

8.4.2 Reviewer's Trial # 6 Sponsor's protocol # 106

Title: Pilot Efficacy Evaluation of Loteprednol Etabonate in Giant Papillary Conjunctivitis

Investigators:

Michael Callahan, M.D.	Birmingham, AL	(Investigator #125)
James Gordon, M.D.	St. Louis, MO	(Investigator #128)
Dennis Hall, M.D.	Atlanta, GA	(Investigator #126)
Barry Horwitz, M.D.	Houston, TX	(Investigator #122)
Michael Insler, M.D.	New Orleans, LA	(Investigator #125)
Elliot Korn, M.D.	St. Louis, MO	(Investigator #127)
Robert Laibovitz, M.D.	Austin, TX	(Investigator #112)

Objective:

This study was designed to evaluate the safety and effectiveness of loteprednol etabonate 0.5% ophthalmic suspension in reducing the ocular signs and symptoms accompanying contact lens-associated giant papillary conjunctivitis (GPC).

Study Design:

This study was a randomized, double-masked, placebo controlled, parallel group comparison study.

Number and Description of Volunteers:

One hundred thirteen adults with bilateral contact lens associated GPC were enrolled in this study.

Test Drug Schedule:

Patients were randomly assigned to treatment with either 0.5% loteprednol etabonate suspension (LE) or the loteprednol etabonate vehicle (placebo) and instructed to instill one drop into each eye four time daily for four weeks.

Follow-up examinations occurred on Days 2 or 3, 7, 14, 21, and 28 of masked therapy.

Results:

Seven investigators enrolled 113 patients (LE = 56; PLA = 57). Of those, 110 patients completed the study as planned while 3 patients discontinued the study for reasons unrelated to treatment. Both masked treatments were well-tolerated and there were no serious, severe or clinically significant adverse medical events reported. Patients treated with LE demonstrated significant reduction in the primary ocular signs of GPC (papillae; $p < 0.001$) and were rated better in the Physician's Global Assessment ($p = 0.017$). During the course of therapy, loteprednol etabonate suspension did not elevate intraocular pressure. Ratings for bulbar injection and the Patient Opinion Assessment demonstrated statistical trends that favored LE treatment.

Applicant's Conclusions:

LE was well tolerated and significantly effective in the treatment of GPC. In addition to significantly reducing the primary ocular sign associated with GPC which was corroborated by the Physician's Global Assessment rating.

Reviewer's Comments: *This study is supportive of the claim for GPC. Some of the investigators in this study are also investigators in the other GPC studies.*

APPEARS THIS WAY
ON ORIGINAL

8.4.2 Reviewer's Trial # 7 Sponsor's protocol # 103

Title: Safety evaluation of the intraocular pressure response to loteprednol etabonate in known steroid responsive individuals.

Investigators:

C. Michael Adams, MD	Birmingham, AL	(Investigator No. 134)
Gregg Berdy, MD	St. Louis, MO	(Investigator No. 130)
James Gordon, MD	St. Louis, MO	(Investigator No. 128)
Bradley Fouraker, MD	St. Louis, MO	(Investigator No. 133)
Barry Horwitz, MD	Houston, TX	(Investigator No. 122)
Robert Laibovitz, MD	Austin, TX	(Investigator No. 112)
Alan Mandell, MD	Memphis, TN	(Investigator No. 113)
Robert Stewart, MD	Houston, TX	(Investigator No. 132)

Study Plan:

This was a prospective, double-masked, randomized, active-controlled, parallel-group comparison of 0.5% loteprednol etabonate in patients with a prior history of steroid-induced IOP elevation. Nineteen (19) patients with prior history of steroid-induced IOP elevation were evaluated. Subjects were randomly assigned to six weeks of treatment with the first masked study drug followed by two weeks of no drug treatment and are then assigned to six weeks of treatment with the second masked study drug followed by two weeks of no drug treatment. Each subject was instructed to dose the masked treatments in one eye only, four times daily while awake during each six-week period of masked treatment. The randomized masked treatments were: loteprednol etabonate (LE) 0.5% and prednisolone acetate (PA) 1.0%.

Enrollment:

Investigators enrolled nineteen patients (LE = 14; PA = 14) with nine patients completing the crossover evaluation. Three patients were non-responsive in IOP to both treatments. Both masked medications were well-tolerated and there were no serious, severe or clinically significant adverse medical events other than IOP. This study was discontinued early due to stability issues of the clinical formulation.

Protocol deviations:

1. The age of patient #113-702, 76 years, exceeded the maximum for enrollment of 75 years.
2. Eight patients were enrolled with ambiguous documentation of steroid response history in the eyes treated with study medication. In one case (#132-742) the response of both eyes was documented; however, only one eye satisfied the criterion elevation while both eyes were enrolled. In 7 cases the problem was due to the investigator's enrolling both eyes for treatment but documenting the steroid response in only one eye. Five of these patients were from investigator #128: (721, 722, 723, 724, and 725); one was from investigator #132: (741); and one from investigator #130: (661).
3. Two patients were allowed to participate less than 6 months after having had ocular surgery. Patient #113-702 was enrolled in the study and began treatment 22 days after YAG capsulotomy on the left eye. Only his right eye received study medication. Patient #130-662 was enrolled in the study and began treatment 3 months after cataract extraction

with IOL implant procedure on the right eye, the eye assigned to be treated with study medication. Enrollment was also only 4 months after the same procedure was performed on the untreated left eye.

