	31	45%	52%	68%	71%	81%
	Placebo	24	44%	32%	50%	48%	67%
Palpebral injection:	LE	64	2%	3%	5%	16%	21%
	Placebo	67	1%	1%	1%	3%	9%
Chemosis:	LE	53	0%	4%	23%	25%	35%
	Placebo	60	0%	2%	22%	27%	41%
Erythema:	LE	50	13%	21%	40%	54%	55%
	Placebo	53	4%	11%	28%	28%	37%

N is the intent-to-treat sample size of patients with the sign or symptom present at baseline.

Reviewer's Comments:

With the exception of the 1st visit and Chemosis, the loteprednol group had higher percentages of symptom resolution.

Intraocular Pressure:

Treatment	Elevation in IOP (mm Hg)	Number of patients			
		Day 7	Day 14	Day 28	Day 42
LE	> 15	0	0	0	1
	10-15	0	0	0	0
	6-9	3	1	4	4
	< 6	62	63	60	59
Placebo	> 15	0	1	0	0
	10-15	0	0	0	0
	6-9	0	0	0	0
	< 6	66	65	65	64

The distributions (above and below) displayed are the change in IOP in the eye with the greatest increase from baseline in IOP.

LOTEPREDNOL	BASELINE	VISIT 3		VISIT 4		VISIT 5		VISIT 6	
		DAY 7	DAY 14	DAY 28	DAY 42				
DISTRIBUTION	N %	N %	N %	N %	N %	N %	N %	N %	N %
< 20 MM HG	64 96%	61 94%	62 97%	61 95%	63 98%				
20 - 25 MM HG	3 4%	4 6%	2 3%	3 5%	0 0%				
26 - 31 MM HG	0 0%	0 0%	0 0%	0 0%	0 0%				
> 31 MM HG	0 0%	0 0%	0 0%	0 0%	1 2%				
N	67	65	64	64	63				
MEAN	14.9	15.5	15.3	16.0	15.6				
STANDARD ERROR	0.3	0.3	0.3	0.3	0.4				
MIN. MAX									
MEDIAN	15.0	15.0	15.0	16.0	15.0				
PLACEBO (PL)									
< 20 MM HG	67 99%	66 100%	59 89%	62 95%	63 98%				
20 - 25 MM HG	1 1%	0 0%	6 9%	3 5%	1 2%				
26 - 31 MM HG	0 0%	0 0%	0 0%	0 0%	0 0%				
> 31 MM HG	0 0%	0 0%	1 2%	0 0%	0 0%				
N	68	66	66	65	64				
MEAN	15.7	15.1	15.6	15.2	14.5				
STANDARD ERROR	0.3	0.3	0.4	0.3	0.3				
MIN. MAX									
MEDIAN	16.0	15.5	15.3	15.0	14.5				

Reviewer's Comments:

Elevation in IOP was seen more frequently in the loteprednol group.

Adverse Experiences: (Greater than 2%)

SPECIAL SENSES	PATIENTS AT RISK	PATIENTS REPORTING EVENT AT LEAST ONCE		TOTAL NUMBER OF EVENTS	SEVERITY OF EVENTS		
					MILD	MODERATE	SEVERE
BODY AS A WHOLE -Any event							
LOTEPREDNOL	67	18	27%	27	13	10	4
PLACEBO	68	15	22%	19	13	5	1
RHINITIS (NOSE)							
LOTEPREDNOL	67	16	24%	19	9	9	1
PLACEBO	68	9	13%	12	4	6	2
ITCHING, EYE (EYE/GEN)							
LOTEPREDNOL	67	11	16%	13	7	5	1
PLACEBO	68	8	12%	9	6	2	1
HEADACHE (HEAD)							
LOTEPREDNOL	67	10	15%	15	9	4	2
PLACEBO	68	8	12%	11	7	3	1
CHEMOSIS (EYE/CONJ)							
LOTEPREDNOL	67	9	13%	9	8	0	1
PLACEBO	68	11	16%	13	10	2	1
DISCHARGE, EYE (EYE/GEN)							
LOTEPREDNOL	67	8	12%	9	4	3	0
PLACEBO	68	9	13%	9	8	1	0
BURNING/STINGING, EYE, NOT ON INSTILLATION (EYE/GEN)							
LOTEPREDNOL	67	6	9%	7	4	2	1
PLACEBO	68	5	7%	5	3	1	1
EPIPHORA (EYE/APP)							
LOTEPREDNOL	67	5	7%	5	4	0	1
PLACEBO	68	9	13%	12	7	5	0
COUGH INCREASED (GEN)							
LOTEPREDNOL	67	4	6%	5	2	3	0
PLACEBO	68	2	3%	2	1	1	0
EYE/VISION, BLURRED (EYE/VIS)							
LOTEPREDNOL	67	4	6%	7	6	1	0
PLACEBO	68	2	3%	2	1	1	0
DISCOMFORT, EYE (EYE/GEN)							
LOTEPREDNOL	67	3	4%	3	1	2	0
PLACEBO	68	2	3%	2	2	0	0
INFECTION (GEN)							
LOTEPREDNOL	67	3	4%	4	2	2	0
PLACEBO	68	0	0%	0	0	0	0
FOREIGN BODY SENSATION (EYE/GEN)							
LOTEPREDNOL	67	3	4%	3	1	2	0
PLACEBO	68	4	6%	4	2	1	1

INJECTION (EYE/CON)							
LOTEPREDNOL	67	3	4%	3	3	0	0
PLACEBO	68	15	22%	19	16	3	0
PHOTOPHOBIA (EYE/VIS)							
LOTEPREDNOL	67	3	4%	3	0	3	0
PLACEBO	68	1	1%	1	0	1	0
PHARYNGITIS (NASP)							
LOTEPREDNOL	67	3	4%	3	2	1	0
PLACEBO	68	2	3%	2	1	1	0
ACCIDENTAL INJURY (GEN)							
LOTEPREDNOL	67	2	3%	2	1	0	1
PLACEBO	68	0	0%	0	0	0	0
FACE EDEMA (HEAD)							
LOTEPREDNOL	67	2	3%	2	0	1	1
PLACEBO	68	2	3%	2	1	1	0
DIARRHEA (EC)							
LOTEPREDNOL	67	2	3%	2	0	2	0
PLACEBO	68	0	0%	0	0	0	0
VOMITING (GEN)							
LOTEPREDNOL	67	2	3%	2	1	1	0
PLACEBO	68	0	0%	0	0	0	0
ASTHMA (BRON)							
LOTEPREDNOL	67	2	3%	2	0	2	0
PLACEBO	68	0	0%	0	0	0	0
SINUSITIS (SINS)							
LOTEPREDNOL	67	2	3%	2	0	2	0
PLACEBO	68	1	1%	1	0	1	0

Reviewer's Summary of Safety and Efficacy

Marginal efficacy has been demonstrated in the resolution of itching and redness. Adverse experiences in this limited study (42 days) were generally confined to mild to moderate ocular events. There was an increased chance of increased IOP during use.

8.1.3 Study #3 Protocol #141

Title: Efficacy and Safety of Lotemax™ BID vs Lotemax™ QID in the Antigen Challenge Model of Acute Allergic Conjunctivitis

Investigators: Mark Abelson, M.D. (Investigator #108)
ORA Clinical Research and Development
863 Tumpike Street
North Andover, MA 01845

Objective: To compare two dose regimens of loteprednol etabonate 0.5% ophthalmic suspension on the prevention of signs and symptoms induced by an ocular antigen challenge, and to evaluate the duration of action of this effect.

Study Design: A randomized, double-masked, placebo controlled, paired comparison, single center study.

Population: There were 60 otherwise normal adults with known allergies to specific antigens.

Schedule: All subjects received loteprednol etabonate 0.5% ophthalmic suspension in one eye and vehicle placebo in the contralateral eye. Study drugs were instilled either BID or QID for 28 days, from Day 7 to Day 35. Visits and antigen challenges were carried out on Days 0, 7 (baseline), 21 and 35.

Study Plan

Study 141, was a prospective, double masked, placebo controlled, single center, paired-comparison of loteprednol etabonate 0.5% ophthalmic suspension (BID or QID) versus placebo (vehicle) in the antigen challenge model of acute allergic conjunctivitis. Sixty (60) subjects who had a minimum pre-determined response to an ocular antigen challenge were enrolled in the study. All subjects received drug in one eye and vehicle in the contralateral eye. Subjects were randomized with respect to which eye received active drug. The first 30 patients received treatment in a BID dosing schedule and the second 30 patients were on a QID dosing schedule.