4. The protocol under Amendment #2 allowed patients to be enrolled with an IOP of 20 or 21 mmHg. But the Becker response criteria define an "Intermediate" response as an IOP from 20 to 31 mmHg. Thus patients were allowed to be enrolled with a positive response at baseline. Patients #128-723, #130-661, #130-662, #132-741, #132-742, #132-743, and #134-681 had an IOP \geq 20 mmHg in at least one eye on at least one screening visit or on the enrollment visit for Period 1. The IOP of patients #130-661 and #130-662 was \geq 20 mmHg in at least one eye on the Period 2 enrollment visit. Since baseline pressures were based on the average of screening and enrollment pressures, patients #130-662, #132-741, #132-742, and #134-681 met the Becker criteria as "responders" at baseline. Similarly, #130-661 and #130-662 were baseline responders in Period 2.
5. Patient #134-681 began treatment on 05/15/91 but no additional doses were taken until 6/5/91. The investigator noted in the casebook that the 14 day follow-up visit occurring on 6/19/92 was 14 days after the beginning of treatment. Therefore, the enrollment visit date on 5/15/91 was selected as baseline while the date of 6/5/91 was used to mark the beginning of treatment (day 0).
6. Three patients were on the protocol on 7/10/91 when the sponsor terminated the study due to the product going out of specification. Patient #132-744 had received 42 days of treatment by the termination date. The investigator judged that she had not successfully completed Period 1 due to "reasons unrelated to treatment". This patient however was examined only on day 23 and 42 of treatment, and therefore a more appropriate reason for termination would be due to "missed visits". Patients #134-681 and #134-683 had received 35 and 40 days, respectively, of treatment when the study was terminated by the sponsor. Both patients were seen on follow-up visit days 14 and 28. The investigator concluded that these patients had successfully completed Period 1 of the protocol.
7. The two eyes of patient #128-722 were to be treated in both periods. However, on the final exam CRF of the second period the investigator commented "OS - treated". It will be assumed that only the left eye (OS) received study medication in the second period. Both eyes of patient #128-724 were to have been treated with PA in the second period as was the case for the first period (LE), however only the left eye (OS) received study medication in the second period. Similarly, patient #128-725 received PA in both eyes in the first period and was supposed to be treated with LE in both eyes of the second period, but only the right eye (OD) was treated.
8. Patient #128-723 was considered to have completed period 1 of the study according to the investigator. Treatment, however, was discontinued after 26 days due to an unacceptable increase in IOP.

Patients #132-742 and #132-743 were considered by the investigator to have completed period 1 of the study. However, the last documented dose of study medication was on day 25 and 28, respectively. It will be assumed that treatment continued as planned to day 41 and 42, respectively.

Patient #128-726 was considered by the investigator to have completed period 2 of the study; however, the last documented dose was taken on day 28. There were no visits after day 28 until the final visit on day 64 where a notation was made that "IOP returned to normal range". It will be assumed that treatment was discontinued on day 28 due to an unacceptable increase in IOP.

Patient #132-743 was considered by the investigator to have been discontinued from Period 2 due to a missed visit. In the opinion of the sponsor this patient successfully completed Period 2. The fact that the Day 42 Visit was 10 days late during which time treatment with the study medication continued did not constitute a reason for assigning an incomplete exit status.

9. The exit form of the casebook indicated that unscheduled visits occurred for patient #132-744; however, no unscheduled visit data were available.

Results:

Nineteen patients were treated in Period 1. The mean baseline pressure in the eyes evaluated for efficacy was 17.0 mmHg in the LE group and 18.1 mmHg in the PA group (t-test for independent groups with equal variance, $T=-1.02$, d.f.=17, $p=0.322$). The baseline IOP of 4 patients met the criteria for an Intermediate response classification (Becker). Two of these were in the LE group, #132-741 and 134-681; two were in the PA group, #130-662 and #132-742.

All 10 patients administered LE completed 6 weeks of treatment. Five of 9 patients administered PA completed 6 weeks of treatment. Treatment was discontinued prematurely on 4 PA patients because of an elevation in IOP judged by the investigator to be clinically significant. The IOP of three of these patients, #113-702, 128-721, and 128-723, did not exceed the criteria IOP elevation specified in the protocol for discontinuing study medication; while, patient #130-662's IOP did exceed the limits set by the protocol.

The IOP of 3 patients was elevated above the limit allowed by the protocol (IOP > 31 mmHg or change from baseline IOP > 15 mmHg). In only one of these patients, #130-662, was treatment prematurely discontinued due to the rise in IOP. The IOP of patient #112-601 (LE) was elevated to 33 mmHg representing an increase from baseline of 17.5 mmHg on the final day (41) of treatment. He was treated with Betoptic (betaxolol hydrochloride) and Timoptic (timolol maleate), and the pressure returned to normal. The IOP of patients #130-662 and #134-682, both in the PA group, were at 40 mmHg and 32 mmHg on day 28 and 42, respectively. These pressures were 20 and 14.5 mmHg above baseline, respectively. No adjunctive therapy was given.

Patient #113-702 (PA), whose right eye only was assigned to treatment, suffered an increase in IOP in both eyes. Although the IOP was not recorded, study medication was stopped on day 35; and Betagan (levobunolol hydrochloride) was prescribed to control the pressure. On day 42 the pressures were 34 mmHg, OU. Continued medical intervention was successful on only the right eye, and on day 48 argon laser trabeculoplasty was performed on the left eye.

The differential response in IOP to LE and PA was assessed by survival analysis on the time to first response. Two response end-points were defined: (1) a change from baseline IOP of ≥ 6 mmHg (Table 9) and (2) an observed IOP ≥ 20 mmHg. Patients failing to respond either by the day of their Day 42 Follow-up Visit or the day on which their IOP was last measured while on study medication were treated as right censored observations.

Based upon the day of the visit on which the IOP was found to have increased by 6 or more mmHg above baseline, the effect of treatment was significant (log-rank statistic, $p=0.013$; Wilcoxon, $p=0.015$). PA treatment was associated with earlier response times and a larger fraction of the total responding in comparison to the LE treatment. The mean time to response for the 7 out of 9 (78%) responders in the PA group was 27.4 vs 38.3 days for the 2 out of 10 responders in the LE group. One non-responding patient of the LE group, #134-681 was right censored at 36 days while the remaining non-responding LE patients were censored in the range of 40-46 days. The 2 PA non-responders were right censored at 41 and 43 days.

Based upon the visit day on which the IOP was ≥ 20 mmHg the effect of treatment determined by survival analysis was marginally significant (log-rank statistic, $p=0.083$; Wilcoxon, $p=0.050$). As before, PA in comparison to LE treatment was associated with earlier response times (mean: 17.3 vs 22.5 days) and a larger fraction of the total responding (89% vs 60%). Survival estimates are plotted in Figure 4.

Reviewer's Comments: *This study was significantly flawed in its execution. No definitive conclusion can be obtained from the study.*

10 Overview of Safety

Ophthalmic steroids are known to cause:

1. Elevations in intraocular pressure (IOP) after repeated use (usually 10 days or more);
2. Cataract development (usually non-dose dependent posterior subcapsular cataracts);
3. Promotion of corneal and scleral thinning in corneal/scleral diseases which cause thinning;
4. Promotion of secondary infections of the cornea.

With the exception of elevations in IOP, the frequency of these conditions is relative low and would not necessarily be expected to be observed in the limited number of patients studied in this application.

Benzalkonium chloride is known to cause superficial punctate keratitis. The extent to which benzalkonium chloride is absorbed into contact lenses will need to be evaluated to adequately address the risks associated with concurrent use of this product and contact lenses. The GPC studies were performed in association with removing contact lenses for the first 48-72 hours and then re-inserting contact lenses, 10-15 minutes after dosing each day. The vast majority of patients wore daily-wear contact lenses.

There have been a number of misclassification/miscodings made in the reported studies. It is therefore not possible to establish exact percentages of particular adverse experiences.

In spite of the theoretical reasons for a decreased rate of IOP elevations, a significant number of IOP elevations were observed.

No unexpected adverse experiences were observed.

The standard steroid class warnings, precautions and adverse reactions appear warranted.

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- 11 Labeling Review *Reviewer recommended additions are identified by shading. Reviewer recommended deletions are identified by single-strikeout lines.*

LOTEMAX®
(Loteprednol Etabonate suspension)
Sterile ophthalmic Suspension

Loteprednol etabonate sterile suspension is a topical anti-inflammatory for ophthalmic use. The active ingredient is a white powder with an empirical formula of $C_{24}H_{31}O_7Cl$ and a molecular weight of 466.7. Its chemical name is: chloromethyl-17 α -[(ethoxycarbonyl-oxy)-11 β -hydroxy-3-oxoandrosta-1,4-diene-17-carboxylate

The chemical structure of loteprednol etabonate is presented below.

[structure]

Each mL contains: Active: Loteprednol etabonate 5 mg (0.5%). Preservative: Benzalkonium chloride 0.01%. Inactive: Povidone (C-30), edetate disodium, glycerine, tyloxapol, hydrochloride acid and/or sodium hydroxide (to adjust pH) and purified water.

Clinical Pharmacology:

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, capillary dilation, 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.

Results from a bioavailability study established that plasma levels of loteprednol etabonate, following the ocular administration of one drop in each eye of LOTEMAX® eight times daily for 2 days or 4 times daily for 41 days were below the limit of quantitation (1 ng/mL) and detection (500 pg/mL) at all sampling times.

This study suggests that limited, if any, systemic absorption occurs with LOTEMAX® Ophthalmic Suspension.

Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism. Following oral administration of radiolabelled loteprednol etabonate to rats, blood levels of carboxylic metabolites were consistently higher than unchanged drug.

Indications and Usage

LOTEMAX® Ophthalmic Suspension is indicated for use in the treatment of giant papillary conjunctivitis.

Contraindications

LOTEMAX® Ophthalmic Suspension 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. LOTEMAX 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.

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.

If this product is used for 10 days or longer, intraocular pressure should be routinely monitored. Steroids should be used with caution in the presence of glaucoma.

The use of steroids after cataract surgery may delay healing and increase the incidence of filtering blebs.

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: 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. The possibility of fungal infections of the cornea should be considered after prolonged steroid dosing. Fungal cultures should be taken when appropriate.

If this product is used for 10 days or longer, intraocular pressure should be monitored (SEE WARNINGS).

Information for Patients: Do not touch dropper tip to any surface, as this may contaminate the suspension. **If inflammation or pain become aggravated, the patient should be advised to consult a physician.**

Carcinogenesis, mutagenesis, impairment of fertility: No studies have been conducted in animals or in humans to evaluate the possibility of these effects with loteprednol etabonate.

Pregnancy: **Teratogenic effects: Pregnancy Category C.** Loteprednol etabonate has been shown to be teratogenic in rabbits when administered at high multiples of the human ocular dose.

Loteprednol etabonate was administered orally to rabbits in doses of up to > 30 times the human topical dose (3 mg/Kg/day) on days 6 to 18 of gestation.

Fetal abnormalities included meningocele, abnormal left common carotid artery and limb flexures. There are no adequate and well controlled studies of loteprednol etabonate in pregnant women. Loteprednol etabonate should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Nursing Mothers: It is not known whether topical 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.** Because of the potential for serious adverse reactions in nursing infants from loteprednol etabonate a decision should be made whether to discontinue nursing or to discontinue the drug.

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 in clinical studies of Lotemax 0.5% Ophthalmic Suspension included foreign body sensation, itching, injection, abnormal vision/blurring, epiphora, discharge, burning on instillation, and photophobia.

Other ocular adverse reactions occurring in less than 5% of patients include chemosis, discomfort, erythema, keratoconjunctivitis, conjunctivitis, corneal abnormalities, dry eyes and eye pain.

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

Dosage and Administration

One to two drops instilled into the conjunctival sac(s) four times daily for up to six weeks.

Contact lenses should be discontinued for at least the first 48 hours of treatment with LOTEMAX. After the first 48 hours, patients should wait at least 10 minutes after dosing LOTEMAX to re-insert contact lenses. If no improvement after two weeks, consult physician. Care should be taken not to discontinue therapy prematurely.

How Supplied

5.05 mL in Plastic Drop-Tainer® dispenser.

STORAGE: Store upright between 4° and 30°C (40° and 86°F).
Shake well before using.