On Day 0, a conjunctival allergen test was performed bilaterally using allergen to which the subject had a history of sensitivity (weed, animal dander, tree or grass) diluted with phosphate buffered saline. Doses ranging from 19 to 1250 allergen units per 25 μ L dose were administered in a dose related manner until a response of 2+ itching and redness at 10 minutes post instillation was achieved. If the maximum dose was reached without achieving this response the subject was excluded from further study participation and an exit form was completed. Subjects who tested positively were asked to return for the Visit 2 qualifying challenge. On Day 7, the subjects were challenged with the highest dose of allergen used on Day 0 to ensure that their response was still present. Subjects who qualified by their response to the second challenge were to begin a twenty eight (28) day period of study medication use. Loteprednol etabonate 0.5% ophthalmic suspension and vehicle placebo were to be instilled into the appropriate eye according to either a BID or QID dosing schedule. Subjects were rechallenged on Day 21, at 15 minutes after the latest dose of test article and on Day 35, subjects were randomly divided into two groups for challenges at 2 hr or 8 hr after the final dose of test article.

Ocular safety evaluations included an external examination, slit lamp examination, tonometry and visual acuity taken prior to enrollment and at scheduled times during the study. Systemic safety evaluations were treated by subject comment with physician follow-up.

Inclusion Criteria

3. 18 years of age or older, of either sex and of any race.
4. Manifest a successful challenge, inducing at least 2+ itching and 2+ redness bilaterally.
5. A positive history of allergy to grasses, animal dander, weeds, or trees. Positive skin tests, prior positive reactions to allergen challenge or verbal subject report consistent with allergy will constitute a positive history.

Exclusion Criteria

1. Contraindications to the use of the study medication(s).
2. Known sensitivity or allergy to the study drug(s) or their components.
3. Presence of any significant illness that could be expected to interfere with the study, particularly any autoimmune disease, e.g., rheumatoid arthritis.
4. Presence of bacterial or viral ocular infection.
5. Presence of blepharitis, follicular conjunctivitis, iritis, or preauricular lymphadenopathy.
6. Presence of mucous discharge, excess lacrimation, or burning as symptoms of ocular disease (possible dry eye).
7. History of dry eye or evidence of dry eye demonstrated by slit lamp examination.
8. Manifest signs and symptoms of clinically active allergic conjunctivitis (>1+ redness and/or the presence of any itching) at the baseline eye examination at visits 1 and 2.

9. Use of ocular medications of any kind, including tear substitutes, or systemic medication that may interfere with a normal vasodilatory response or with normal lacrimation for an appropriate wash-out period prior to the start of the study and for the duration of the study (i.e., non-steroidal anti-inflammatories, anti-histamines, etc. within 72 hours, corticosteroids within 7 days, mast cell stabilizers within 14 days).
10. Contact lenses worn 3 days prior to or during study period.
11. Pregnant or nursing women; or women of childbearing potential who test positive to a pregnancy test.
12. Participation in a clinical trial or use of an investigational drug or device within the last 30 days.

Efficacy Criteria

Intraocular differences in itching and mean redness (the mean score of redness in the ciliary, episcleral and conjunctival vessel beds) were the primary efficacy variables. Secondary variables included chemosis, tearing, lid swelling and mucous discharge.

Most signs and symptoms were rated on a four point scale (0 - 4) where 0 = absent, 1 = mild, 2 = moderate, 3 = severe and 4 = unusually severe. Increments of 0.5 units were also assessed, e.g., a score of 1.5 would rate between mild and moderate. Tearing was rated on a 0-3 scale where 0 = none, 1 = mild (eyes felt slightly watery), 2 = moderate (blows nose occasionally) and 3 = severe (tears rolling down cheeks).

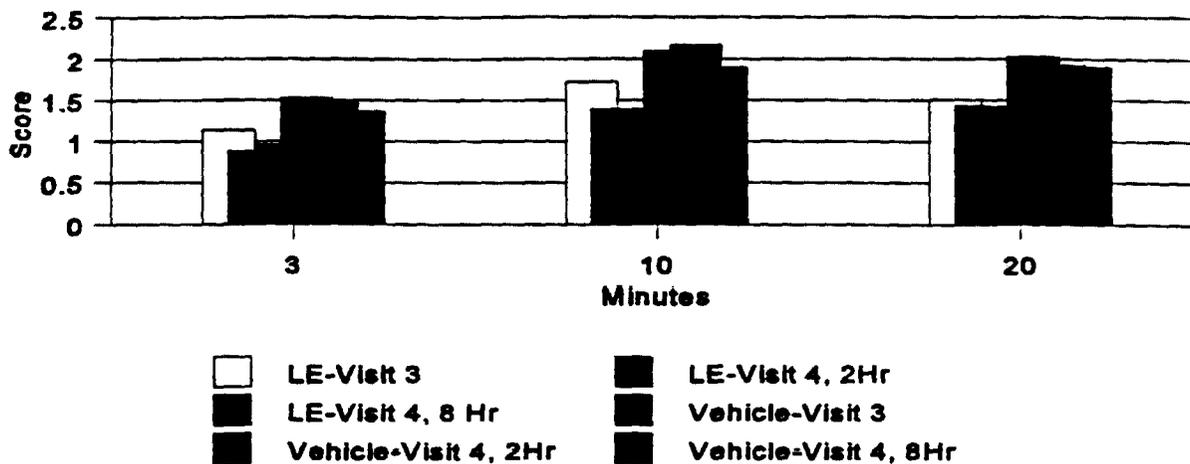
For itching expanded definitions were provided

- 0 = none
- 1 = an intermittent tickle sensation in the inner corner
- 2 = a mild continuous itch, not requiring rubbing
- 3 = a definite itch; you would like to be able to rub
- 4 = an incapacitating itch which would require eye rubbing

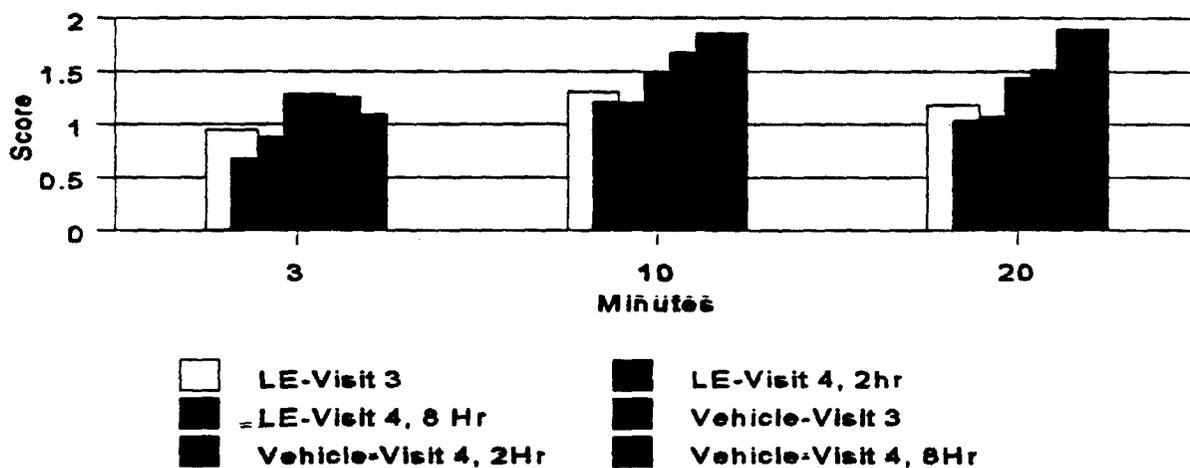
Demographics

Mean Age	33.2 ± 10.8 years (min=19, max=85)	
Gender	Male=33 (55%)	Female=27 (45%)
Race	Caucasian=58 (97%)	Hispanic=2 (3%)
Iris Pigmentation	Light=36 (60%)	Dark=24 (40%)