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

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12 Conclusions

The submitted studies in NDA 20-583 demonstrate safety and efficacy for the treatment of giant papillary conjunctivitis.

13 Recommendations

1. Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 20-583 is recommended for approval for the treatment of giant papillary conjunctivitis. Approval for the steroid class indication is not recommended.
2. The applicant should submit a revised classification/coding of the adverse experiences.
3. The applicant should determine the extent to which benzalkonium chloride and loteprednol are absorbed in soft contact lenses.
4. The applicant should submit revised labeling consistent with the recommendations in this review.
5. The pH range should be made tighter.

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

cc: HFD-540
HFD-340
HFD-540/CSO/Chapman
HFD-540/CHEM/Tso
HFD-160/CHEM/Gilman
HFD-160/MICRO/Cooney
HFD-540/PHARM/Shriver
HFD-540/MO/Chambers

11/20/95

3 Material Reviewed

NDA 20-841 Studies by reference see Medical Officer's Review

NDA 20-583 2.1, 2.14, See also Medical Officer's Review (MOR #1)

4 Chemistry/Manufacturing Controls - see Chemistry Review

Raw Material	Quantity mg/mL	% label excess	Range
Loteprednol etabonate	5		
Povidone			
Benzalkonium Chloride,			
Edetate disodium			
Glycerin			
Tyloxapol			
Purified water	QS to 1 mL		
Sodium Hydroxide	Adjust pH		
Hydrochloric acid	Adjust pH		

Additional Specifications:

pH

Osmolality

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.

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

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

7 **Description of Clinical Data Sources**

Review Number	Protocol	Indication	Location	Design	Treatment Arms	Number in each arm	Age Range	% (n/N) B/W/O	Duration of treatment
10	126	Uveitis	US	Parallel Double masked	Loteprednol Vehicle	109 110	17-79	(25/75) 5/89/6	42 days

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NDA 20-583 Lotemax (loteprednol etabonate ophthalmic suspension)

8 Clinical Studies

8.3 Indication # 3 Acute Anterior Uveitis
 8.3.2 Reviewer's Trial # 10 Sponsor's protocol # 126

Title: Comparison of the Safety and Efficacy of Loteprednol Etabonate and Prednisolone Acetate in Acute Anterior Uveitis

Objective:

To evaluate the anti-inflammatory effectiveness of loteprednol etabonate in the treatment of acute anterior uveitis (AAU).

Study Design:

A randomized, double-masked, active-controlled, parallel group, multi-center (19) comparison study.

Dosing Schedule:

All subjects received either loteprednol etabonate 0.5% ophthalmic suspension (LE), or prednisolone acetate 1% (PA), unilaterally, for 28 days. The dosing regimen was: Days 0 to 7, q1h, up to 16/day; Days 8 to 14, q2h, up to 8/day; Days 15 to 21, qid; Days 22 to 25, bid; and Days 26 to 28, qd (morning).

Study Schedule

	Visit #1 (Day 0)	Visit #2 (36-72 hrs)	Visit #3,4&5 (Days 7,14&21)	Visit #6 (Day 28)	Visit #7 (Day 31)
Informed Consent	x				
Inclusion/Exclusion	x				
Demographics, History	x				
HLA-B27 Test	x				
Pregnancy Test	x			x	
Visual Acuity	x	x	x	x	x
Ocular Symptoms	x	x	x	x	x
Slit-Lamp Biomicroscopy	x	x	x	x	x
Intraocular Pressure	x	x	x	x	x
Funduscopy Examination	x	x		x	
Issue Medication	x	x	x		
Recover Medication				x	
Exit Form				x	
Dismiss Patient					x

NDA 20-583 Lotemax (loteprednol etabonate ophthalmic suspension)

Inclusion Criteria:

To be eligible for participation in the study, patients had to meet all of the following criteria before dosing:

- Age 18-75 years.
- Clinical diagnosis of acute anterior uveitis with the following signs and symptoms
 - i. an active anterior chamber cell reaction of at least 1+ and no presence of hypopyon.
 - ii. presence of at least 1+ ocular pain
 - iii. presence of at least 1+ flare
- If the patient had previous episodes of acute anterior uveitis, the most recent attack should have been greater than six weeks prior to enrollment.
- Willing to comply with the protocol instructions.
- Has read (or has had read to), understood, and signed an Informed Consent.
- Females of childbearing potential who are using adequate birth control must test negative to a blood or urine pregnancy test.

Exclusion Criteria:

Patients with any of the following conditions at the Enrollment Examination were to be excluded from the study

- Pregnant or lactating female.
- Female of childbearing potential who is not properly using an adequate birth control method.
- History of allergy or sensitivity to an ophthalmic medication, corticosteroid, LE, or to any components (including the preservative) of the current study medications.
- Any abnormality preventing reliable tonometry in either eye.
- Ocular hypertension with intraocular pressure greater than or equal to 25 mm Hg in either eye.
- Uncontrolled glaucoma of any kind in either eye or cup/disc ratio greater than 0.7.
- Presence of hyphema.
- Presumptive diagnosis, known history, or clearly overt symptoms of acute anterior uveitis secondary to a local or systemic infectious disease (e.g., tuberculosis, syphilis, herpes, etc.)
- History of anterior uveitis secondary to systemic inflammatory disease that necessitates an unstable dosing regimen of a systemic therapy (e.g. systemic lupus erythematosus, Wegeners' granulomatosis, etc.). Dosing regimen was considered unstable if there had been changes in dose or frequency within the past month or if a change in dose or frequency was anticipated during the course of the study.
- Concomitant posterior uveitis, pars planitis, choroiditis or significant macular edema.
- Unstable dosing regimen of any systemic or topical medication that could effect the inflammatory response (e.g., corticosteroids, immunosuppressive medications, non-steroidal anti-inflammatory medications, etc.). Dosing regimen was considered unstable if a change in dose or frequency occurred in the past month or, was anticipated during the course of the study.
- History of severe/serious ocular pathology or other medical condition that could result in the patient's ability to safely complete the study.
- Participation by the patient in an Investigational study under any other IND within the past 30 days.
- Previous treatment with masked medication on this study.
- Unlikely to comply with the protocol instructions for any reason (confusion, infirmity, drug or alcohol abuse).

Efficacy Criteria

Efficacy measures were the signs and symptoms most often associated with uveitis, as well as additional signs and symptoms sometimes seen in this condition. The rating scale used for the primary and secondary measures is shown below:

Cells: Determined using a slit beam at 1mm height by 1 mm width with maximum luminance of the Haag-Streit (or equivalent) slit lamp. Pigment cells and red blood cells were to be ignored.

0	Less than or equal to 5 cells
1.0	6 to 10 cells
2.0	11 to 20 cells
3.0	21 to 40 cells
4.0	greater than 40 cells
5.0	Hypopyon

Flare:

0	None to trace
1	Mild Clearly noticeable, visible
2	Moderate Without plastic aqueous
3	Marked With plastic aqueous
4	Severe With fibrin deposits and/or clots

Pain:

0	None
1	Mild
2	Moderate
3	Severe

Photophobia:

0	None
1	Mild
2	Moderate
3	Severe

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<u>Investigators:</u>	Number enrolled	
	LE	PA
Delmar Caldwell, MD	New Orleans, LA #216	3 4
G. Richard Cohen, MD	Boca Raton, FL #187	3 4
Janet Davis, MD	Miami, FL #188	3 2
L. Raymond DeBarge, MD	Fort Oglethorpe, GA #183	1 3
John Foley, MD	Exmore, VA #219	2 2
Stephen Foster, M.D.	Boston, MA #150	12 11
Kenneth Fox, M.D.	Fredericksburg, VA #151	3 4
Mitchell Friedlaender, MD	La Jolla, CA #124	6 6
Adam Kaufman, MD	Cincinnati, OH #190	6 6
Kenneth Olander, MD, PhD	Milwaukee, WI #184	4 4
Charles Ostrov, MD	Minneapolis, MN #189	2 4
James Rosenbaum, M.D.	Portland, OR #164	2 1
Kenneth Sall, MD	Bellflower, CA #218	3 2
John Sheppard, MD	Norfolk, VA #215	6 6
Donald Stewart, III, MD	Charlotte, NC #182	10 11
William Stewart, MD	Charleston, SC #109	3 3
Joseph Tauber, M.D.	Kansas City, MO #168	7 8
Stefan Trocme, M.D.	Galveston, TX #169	3 4
Paul Zimmerman, MD	Salt Lake City, UT #185	5 6
Total		84 91

List of patients not completing study

TERMINATED: ADVERSE EVENT:

216:6223 LE	72/MALE /BLACK	3.0	7	CME AND DECREASED VISUAL ACUITY
150:6172 LE	43/FEMALE/CAUC	5.0	22	OCULAR SYMPTOMS. BLURRED VISION. DRYNESS. BURNING
150:6083 PA	30/FEMALE/ASIAN	2.0	3	PT DEVELOPED INTERSTITIAL KERATITIS OD WHICH MAY BE SECONDARY TO PREVIOUS HX OF TB OR TO HSV OR SYPHILIS. LAST DOSE UNK.
185:6071 PA	68/FEMALE/CAUC	3.0	7	INCREASE IN ARMD

LOST TO F/U

150:6170 LE	38/MALE/CAUC	1.0	0
215:6197 LE	37/FEMALE/BLACK	1.0	0
215:6207 LE	26/FEMALE/BLACK	3.0	6
151:6016 LE	32/MALE /CAUC	3.0	7
185:6075 LE	24/FEMALE/CAUC	3.0	7
215:6196 LE	34/MALE /BLACK	4.1	18
184:6064 PA	28/FEMALE/BLACK	1.0	0
150:6167 PA	31/MALE /CAUC	4.0	13
185:6074 PA	40/MALE /CAUC	5.0	21

DISCONTINUATION (ADMINISTRATIVE):

187:6095 LE	84/MALE /CAUC	1.0	0	PT HAD DEATH IN FAMILY. HAD TO LEAVE TOWN
185:6080 LE	35/MALE /CAUC	2.0	2	P.I. FELT PT WAS NO COMPLIANT WITH GTTS
150:6168 LE	21/FEMALE/CAUC	2.0	3	PT WAS TAKING CON MEDS BELIEVED TO BE FORBIDDEN BY PROTOCOL. PHARMOS CONFIRMED. CHOICE TO D/C PT. ERROR-NOT FORBIDDEN.
150:6164 LE	40/MALE/CAUC	3.0	8	PT ON CONCURRENT THERAPY REQUIRING SCOPOLAMINE & NAPROSYN. (NSAID) - MANDATORY. DISCONTINUATION PER PROTOCOL.
150:6179 LE	39/MALE/CAUC	3.1	9	INVESTIGATOR FELT PT SHOULD BE PUT BACK ON NSAIDS. ALTHOUGH PT BASELINE CONDITION OF BACK/JOINT PAIN DID NOT WORSEN.
151:6014 LE	31/FEMALE/CAUC	5.0	25	PATIENT MOVING OUT OF TOWN
182:6188 PA	40/MALE/BLACK	2.0	6	PATIENT REQUESTED TO BE DISCONTINUED FROM THE STUDY
190:6140 PA	40/FEMALE/BLACK	1.0	6	PT'S EYE FELT BETTER AND SHE REFUSED TO RETURN FOR FOLLOW-UP DATE/TIME OF LAST DOSE NOT KNOWN STOPPED APPROX 6/11/96
215:6205 PA	59/FEMALE/CAUC	3.0	7	PT NOT ELIGIBLE TO BE ENROLLED UNSTABLE DOSING OF STEROID DROPS/NOT RESOLVED TO 0 FOR 6WKS