Redness - BID Group



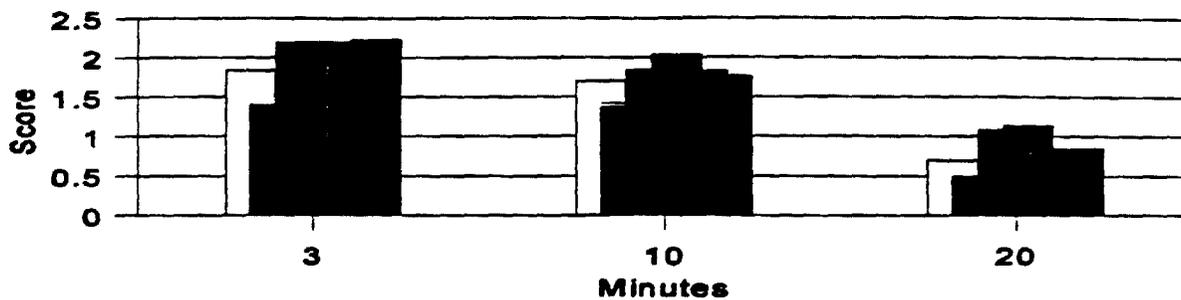
Redness - QID Group



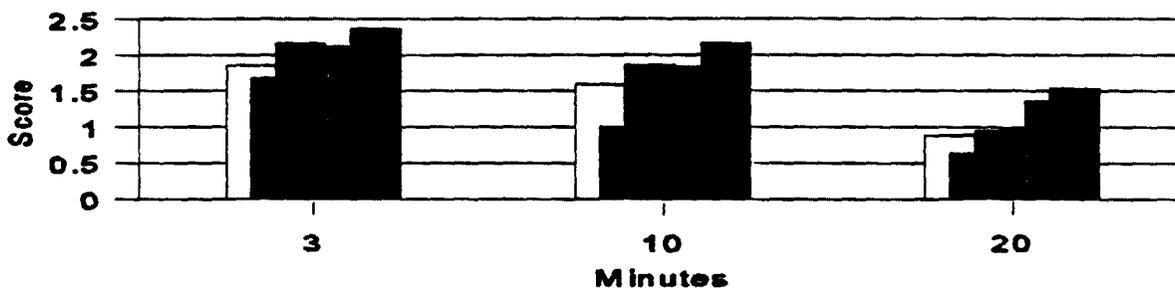
Reviewer's Comments:

There are minimal differences between groups, although the loteprednol eye generally does better than the vehicle eye.

Itching - BID Group



Itching - QID Group



Reviewer's Comments:

There are minimal differences between groups, although the loteprednol eye generally does better than the vehicle eye.

Visit 3 -BID Group

	LE Eye (n = 28)		Vehicle Eye (n = 28)		Efficacy Score** (n = 28)		P-Value (2-Tail)
	Mean	Sd	Mean	Sd	Mean	Sd	
Mean Redness							
3 Min Post Challenge	1.14	0.81	1.53	0.82	-0.39	0.71	0.0077
10 Min Post Challenge	1.72	0.91	2.10	0.74	-0.38	0.91	0.0381
20 Min Post Challenge	1.51	1.00	2.03	0.84	-0.52	1.04	0.0128
Itching							
3 Min Post Challenge	1.84	1.16	2.20	0.83	-0.36	0.96	0.0596
10 Min Post Challenge	1.70	1.00	2.04	0.83	-0.34	0.89	0.0544
20 Min Post Challenge	0.70	0.72	1.14	0.61	-0.45	0.63	0.0008

Visit 3 -QID Group

Mean Redness							
3 Min Post Challenge	0.95	0.75	1.29	0.88	-0.34	0.56	0.0035
10 Min Post Challenge	1.31	0.95	1.50	0.94	-0.19	0.84	0.2385
20 Min Post Challenge	1.18	1.01	1.44	1.06	-0.26	0.80	0.0928
Itching							
3 Min Post Challenge	1.86	0.94	2.12	0.99	-0.27	0.90	0.1259
10 Min Post Challenge	1.59	0.92	1.84	0.95	-0.25	0.81	0.1144
20 Min Post Challenge	0.89	0.99	0.98	1.04	-0.09	0.84	0.5782

** Efficacy Score = (Difference Score - Treated vs Vehicle Eye)

Visit 4 - BID, 2 Hour Challenge

	LE Eye		Vehicle Eye		Efficacy Score**		P-Value (2-Tail)
	Mean	Sd	Mean	Sd	Mean	Sd	
N=15							
Mean Redness							
3 Min Post Challenge	0.88	0.72	1.47	0.97	-0.59	1.07	0.0510
10 Min Post Challenge	1.39	0.79	2.17	0.78	-0.78	0.95	0.0070
20 Min Post Challenge	1.43	0.90	1.93	1.04	-0.50	1.15	0.1132
Itching							
3 Min Post Challenge	1.40	1.20	1.90	0.95	-0.50	1.07	0.0916
10 Min Post Challenge	1.37	0.93	1.83	0.77	-0.47	0.90	0.0632
20 Min Post Challenge	0.50	0.60	0.83	0.70	-0.33	0.75	0.1064

Visit 4 - BID Group, 8 Hour Challenge

N=13

Mean Redness

3 Min Post Challenge	0.96	0.87	1.37	0.96	-0.41	0.72	0.0620
10 Min Post Challenge	1.24	0.94	1.90	1.12	-0.65	0.81	0.0133
20 Min Post Challenge	1.29	1.11	1.91	1.17	-0.62	0.86	0.0236

Itching

3 Min Post Challenge	2.19	0.97	2.23	0.93	-0.04	0.25	0.5845
10 Min Post Challenge	1.85	0.69	1.77	0.88	0.08	0.93	0.7711
20 Min Post Challenge	1.08	1.12	0.85	0.66	0.23	1.15	0.4824

Visit 4 - QID Group, 2 Hour Challenge

	LE Eye		Vehicle Eye		Efficacy Score**		P-Value (2-Tail)
	Mean	Sd	Mean	Sd	Mean	Sd	
N=14							
Mean Redness							
3 Min Post Challenge	0.68	0.63	1.26	0.85	-0.58	0.55	0.0017
10 Min Post Challenge	1.21	0.83	1.68	1.04	-0.46	0.81	0.0512
20 Min Post Challenge	1.04	0.92	1.52	0.98	-0.49	0.73	0.0264
Itching							
3 Min Post Challenge	1.68	1.15	1.75	1.20	-0.07	0.55	0.6349
10 Min Post Challenge	1.00	0.88	1.61	1.10	-0.61	1.26	0.0943
20 Min Post Challenge	0.64	0.60	1.36	0.95	-0.71	0.97	0.0168

Visit 4 - QID Group, 8 Hour Challenge

	LE Eye		Vehicle Eye		Efficacy Score**		P-Value (2-Tail)
	Mean	Sd	Mean	Sd	Mean	Sd	
N=12							
Mean Redness							
3 Min Post Challenge	0.88	0.79	1.10	0.69	-0.22	0.71	0.3004
10 Min Post Challenge	1.19	0.97	1.86	0.67	-0.67	0.75	0.0104
20 Min Post Challenge	1.07	1.04	1.90	0.83	-0.83	0.75	0.0027
Itching							
3 Min Post Challenge	2.17	0.94	2.37	0.91	-0.21	0.40	0.0960
10 Min Post Challenge	1.87	1.09	2.17	1.21	-0.29	0.54	0.0891
20 Min Post Challenge	0.96	0.89	1.54	1.20	-0.58	1.02	0.0728

Mean Intraocular Pressure (mmHg)

Visit	Day	N	LE Eye			Vehicle Eye		
			Mean	SD	Range	Mean	SD	Range
BID Dosing Group								
2	7	28	15.04	2.69	10.0 - 21.0	14.93	2.88	10.0 - 21.0
3	21	28	14.43	2.90	8.0 - 22.0	14.25	2.82	7.0 - 20.0
4 (2hr)	35	15	15.93	2.76	12.0 - 20.0	15.93	2.66	12.0 - 20.0
4 (8hr)	35	13	14.54	2.63	11.0 - 21.0	14.85	2.48	11.0 - 20.0
QID Dosing Group								
2	7	29	15.38	2.47	11.0 - 18.0	15.38	2.51	11.0 - 18.0
3	21	29	14.38	2.11	11.0 - 16.0	14.41	2.56	11.0 - 20.0
4 (2hr)	35	14	14.93	2.87	11.0 - 17.0	14.43	2.68	10.0 - 17.0
4 (8hr)	35	12	15.00	2.86	10.0 - 19.0	14.83	2.89	10.0 - 18.0

Reviewer's Comments:

There were no elevations above 10 mmHg in either group.

Adverse Events:

Headaches were the most commonly reported events during this study.

Reviewer's Summary of Safety and Efficacy

Marginal efficacy has been demonstrated in the relief of itching and redness. Adverse experiences cannot be well determined from this study.