LACK OF EFFICACY

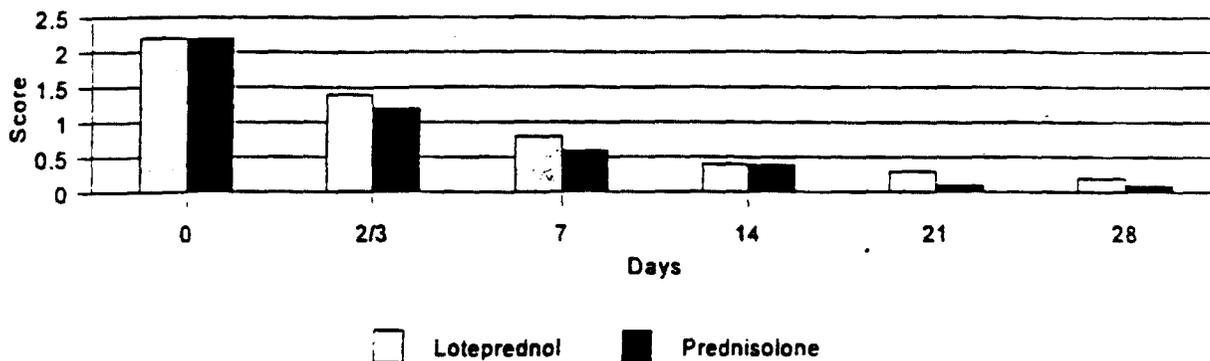
185:6077 LE	25/FEMALE/ASIAN	2.0	2
185:6241 LE	54/FEMALE/HISP	2.0	2
109:6004 LE	39/MALE /BLACK	2.0	3
164:6151 LE	54/FEMALE/OTHER	2.0	3
182:6183 LE	43/MALE /CAUC	3.0	6
182:6048 LE	27/MALE /CAUC	3.0	7
183:6052 LE	33/FEMALE/CAUC)	3.1	10
124:6146 LE	37/MALE /CAUC 4.0	16	
182:6181 LE	26/MALE /BLACK	5.0	21
150:6175 PA	52/FEMALE/OTHER	1.1	2
124:6234 PA	72/MALE /CAUC	2.0	3
185:6079 PA	25/MALE /CAUC	2.1	4
150:6171 PA	27/MALE /ASIAN	2.1	5
168:6256 PA	18/FEMALE/BLACK	3.1	9
185:6073 PA	46/MALE /CAUC	3.0	9
168:6265 PA	39/FEMALE/BLACK	4.0	14

APPEARS THIS WAY
ON ORIGINAL

		LOTEPREDNOL	PREDNISOLONE	
AGE (yrs)				
	N	84	91	
	MEAN	41	42	p = .97
	SE	1.6	1.7	
	MIN	19	18	
	MAX	84	88	
GENDER				
MALE	N	44 (52%)	50 (55%)	p = .88
FEMALE	N	40 (48%)	41 (45%)	
RACE				
CAUCASIAN	N	53 (63%)	54 (59%)	p = .37
NON-CAUCASIAN	N	31 (37%)	37 (41%)	
IRIS PIGMENTATION				
LIGHT	N	36 (43%)	29 (32%)	p = .11
DARK	N	48 (57%)	62 (68%)	
HLA -B27 RESPONSE				
POSITIVE	N	5 (6%)	10 (11%)	p = .08
NEGATIVE	N	79 (94%)	81 (89%)	
TYPE OF PATHOLOGY				
NONGRANULOMATOUS		80 (95%)	86 (94%)	p = .83
GRANULOMATOUS		4 (5%)	5 (6%)	
BASELINE CELL				
< = 2	N	57 (68%)	61 (67%)	p = .89
> 2	N	27 (32%)	30 (33%)	

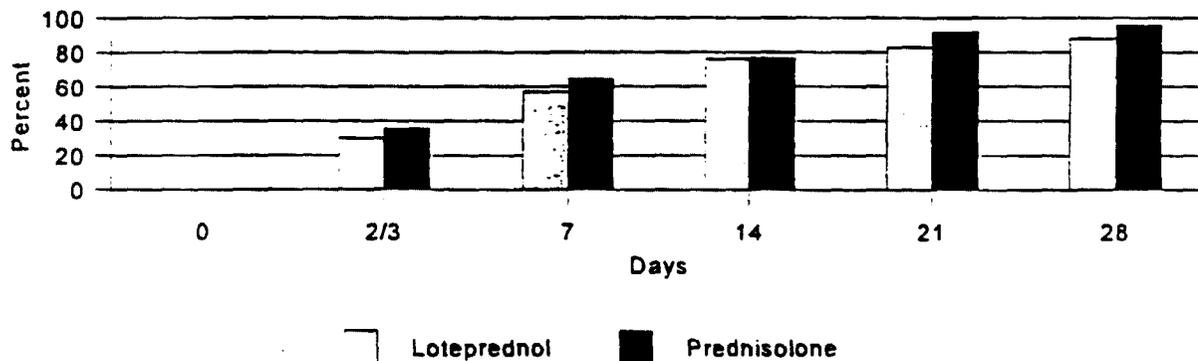
Reviewer's Comments: *The category "NON-CAUCASIAN" should be more specifically identified*

Anterior Chamber Cells



Loteprednol	2.2	1.4	0.8	0.4	0.3	0.2
Prednisolone	2.2	1.2	0.6	0.4	0.1	0.1

Resolution of Cells



Loteprednol	0	30	57	76	83	88
Prednisolone	0	36	65	77	92	96

Reviewer's Comments: *Prednisolone acetate was superior to loteprednol.*

Anterior Chamber Cells -

Percent of patients resolved at each visit

Visit	Treatment Group	N at risk	N	%	Treatment difference	95% C.I.	p value
2	LE	77	23	30%			
(Day 2-3)	PA	83	30	36%	-6%	(-21%,8%)	0.381
3	LE	74	42	57%			
(Day 7)	PA	80	52	65%	-8%	(-24%,7%)	0.211
4	LE	59	45	76%			
(Day 14)	PA	75	58	77%	-1%	(-15%,13%)	0.952
5	LE	59	49	83%			
(Day 21)	PA	75	69	92%	-9%	(-20%,2%)	0.110
6	LE	58	51	88%			
(Day 28)	PA	74	71	96%	-8%	(-17%,1%)	0.115
Final Visit (LOCF)	LE	81	58	72%			
	PA	89	77	87%	-15%	(-27%,-3%)	0.015