8.1.4 Study #4 Protocol # 145

Title: Comparison of dose regimen study assessing the efficacy of various concentrations of loteprednol etabonate ophthalmic suspension in the antigen challenge model of acute allergic conjunctivitis.

Objective: **Paired Comparison Study:** To compare three doses of loteprednol etabonate (0.1%, 0.2% and 0.3%) ophthalmic suspension on the prevention of signs and symptoms induced by an ocular antigen challenge, and to evaluate the duration of action of this effect.

Parallel Group Study: To evaluate the loteprednol etabonate 0.5% ophthalmic suspension compared to vehicle placebo on the prevention of signs and symptoms induced by an ocular antigen challenge.

Study Design: Study 145, was a prospective, double masked, placebo controlled, single center, study which consisted of two separate parts.

Paired Comparison Study: A randomized, double-masked, placebo controlled, paired comparison, single center study (0.1%, 0.2% and 0.3%).

Parallel Group Study: A randomized, double-masked, placebo controlled, parallel group, single center study (0.5%).

Population: There were 120 otherwise normal adults with known allergies to specific antigens.

Test Drug Schedule: Paired Comparison Study: All subjects received loteprednol etabonate ophthalmic suspension (either 0.1%, 0.2% and 0.3%) in one eye and placebo (vehicle) in the contralateral eye. Subjects were randomized with respect to which eye received which drug.

Parallel group Study: Subjects received either active drug (0.5%) or placebo (vehicle) in both eyes.

For all subjects, study drugs were instilled QID for 28 days, from Day 7 to Day 35. Visits and antigen challenges were carried out on Days 0, 7 (baseline), 21 and 35.

Investigator

Mark B. Abelson, M.D.
ORA Clinical Research and Development
863 Tumpike Street
North Andover, MA 01845

Study Plan

One hundred and twenty (120) subjects who had a minimum pre-determined response to an ocular antigen challenge were enrolled in the study. Ninety (90) subjects were to receive drug in one eye and vehicle in the contralateral eye. These subjects were randomized with respect to which eye received active drug and to which dose of drug was received. Thirty (30) subjects were randomized to receive either 0.5% loteprednol etabonate ophthalmic suspension or vehicle placebo bilaterally.

All subjects were administered a pre-study challenge on Day 0 to determine their response to rising doses of allergen. On Day 7 the subjects were challenged with the highest dose of allergen used on Day 0 to ensure that their response was still present. Subjects who qualified by their response to the second challenge were to begin a twenty eight (28) day period of study medication use. In ninety (90) randomized subjects loteprednol etabonate ophthalmic suspension (0.1%, 0.2% or 0.3%) and placebo (vehicle) were to be instilled into the appropriate eye according to a QID dosing schedule. Subjects were rechallenged on Day 21 (14 days of treatment) at 30 minutes after the latest dose of test article and on Day 35, subjects were divided into two groups from a predetermined randomization for challenges at 2 hr or 4 hr after the final dose of test article. The remaining 30 subjects were randomized to receive either loteprednol etabonate 0.5% ophthalmic suspension or placebo (vehicle) bilaterally on a QID schedule. Subjects were rechallenged on Day 21 (14 days of treatment) at 30 minutes after the latest dose of test article and on Day 35 (28

days of treatment) at 2 hours after the final dose of test article.

Ocular safety evaluations included an external examination, slit lamp examination, tonometry and visual acuity taken prior to enrollment and at scheduled times during the study. Systemic safety evaluations were treated by subject comment with physician follow-up.

Inclusion Criteria

- 18 years of age or older.
- Of either sex and of any race.
- Manifest a successful challenge, inducing at least 2+ itching and 2+ redness bilaterally.
- A positive history of allergy to grasses, animal dander, weeds, or trees. Positive skin tests, prior positive reactions to allergen challenge or verbal subject report consistent with allergy will constitute a positive history.

Exclusion Criteria

- Contraindications to the use of the study medication(s).
- Known sensitivity or allergy to the study drug(s) or their components.
- Presence of any significant illness that could be expected to interfere with the study, particularly any autoimmune disease, e.g., rheumatoid arthritis.
- Presence of bacterial or viral ocular infection.
- Presence of blepharitis, follicular conjunctivitis, iritis, or preauricular lymphadenopathy.
- Presence of mucous discharge, excess lacrimation, or burning as symptoms of ocular disease (possible dry eye).
- History of dry eye or evidence of dry eye demonstrated by slit lamp examination.
- Manifest signs and symptoms of clinically active allergic conjunctivitis (>1+ redness and/or the presence of any itching) at the baseline eye examination at visits 1 and 2.
- Use of ocular medications of any kind, including tear substitutes, or systemic medication that may interfere with a normal vasodilatory response or with normal lacrimation for an appropriate wash-out period prior to the start of the study and for the duration of the study (i.e., non-steroidal anti-inflammatories, anti-histamines, etc. within 72 hours, corticosteroids within 7 days, mast cell stabilizers within 14 days).
- Contact lenses worn 3 days prior to or during study period.
- Pregnant or nursing women; or women of childbearing potential who test positive to a pregnancy test.
- Participation in a clinical trial or use of an investigational drug or device within the last 30 days.

Efficacy Criteria

For subjects in the paired comparison arm of the study interocular differences (efficacy scores) in itching and mean redness (the mean score of redness in the ciliary, episcleral and conjunctival vessel beds) were the primary efficacy variables. Secondary variables were interocular differences (efficacy scores) in chemosis, tearing and lid swelling. Mucous discharge was evaluated in all subjects. For the subjects in the parallel group comparison the same parameters were recorded, however the variables were the difference in mean scores between those subjects who received active medication and those who received placebo (vehicle).

Most signs and symptoms were rated on a four point scale (0 - 4) where 0 = absent, 1 = mild, 2 = moderate, 3 = severe and 4 = unusually severe. Increments of 0.5 units were also assessed, e.g., a score of 1.5 would rate between mild and moderate. Tearing was rated on a 0-3 scale where 0 = none, 1 = mild (eyes felt slightly watery), 2 = moderate (blows nose occasionally) and 3 = severe (tears rolling down cheeks). Mucous discharge was rated as either absent (0) or present (1).

For itching expanded definitions were provided

- 0 = none
- 1 = an intermittent tickle sensation in the inner corner
- 2 = a mild continuous itch, not requiring rubbing
- 3 = a definite itch; you would like to be able to rub
- 4 = an incapacitating itch which would require eye rubbing

Product Batches:

loteprednol etabonate 0.1% ophthalmic suspension	- Batch # 004-95
loteprednol etabonate 0.2% ophthalmic suspension	- Batch # 002-95
loteprednol etabonate 0.3% ophthalmic suspension	- Batch # 001-95
loteprednol etabonate 0.5% ophthalmic suspension	- Batch # 001-93
placebo (vehicle) - for 0.5%	- Batch # 002-93
placebo (vehicle) - for 0.1%, 0.2% and 0.3%	- Batch # 003-95

Procedure	Visit 1 Day 0	Visit 2 Day 7 (Day 7-9)	Visit 3 Day 21 (Visit 2 + 14) (Day 21-23)	Visit 4 Day 35 (Visit 3 + 14) (Day 35-37)
Informed Consent	X			
Inclusion/Exclusion	X			
Demographics	X			
Medical/Surgical History	X			
Medication History	X	X	X	X
Urine Pregnancy Test	X			X
Ophthalmic Exam: Visual Acuity & Slit Lamp	X	X	X	X
Ocular Symptoms of Allergic Conjunctivitis	X	X	X*	X*
Intraocular Pressure		X	X	X
Antigen Challenge	X	X	X	X
Photograph **			X	X
Assignment of subject to 2 hr or 4 hr challenge schedule				X
Dispense Medication		X		
Recover Medication				X
Exit Form				X

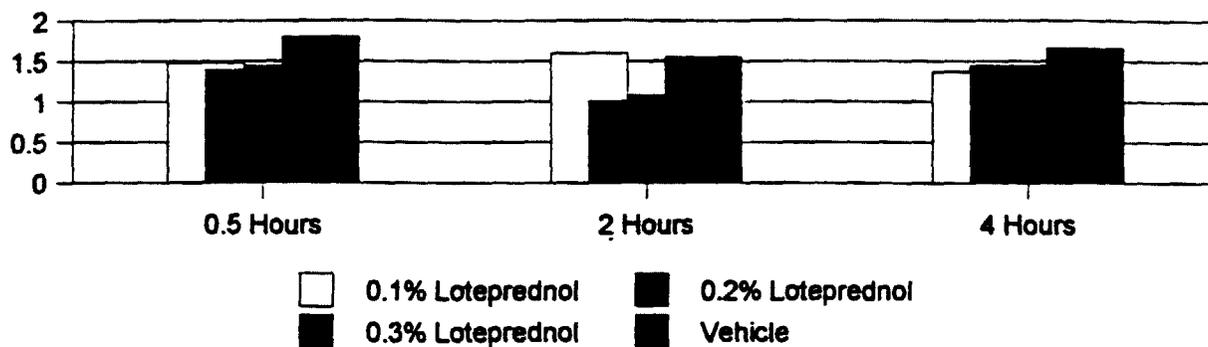
* Evaluation of Allergic conjunctivitis at 3, 10 and 20 minutes after allergen challenge

** Photographs taken immediately after 10 minute evaluation

Treatment	Enrolled	Completed Study	Reason Study Incomplete		
			Lack of Efficacy	Adverse Event	Other (Unrelated)
Paired Comparison					
Loteprednol etabonate 0.1% ophthalmic suspension	28	26 (93%)	0	0	2 (7%)
Loteprednol etabonate 0.2% ophthalmic suspension	31	31 (100%)	0	0	0
Loteprednol etabonate 0.3% ophthalmic suspension	29	29 (100%)	0	0	0
Parallel Group					
Loteprednol etabonate 0.5% ophthalmic suspension	16	16 (100%)	0	0	0
Vehicle placebo	16	14 (88%)	0	0	2 (12%)

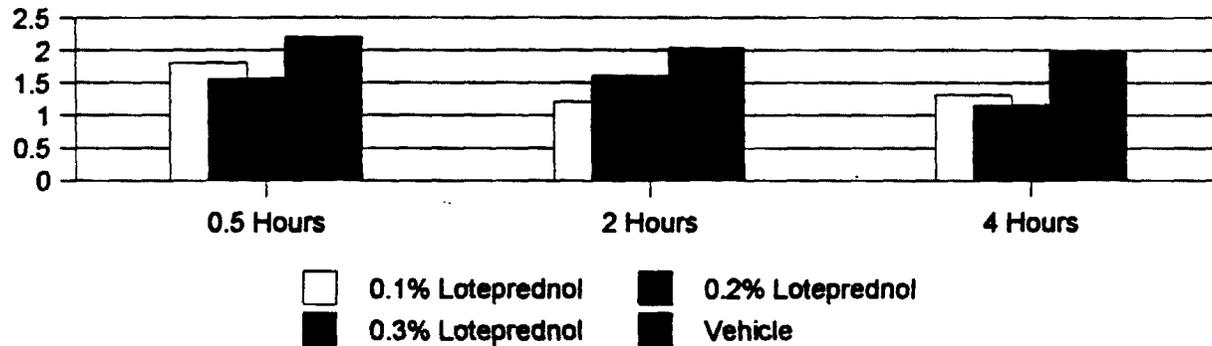
	All subjects	0.1% group	0.2% group	0.3% group	0.5% group	
Age	n	120	28	31	29	32
(years)	mean	36.4±11	36.5±11	35.7±11	38.6±12	35.0±10
	Min-Max					
Gender						
Male	n (%)	61 (51%)	18 (64%)	13 (42%)	15 (52%)	15 (47%)
Female	n (%)	59 (49%)	10 (36%)	18 (58%)	14 (48%)	17 (53%)
Race						
Caucasian	n	119 (99%)	28 (100%)	31 (100%)	28 (97%)	32 (100%)
Hispanic	n	1 (1%)	0	0	1 (3%)	0
Iris Pigmentation						
Light	n	80 (67%)	22 (79%)	20 (65%)	19 (66%)	19 (59%)
Dark	n	40 (33%)	6 (21%)	11 (35%)	10 (34%)	13 (41%)

Itching



0.1% Loteprednol	1.48	1.6	1.37
0.2% Loteprednol	1.39	1.01	1.45
0.3% Loteprednol	1.45	1.08	1.01
Vehicle	1.81	1.56	1.67

Redness



0.1% Loteprednol	1.81	1.21	1.32
0.2% Loteprednol	1.56	1.61	1.16
0.3% Loteprednol	1.57	1.35	1.06
Vehicle	2.21	2.04	1.97

Reviewer's Comments:

All of the loteprednol groups perform slightly better than the vehicle group. The 0.3% loteprednol group is usually better than the other two groups although the differences are very small.

Itching	LE Eye		Vehicle Eye		Efficacy Score**		p-value (2-tail)
	Mean	SD.	Mean	Sd.	Mean	Sd.	
0.1% Group (n = 27)							
3 min post-challenge	1.93	0.97	2.19	0.94	-0.26	0.98	0.1828
10 min post-challenge	1.56	0.98	1.83	0.99	-0.28	1.13	0.2126
20 min post-challenge	0.96	0.89	1.17	1.13	-0.20	0.84	0.2162
0.2% Group (n = 31)							
3 min post-challenge	1.79	1.32	2.27	1.06	-0.48	1.04	0.0144
10 min post-challenge	1.60	1.17	2.29	0.87	-0.69	0.92	0.0002
20 min post-challenge	0.79	0.92	1.24	1.02	-0.45	1.01	0.0187
0.3% Group (n = 29)							
3 min post-challenge	2.07	1.00	2.40	0.95	-0.33	0.79	0.0321
10 min post-challenge	1.41	0.95	1.83	0.96	-0.41	0.78	0.0080
20 min post-challenge	0.88	0.91	1.09	1.01	-0.21	0.80	0.1728
Redness							
	LE Eye		Vehicle Eye		Efficacy Score**		p-value (2-tail)
	Mean	Sd.	Mean	Sd.	Mean	Sd.	
0.1% Group (n - 27)							
3 min post-challenge	1.44	0.79	1.83	0.80	-0.40	0.74	0.0100
10 min post-challenge	2.00	0.86	2.20	0.90	-0.20	0.77	0.1961
20 min post-challenge	1.98	0.91	2.21	0.85	-0.23	0.85	0.1638
0.2% Group (n - 31)							
3 min post-challenge	1.24	0.84	1.77	0.95	-0.54	0.63	0.0001
10 min post-challenge	1.73	1.11	2.37	0.96	-0.64	0.91	0.0005
20 min post-challenge	1.72	1.11	2.32	0.98	-0.60	0.87	0.0006
0.3% Group (n - 29)							
3 min post-challenge	1.20	0.85	1.99	0.93	-0.80	0.84	0.0001
10 min post-challenge	1.81	0.75	2.61	0.66	-0.80	0.68	0.0001
20 min post-challenge	1.70	0.91	2.59	0.75	-0.89	0.86	0.0001

Itching- 2 Hr Challenge	LE Eye		Vehicle Eye		Efficacy Score**		p-value (2-tail)
	Mean	Sd.	Mean	Sd.	Mean	Sd.	
0.1% Group (n = 12)							
3 min post-challenge	1.62	1.00	1.71	1.27	-0.08	0.56	0.6147
10 min post-challenge	1.92	1.08	1.96	1.16	-0.04	0.54	0.7949
20 min post-challenge	1.25	1.01	1.33	1.01	-0.08	0.47	0.5505
0.2% Group (n = 15)							
3 min post-challenge	1.63	1.17	2.07	0.78	-0.43	1.12	0.1548
10 min post-challenge	0.93	1.16	1.57	0.86	-0.63	1.17	0.0551
20 min post-challenge	0.47	0.74	0.83	0.84	-0.37	0.97	0.1662
0.3% Group (n = 15)							
3 min post-challenge	1.67	1.25	2.13	1.08	-0.47	0.93	0.0737
10 min post-challenge	1.07	1.02	1.73	1.08	-0.67	1.01	0.0230
20 min post-challenge	0.50	0.73	0.73	0.88	-0.23	0.58	0.1306
Redness- 2 Hr Challenge							
	LE Eye		Vehicle Eye		Efficacy Score**		p-value
	Mean	Sd.	Mean	Sd.	Mean	Sd.	(2-tail)
0.1% Group (n = 12)							
3 min post-challenge	0.72	0.71	1.25	0.91	-0.53	0.51	0.0044
10 min post-challenge	1.62	0.75	1.72	0.94	-0.10	0.76	0.6677
20 min post-challenge	1.29	0.92	2.06	0.93	-0.76	0.84	0.0092
0.2% Group (n = 15)							
3 min post-challenge	1.16	0.96	1.59	0.99	-0.43	0.75	0.0414
10 min post-challenge	1.76	0.86	2.13	0.89	-0.38	0.79	0.0845
20 min post-challenge	1.92	0.86	2.02	1.01	-0.10	1.11	0.7312
0.3% Group (n = 15)							
3 min post-challenge	0.81	0.77	2.00	0.77	-1.19	0.72	<0.0001
10 min post-challenge	1.53	1.14	2.79	0.67	-1.26	1.00	0.0003
20 min post-challenge	1.70	1.11	2.80	0.80	-1.10	1.01	0.0009