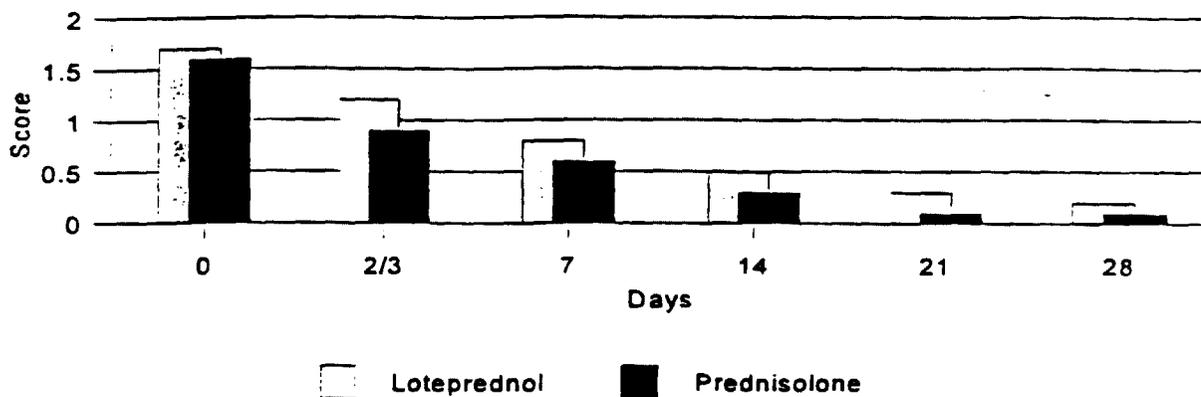
Mean

	Day	0	2-3	7	14	21	28	Final
LE	N	81	77	74	59	59	58	81
	MEAN	2.2	1.4	0.8	0.4	0.3	0.2	0.7
	MIN							
	MAX							
PA	N	89	83	80	75	75	74	89
	MEAN	2.2	1.2	0.6	0.4	0.1	0.1	0.3
	MIN							
	MAX							

Distribution of Change from Baseline

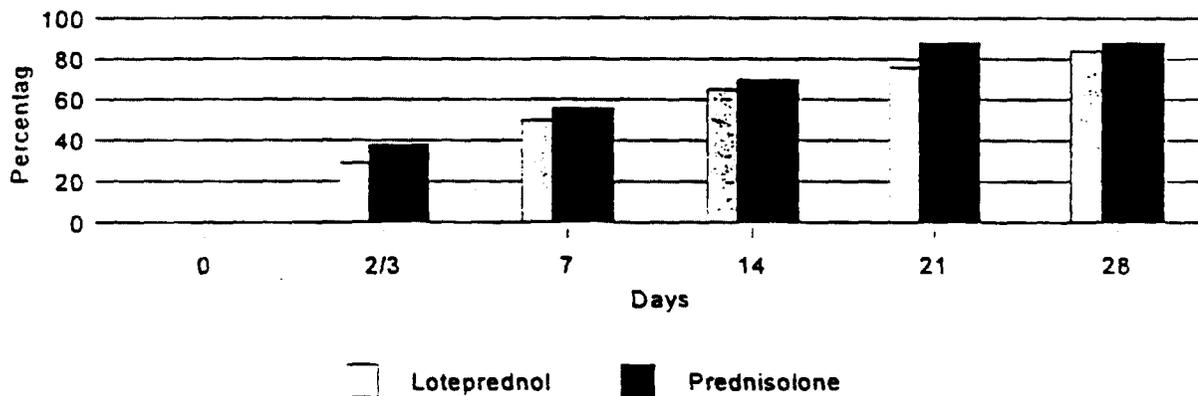
LE	>+2							
	+2							
	+1							
	0		20	11	1	2	3	11
	-1							
	-2							
	<-2							
PA	>+2							
	+2							
	+1							
	0		22	7	1	0	1	6
	-1							
	-2							
	<-2							

Anterior Chamber Flare



Loteprednol	1.7	1.2	0.8	0.5	0.3	0.2
Prednisolone	1.6	0.9	0.6	0.3	0.1	0.1

Resolution of Flare



Loteprednol	0	29	50	65	76	84
Prednisolone	0	38	56	70	88	88

Reviewer's Comments: *Prednisolone acetate was superior to loteprednol.*

Anterior chamber flare
Percent of patients resolved at each visit

Visit	Treatment Group	N at risk	N	%	Treatment difference	95% C.I.	p value
2	LE	75	22	29%			
(Day 2-3)	PA	82	31	38%	- 9%	(-23%.6%)	0.151
3	LE	72	36	50%			
(Day 7)	PA	79	44	56%	- 6%	(-22%.10%)	0.258
4	LE	57	37	65%			
(Day 14)	PA	74	52	70%	-5%	(-22%.11%)	0.497
5	LE	58	44	76%			
(Day 21)	PA	74	65	88%	- 8%	(-25%.1%)	0.103
6	LE	56	47	84%			
(Day 28)	PA	73	64	88%	- 4%	(-16%.8%)	0.592
Final Visit (LOCF)	LE	79	52	66%			
	PA	88	72	82%	-16%	(-29%. 3%)	0.017

Mean

	Day	0	2-3	7	14	21	28	Final
	N	79	75	72	57	58	56	79
LE	MEAN	1.7	1.2	0.8	0.5	0.3	0.2	0.6
	MIN							
	MAX							
PA	N	88	82	79	74	74	73	88
	MEAN	1.6	0.9	0.6	0.3	0.1	0.1	0.3
	MIN							
	MAX							