Itching- 4 Hr Challenge	LE Eye		Vehicle Eye		Efficacy Score**		p-value (2-tail)
	Mean	Sd.	Mean	Sd.	Mean	Sd.	
0.1% Group (n = 14)							
3 min post-challenge	1.57	1.17	1.82	1.20	-0.25	1.25	0.4683
10 min post-challenge	1.61	0.98	1.93	0.94	-0.32	1.30	0.3700
20 min post-challenge	0.93	1.07	1.36	1.15	-0.43	1.55	0.3212
0.2% Group (n = 16)							
3 min post-challenge	1.69	0.96	1.69	1.08	0.00	0.82	1.0000
10 min post-challenge	1.75	0.93	1.94	1.11	-0.19	0.93	0.4320
20 min post-challenge	0.91	0.78	1.31	1.21	-0.41	0.78	0.0545
0.3% Group (n = 14)							
3 min post-challenge	1.14	0.89	1.86	1.05	-0.71	0.97	0.0168
10 min post-challenge	1.25	0.80	1.89	0.90	-0.64	0.99	0.0302
20 min post-challenge	0.64	1.01	1.21	0.61	-0.57	0.96	0.0438
Redness- 4 Hr Challenge							
0.1% Group (n - 14)							
3 min post-challenge	0.80	0.77	1.35	0.85	-0.55	0.83	0.0283
10 min post-challenge	1.57	1.02	2.06	0.86	-0.49	0.85	0.0519
20 min post-challenge	1.58	0.87	2.35	0.97	-0.76	0.97	0.0113
0.2% Group (n - 16)							
3 min post-challenge	0.92	0.91	1.40	0.97	-0.48	0.92	0.0540
10 min post-challenge	1.25	0.87	2.39	0.85	-1.14	0.94	0.0002
20 min post-challenge	1.32	1.02	2.37	1.02	-1.05	1.14	0.0022
0.3% Group (n - 14)							
3 min post-challenge	0.70	0.77	1.25	0.71	-0.55	0.58	0.0038
10 min post-challenge	1.23	1.07	2.31	0.95	-1.08	0.86	0.0004
20 min post-challenge	1.25	1.24	2.27	0.92	-1.02	0.94	0.0013

Visit 3 (Day 21) - Parallel Group	LE Treatment Group N = 16)		Vehicle Treatment Group (N = 15)		Mean Diff. Score	p-value (2-tail)
	Mean	Sd.	Mean	Sd.		
Itching						
3 min post-challenge	1.55	0.89	2.27	0.98	-0.72	0.0379
10 min post-challenge	1.94	0.90	2.23	0.68	-0.29	0.3144
20 min post-challenge	1.09	0.79	1.50	0.91	-0.41	0.1930
Mean Redness						
3 min post-challenge	1.05	0.89	1.79	0.81	-0.74	0.0145
10 min post-challenge	1.86	0.87	2.19	0.94	-0.33	0.3194
20 min post-challenge	1.88	0.93	2.04	0.90	-0.16	0.6231
Ciliary						
3 min post-challenge	0.89	0.88	1.62	0.82	-0.73	0.0244
10 min post-challenge	1.69	0.80	2.17	1.02	-0.48	0.1547
20 min post-challenge	1.77	0.92	1.98	0.98	-0.22	0.5293
Conjunctival						
3 min post-challenge	1.17	0.88	1.78	0.86	-0.61	0.0602
10 min post-challenge	1.95	0.91	2.23	0.94	-0.28	0.4076
20 min post-challenge	1.94	0.96	2.10	0.88	-0.16	0.6259
Episcleral						
3 min post-challenge	1.08	0.96	1.70	0.79	-0.62	0.0591
10 min post-challenge	1.94	0.92	2.17	0.90	-0.23	0.4891
20 min post-challenge	1.92	0.95	2.03	0.89	-0.11	0.7386
Chemosis						
3 min post-challenge	0.28	0.34	0.58	0.39	-0.30	0.0278
10 min post-challenge	0.69	0.47	0.85	0.53	-0.16	0.3745
20 min post-challenge	0.73	0.60	0.83	0.64	-0.10	0.6602
Lid Swelling						
3 min post-challenge	0.20	0.40	0.17	0.36	+0.03	0.7926
10 min post-challenge	0.28	0.45	0.30	0.48	-0.02	0.9114
20 min post-challenge	0.31	0.49	0.28	0.43	+0.03	0.8616
Tearing						
3 min post-challenge	0.00	0.00	0.30	0.80	-0.30	0.1671
10 min post-challenge	0.00	0.00	0.27	0.80	-0.27	0.2170
20 min post-challenge	0.03	0.13	0.38	1.00	-0.35	0.1983

Reviewer's Comments:

The efficacy of the 0.5% loteprednol appears to be approximately equal to the efficacy observed for the 0.2% and 0.3%.

Visit 4 (Day 35) Parallel Group	LE Treatment Group (N = 16)		Vehicle Treatment Group (N = 14)		Mean Diff. Score	p-value (2-tail)
	Mean	Sd.	Mean	Sd.		
Itching						
3 min post-challenge	1.05	0.95	2.38	0.79	-1.33	0.0003
10 min post-challenge	1.47	0.76	2.05	0.79	-0.58	0.0482
20 min post-challenge	0.59	0.58	1.07	0.90	-0.48	0.0895
Mean Redness						
3 min post-challenge	0.67	0.67	1.47	1.01	-0.80	0.0151
10 min post-challenge	1.51	0.84	2.13	0.84	-0.62	0.0523
20 min post-challenge	1.62	0.83	2.15	0.99	-0.53	0.1198
Ciliary						
3 min post-challenge	0.47	0.69	1.32	1.07	-0.85	0.0141
10 min post-challenge	1.52	0.81	2.00	0.95	-0.48	0.1427
20 min post-challenge	1.59	0.83	2.04	1.14	-0.45	0.2308
Conjunctival						
3 min post-challenge	0.80	0.68	1.59	0.97	-0.79	0.0143
10 min post-challenge	1.55	0.82	2.20	0.82	-0.65	0.0384
20 min post-challenge	1.69	0.82	2.25	0.96	-0.56	0.0944
Episcleral						
3 min post-challenge	0.75	0.71	1.50	1.00	-0.75	0.0235
10 min post-challenge	1.47	0.92	2.20	0.79	-0.73	0.0285
20 min post-challenge	1.58	0.90	2.18	0.92	-0.60	0.0819
Chemosis						
3 min post-challenge	0.14	0.27	0.38	0.46	-0.24	0.0947
10 min post-challenge	0.55	0.48	0.91	0.50	-0.36	0.0522
20 min post-challenge	0.53	0.47	0.82	0.58	-0.29	0.1408
Lid Swelling						
3 min post-challenge	0.06	0.17	0.21	0.47	-0.15	0.2684
10 min post-challenge	0.28	0.41	0.38	0.53	-0.10	0.5868
20 min post-challenge	0.28	0.41	0.36	0.49	-0.08	0.6457
Tearing						
3 min post-challenge	0.00	0.00	0.18	0.67	-0.18	0.3356
10 min post-challenge	0.00	0.00	0.18	0.46	-0.18	0.1739
20 min post-challenge	0.00	0.00	0.04	0.13	-0.04	0.3356

Reviewer's Comments:

There is very little difference between evaluations at Day 21 and Day 35.

IOP (mmHg)			LE Eye			Vehicle Eye		
Visit	Day	n	Mean	SD	Range (mm Hg)	Mean	SD	Range (mm Hg)
0.1% treatment group								
2	7	27	15.48	2.46	12 - 21	15.59	2.61	12 - 21
3	21	28	15.25	2.46	11 - 20	15.18	2.55	11 - 20
4 (2 hr)	35	13	15.62	2.47	11 - 18	14.31	3.28	8 - 18
4 (4 hr)	35	14	14.57	1.87	12 - 21	14.43	2.10	10 - 18
0.2% treatment group								
2	7	31	15.65	2.25	10 - 21	15.52	2.41	10 - 21
3	21	31	15.87	2.75	10 - 21	15.68	2.60	10 - 20
4 (2 hr)	35	15	15.87	2.17	10 - 22	15.53	2.23	12 - 20
4 (4 hr)	35	16	16.19	3.53	10 - 20	15.81	2.93	11 - 20
0.3% treatment group								
2	7	29	15.47	2.73	10 - 20	16.14	2.71	10 - 22
3	21	29	16.28	2.62	12 - 22	16.10	2.72	12 - 22
4 (2 hr)	35	15	17.73	3.26	12 - 24	16.40	2.44	12 - 20
4 (4 hr)	35	14	16.14	2.66	12 - 20	15.21	2.81	12 - 20

IOP	Visit	Day	LE Treatment Group				Vehicle Treatment Group						
			OD		OS		OD		OD				
	n	Mean	SD	Mean	SD	Range	n	Mean	SD	Mean	SD	Range	
2	7	16	15.75	3.11	15.73	3.06	10 - 20	15	16.60	1.45	16.73	1.87	15 - 20
3	21	16	17.00	2.03	17.00	1.71	13 - 22	15	16.13	2.53	16.67	2.16	11 - 20
4 (2 hr)	35	16	17.50	2.34	17.69	2.27	12 - 20	14	15.67	3.59	16.07	3.83	10 - 22

Reviewer's Comments:

Intraocular pressures are generally higher in the loteprednol group compared to the vehicle group after 14 days of treatment or more.

Adverse Experiences

LE 0.1%				
ID	Eye	Medical Event	Date of Onset	Intensity
5103	OD	COLD	11/05/95	MILD
5123	OD	HEADACHE	11/17/95	MILD
5128	OS	ASTHMA	10/17/95	MILD
5135	OD	HEADACHE	10/01/95	MILD
5135	OD	HEADACHE	10/03/95	MILD
5135	OD	HEADACHE	11/04/95	MILD
5143	OS	HEADACHE	11/02/95	MILD
5143	OS	HEADACHE	11/05/95	MILD
5143	OS	COLD	11/07/95	MILD
5143	OS	HEADACHE	11/07/95	MILD
5148	OS	HEADACHE	11/05/95	MODERATE
5149	OS	HEADACHE	11/18/95	MODERATE
5150	OS	INTERMITTENT ITCHING OU	10/29/95	MILD
5150	OS	INTERMITTENT TEARING OU	10/29/95	MILD
5151	OD	STREP THROAT	11/14/95	MODERATE
5173	OS	HEADACHE	10/31/95	MILD
5173	OS	HEADACHE	11/19/95	MODERATE
5176	OD	COLD	11/15/95	MILD
5182	OS	HEADACHE	10/30/95	MILD
5190	OD	WHEEZING	11/01/95	MILD
5192	OD	COLD	10/31/95	MILD
5201	OS	EYELID SWELLING R/L	11/23/95	MILD
5201	OS	DRYNESS R/L	10/23/95	MILD
5201	OS	ECZEMA	11/15/95	MILD
5208	OD	JOINT DETERIORATION 2 DEGREE TRAUMA	10/07/95	MODERATE

LE 0.2%				
ID	Eye	Medical Event	Date of Onset	Intensity
5105	OD	TOOTHACHE	10/18/95	MODERATE
5105	OD	TOOTHACHE	10/02/95	MODERATE
5105	OD	HEADACHE	11/01/95	MODERATE
5105	OD	HEADACHE	11/04/95	MODERATE
5111	OD	MILD COLD	10/29/95	MILD
5127	OS	SINUS CONGESTION	10/18/95	MILD
5127	OS	CHEST CONGESTION	10/19/95	MILD
5127	OS	SINUS CONGESTION	10/03/95	MILD
5127	OS	CHALAZION RUL	11/15/95	MILD
5139	OD	BACKACHE	10/18/95	MILD
5139	OD	HEADACHE	11/18/95	MILD
5153	OS	ASTHMA	11/11/95	MILD
5153	OS	SINUS CONGESTION	11/11/95	MILD
5153	OS	ASTHMA	10/29/95	MILD
5164	OD	HEADACHE	10/17/95	MILD
5164	OD	HEADACHE	11/04/95	MILD
5180	OS	COLD	10/13/95	MODERATE
5185	OD	HEADACHE	10/20/95	MILD
5185	OD	HEADACHE	11/14/95	MODERATE
5187	OS	COLD	10/16/95	MILD
5196	OD	HEADACHE	10/28/95	MODERATE
5200	OS	HEADACHE	10/22/95	MILD
5207	OD	HEADACHE	10/19/95	MILD
5207	OD	HEADACHE	11/03/95	MILD
5207	OD	HEADACHE	11/16/95	MILD
5207	OD	HEADACHE	11/17/95	MILD
5218	OS	HEADACHE	10/20/95	MILD
5218	OS	RESPIRATORY INFECTION	10/30/95	MODERATE

LE 0.3%				
ID	Eye	Medical Event	Date of Onset	Intensity
5117	OD	CONGESTION	11/17/95	MILD
5117	OD	BACKACHE	11/04/95	MILD
5117	OD	BACKACHE	11/08/95	MILD
5119	OS	SINUS CONGESTION	10/19/95	MILD
5121	OS	SUBDERMAL HEMORRHAGE OD	11/18/95	MILD
5134	OD	HEADACHE	11/03/95	MILD
5145	OS	URINARY TRACT INFECTION	11/03/95	MODERATE
5146	OS	INDIGESTION	10/17/95	MILD
5146	OS	CAKING OF LASHES	10/23/95	MILD
5146	OS	HEADACHE	11/11/95	MODERATE
5152	OD	HEADACHE	10/17/95	MILD
5152	OD	BACKACHE	11/04/95	MILD
5152	OD	BACKACHE	11/15/95	MILD
5157	OS	HEADACHE	11/03/95	MODERATE
5158	OS	HEADACHE	11/18/95	MILD
5157	OS	CRAMPS (MENSTRUAL)	10/18/95	MILD
5158	OS	HEADACHE	10/31/95	MILD
5158	OS	HEADACHE	11/07/95	MILD
5158	OS	HEADACHE	11/16/95	MILD
5158	OS	HEADACHE	11/18/95	MILD
5172	OD	ASTHMA-WHEEZING	10/23/95	MILD
5189	OD	HEADACHE	10/21/95	MILD
5189	OD	HEADACHE	10/25/95	MODERATE
5189	OD	HEADACHE	10/30/95	MODERATE
5189	OD	HEADACHE	10/22/95	MILD
5189	OD	HEADACHE	11/12/95	MILD
5189	OD	HEADACHE	11/16/95	MILD
5206	OD	SINUS CONGESTION	10/22/95	MILD
5211	OS	COLD	11/17/95	MILD

LE 0.5%				
ID	Eye	Medical Event	Date of Onset	Intensity
5106	OD	COLD	10/16/95	MILD
5106	OD	BODY ACHES	10/27/95	MILD
5124	OS	HEADACHE	10/18/95	MILD
5128	OS	HEADACHE	10/30/95	MILD
5131	OD	COLD	11/18/95	MILD
5142	OS	HEADACHE	11/03/95	MODERATE
5155	OD	HEADACHE	11/18/95	MODERATE
5155	OS	SINUS CONGESTION	10/16/95	MILD
5155	OS	ECZEMATOUS RASH	10/26/95	MODERATE
5155	OS	SINUS CONGESTION	10/23/95	MILD
5155	OS	HEADACHE	10/23/95	MILD
5159	OD	KNEE PAIN	11/02/95	MILD
5160	OS	HEADACHE	10/27/95	MILD
5160	OS	HEADACHE	11/01/95	MILD
5160	OS	HEADACHE	11/08/95	MILD
5162	OD	COLD	10/16/95	MILD
5162	OD	HEADACHE	10/30/95	MILD
5162	OD	CRUSTING ON EYELIDS IN AM	10/23/95	MILD
5162	OD	HEADACHE	11/13/95	MILD
5168	OS	HEADACHE	10/19/95	MILD
5168	OS	HEADACHE	11/02/95	MILD
5174	OD	ITCHY THROAT	10/15/95	MODERATE
5174	OD	NASAL CONGESTION	10/15/95	MODERATE
5174	OD	HEADACHE	11/03/95	MODERATE
5174	OD	HEADACHE	10/22/95	MODERATE
5174	OD	SINUS CONGESTION	10/22/95	MODERATE
5174	OD	ITCHY THROAT	10/22/95	MODERATE
5174	OD	STINGING OD	11/02/95	MILD

5174	OD	HEADACHE	11/10/95	MILD
5183	OS	HEADACHE	10/24/95	MILD
5183	OS	OCULAR IRRITATION	11/04/95	MILD
5183	OS	BLURRED VA	11/04/95	MILD
5188	OD	SINUS CONGESTION	10/15/95	MILD
5188	OD	HEADACHE	10/21/95	MILD
5188	OD	HEADACHE	11/01/95	MILD
5188	OD	HEADACHE - SINUS	11/13/95	MODERATE
5199	OS	HEADACHE	11/01/95	MODERATE
5209	OD	ALLERGIC CONJUNCTIVITIS	11/05/95	MILD
5216	OS	HEADACHE	11/18/95	MODERATE
5217	OS	BACK PAIN	10/18/95	MODERATE
5217	OS	BACK PAIN	10/30/95	MILD
5217	OS	HEADACHE	11/07/95	MODERATE
5217	OS	HEADACHE	11.09/95	MILD
5217	OS	HEADACHE	11/15/95	MILD

Reviewer's Comments:

Due to the design of the study, few adverse events are expected. No new events were observed in this study.

**APPEARS THIS WAY
ON ORIGINAL**

9. Reviewer's Overview of Efficacy

Marginal efficacy has been demonstrated in the resolution of itching and redness. This constitutes a marginal demonstration of the efficacy for the relief of signs and symptoms of seasonal allergic conjunctivitis. Taken with the studies submitted for NDA 20-583, adequate efficacy has been demonstrated.

10. Reviewer's Overview of Safety

The total number of patients studied with the loteprednol etabonate ophthalmic suspension, 0.2% is too small by itself to establish safety, however, taken with the patients studied with the 0.3%-0.5%, adequate safety has been established for use in the relief of signs and symptoms of allergic conjunctivitis.

Adverse experiences in the limited studies (duration and number of patients) were generally confined to mild to moderate ocular events. There was an increased chance of increased IOP during use.

**APPEARS THIS WAY
ON ORIGINAL**

THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE

8 pages

12 Conclusions

The submitted studies in NDA 20-803 taken together with the studies in NDA 20-583 and NDA 20-841 demonstrate safety and efficacy for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

13 Recommendations

1. Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 20-583 is recommended for approval for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis. Approval for the steroid class indication is not recommended.
2. The applicant should submit revised labeling consistent with the recommendations in this review.
3. The proposed tradename should be specified.
4. Table 4 in Clinical Study Report 145 (Volume 17, Page 55) should be corrected. The standard deviations are in error.
5. The pH range and other specifications in the NDA summary differs from other sections of the NDA [Table 2.5.2.3 vs Table 2.5.2.5]. The specifications should be clarified and be consistent.
6. Issues related to water loss and the formation of "aggregate" material after storage of inverted containers will need to be resolved prior to approval.
 - A. What is the aggregate composed of?
 - B. Does the aggregate recombine with the suspension on shaking? If so, how quickly?
 - C. Can the aggregate be cleared by dispensing a couple of drops of the suspension? If so, does this affect the composition of the rest of the suspension?

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-803
HFD-550
HFD-340
HFD-550/PM/LoBianco
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Cooney
HFD-550/PHARM/Weir
HFD-550/MO/Chambers

NDA 20-803: loteprednol etabonate ophthalmic suspension, 0.2%

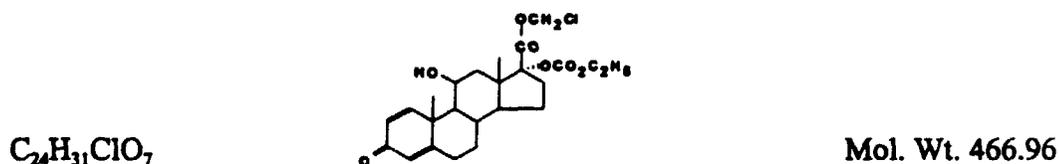
ALREX™

loteprednol etabonate ophthalmic suspension, 0.2%

STERILE OPHTHALMIC SUSPENSION**DESCRIPTION:**

ALREX™ (loteprednol etabonate ophthalmic suspension) contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

Loteprednol etabonate is represented by the following structural formula:



Chemical name: chloromethyl 17 α -[(ethoxycarbonyl)oxy]-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate

Each mL contains: ACTIVE: Loteprednol Etabonate 2 mg (0.2%);
 INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water and Tyloxapol.
 Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.3-5.6. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg.
 PRESERVATIVE ADDED: Benzalkonium Chloride 0.01%.

CLINICAL PHARMACOLOGY:

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into

NDA 20-803 Alrex (loteprednol etabonate ophthalmic suspension)

cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/mL) systemic absorption occurs with ALREX.

Clinical Studies:

In two double-masked, placebo-controlled six-week environmental studies of 268 patients with seasonal allergic conjunctivitis, ALREX, when dosed four times per day was superior to placebo in the treatment of the signs and symptoms of seasonal allergic conjunctivitis. ALREX provided reduction in bulbar conjunctival injection and itching, beginning approximately 2 hours after instillation of the first dose and throughout the first 14 days of treatment.

INDICATIONS AND USAGE:

ALREX Ophthalmic Suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

CONTRAINDICATIONS:

ALREX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. ALREX is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS:

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral

infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

PRECAUTIONS:

General: For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored even though it may be difficult in children and uncooperative patients (see WARNINGS).

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Information for Patients: This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If redness or itching becomes aggravated, the patient should be advised to consult a physician.

Patients should be advised not to wear a contact lens if their eye is red. ALREX should not be used to treat contact lens related irritation. The preservative in ALREX, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling ALREX before they insert their contact lenses.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (1500 and 750 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

Pregnancy: Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (85 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects

was 0.5 mg/kg/day (15 times the maximum daily clinical dose). Oral treatment of rats during organogenesis with 0.5 to 100 mg/kg/day resulted in embryotoxicity (increased post-implantation losses at 100 mg/kg/day, and decreased fetal body weight and skeletal ossification with ≥ 50 mg/kg/day) and teratogenicity (absent innominate artery at ≥ 5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥ 50 mg/kg/day). Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥ 5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

Nursing Mothers: It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when ALREX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:

Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2%-0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, injection, and photophobia. Other ocular adverse reactions occurring in less than 5% of patients include conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied.

Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer

with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥ 10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo. Among the smaller group of patients who were studied with ALREX, the incidence of clinically significant increases in IOP (≥ 10 mm Hg) was 1% (1/133) with ALREX and 1% (1/135) with placebo.

DOSAGE AND ADMINISTRATION:
SHAKE VIGOROUSLY BEFORE USING.

One drop instilled into the affected eye(s) four times daily.

HOW SUPPLIED:

ALREX™ (loteprednol etabonate ophthalmic suspension) is supplied in a plastic bottle with a controlled drop tip in the following sizes:

2.5 mL (NDC 24208-353-25) - AB35304
5 mL (NDC 24208-353-05) - AB35307
10 mL (NDC 24208-353-10) - AB35309

DO NOT USE IF NECKBAND IMPRINTED WITH "Protective Seal" and YELLOW (mortar and pestle graphic) IS NOT INTACT.

Storage: Store upright between 15° - 25°C (59° - 77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Rx only

Manufactured by:

Bausch & Lomb Pharmaceuticals, Inc., Tampa, Florida 33637

Under Agreement with Pharmos Corporation.

U.S. Patent No. 4,996,335

U.S. Patent No. 5,540,930

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XO50331 (Folded) Rev. 3/98-8C

XM10033 (Flat)

Package and Container Labeling- Submitted and consistent with Package Insert.

Reviewer's Comments: *Acceptable.*

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Phase 4 Commitments:

"We therefore commit to the following:

Reviewer's Comments: *Acceptable.*

Safety update: No new safety information is available for this product.

Reviewer's Comments: *Acceptable.*

Recommendation:

NDA 20-803, ALREX (loteprednol etabonate ophthalmic suspension) 0.2% is recommended for approval.

~
Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-803
 HFD-550
 HFD-550/PM/LoBianco
 HFD-830/CHEM/Fenselau
 HFD-805/MICRO/Cooney
 HFD-550/PHARM/Weir
 HFD-550/MO/Chambers