Distribution of
Change from Baseline

LE	>+2							
	+2							
	+1							
	0		31	16	7	6	2	9
	-1							
	-2							
	<-2							
PA	>+2							
	+2							
	+1							
	0		26	15	6	3	2	4
	-1							
	-2							
	<-2							

Summary of IOP Changes -

Mean

	<u>Day</u>	<u>0</u>	<u>2-3</u>	<u>7</u>	<u>14</u>	<u>21</u>	<u>28</u>
	N	80	75	74	62	60	59
LE	MEAN	12.9	12.9	13.5	13.7	13.6	13.9
	MIN						
	MAX						
PA	N	89	84	79	76	75	75
	MEAN	14.1	15.5	15.4	15.2	15.9	15.9
	MIN						
	MAX						

Reviewer's Comments: *The IOP was higher in the prednisolone group than the loteprednol group, however, this could be due to more effective treatment of uveitis since uveitis is known to decrease IOP.*

**APPEARS THIS WAY
ON ORIGINAL**

Events elicited by use of checklist:

	Loteprednol Etabonate (N=84)		Prednisolone acetate (N=91)	
Events on checklist				
SPECIAL SENSES				
DRY EYES (EYE/GEN)	7	8%	7	8%
ITCHING, EYE (EYE/GEN)	7	8%	6	7%
KERATIC PRECIPITATE (EYE/COP)	6	7%	1	1%
DISCHARGE, EYE (EYE/GEN)	5	6%	0	0%
DISCOMFORT, EYE (EYE/GEN)	5	6%	5	5%
CELLS, ANTERIOR CHAMBER (EYE/AH)	4	5%	2	2%
PHOTOPHOBIA (EYE/VIS)	4	5%	3	3%
EPIPHORA (EYE/APP)	3	4%	2	2%
FLARE, ANTERIOR CHAMBER (EYE/AH)	3	4%	2	2%
CORNEAL ABNORMALITY (EYE/COP)	2	2%	1	1%
INJECTION (EYE/CON)	2	2%	1	1%
EYE PAIN (EYE/GEN)	1	1%	3	3%
CILIARY FLUSH (EYE/UVE)	0	0%	1	1%
Events not on checklist (>1%)				
SPECIAL SENSES				
ABNORMAL VISION (EYE/VIS)	14	17%	13	14%
BURN/STING, ON INSTILL	2	2%	1	1%
BURN/STING, NOT ON INSTILL	2	2%	0	0%
INTRAOCULAR PRESSURE, INCREASED	2	2%	7	8%
UVEITIS (EYE/UVE)	2	2%	1	1%
VITREOUS DISORDER (EYE/VH)	2	2%	0	0%
BODY AS A WHOLE (>1%)				
ANY EVENT	8	10%	6	7%
HEADACHE (HEAD)	3	4%	5	5%
ACCIDENTAL INJURY (GEN)	2	2%	0	0%
DIGESTIVE SYSTEM				
DIARRHEA (EC)	2	2%	0	0%
NERVOUS SYSTEM				
DRY MOUTH (ANS/PSYM/L)	2	2%	0	0%

APPEARS THIS WAY
ON ORIGINAL

Study #4 Conclusions:

1. Prednisolone acetate has demonstrated superiority over loteprednol in the treatment of anterior uveitis.
2. Both products have an acceptable safety profile.
3. There were no significant differences with respect to age, race or eye color (data not shown).

9. Summary of Efficacy:

This study was consistent with the previously submitted study. Each study demonstrates the superiority of prednisolone acetate over loteprednol.

10. Summary of Safety:

No additional safety issues have been identified.

APPEARS THIS WAY
ON ORIGINAL

11 Labeling Review -

Reviewer recommended additions are identified by shading. Reviewer recommended deletions are identified by ~~single-strikeout lines~~. This review incorporates requested indications from NDA 20-583 as well as those from NDA 20-841.

Two different package inserts have been proposed. One utilizes the class labeling for steroids together with a clear notation that the product is not as effective as prednisolone acetate. The second insert does not include the uveitis indication and therefore does not include the comparative statements to prednisolone.

**APPEARS THIS WAY
ON ORIGINAL**

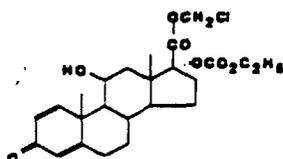
LOTEMAX™

loteprednol etabonate
ophthalmic suspension, 0.5%

STERILE OPHTHALMIC SUSPENSION**DESCRIPTION:**

LOTEMAX™ (loteprednol etabonate ophthalmic suspension), is 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:



$C_{24}H_{31}ClO_7$

Mol. Wt. 466.96

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

Each mL contains: ACTIVE: Loteprednol Etabonate 5 mg (0.5%);
INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water, 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 ???.
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 and it is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Therefore, loteprednol etabonate is designed to exert

its effects and be hydrolyzed 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 unlimited, systemic absorption occurs with LOTEMAX Ophthalmic Suspension.

Clinical Studies:

Post-operative Inflammation:

In two placebo controlled clinical studies of patients following cataract surgery, LOTEMAX was more effective than its vehicle in clearing post-operative inflammation as measured by cell and flare counts during the first two weeks of therapy.

Uveitis:

In two controlled clinical studies of patients with uveitis, LOTEMAX was less effective than prednisolone acetate, 1% in clearing the inflammation as measured by cell and flare counts during the first four weeks of therapy.

Giant Papillary Conjunctivitis:

In two placebo controlled clinical studies, LOTEMAX was more effective than its vehicle in reducing the signs and symptoms of giant papillary conjunctivitis after 1 week of treatment and continuing for up to 6 weeks.

Seasonal Allergic Conjunctivitis:

In a placebo controlled clinical study, LOTEMAX was more effective than its vehicle in reducing the signs and symptoms of allergic conjunctivitis during peak periods of pollen exposure.

INDICATIONS AND USAGE:

LOTEMAX is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation.

LOTEMAX is less effective than prednisolone acetate ophthalmic suspension, 1% in the treatment of inflammation and should not be used in patients who require a more potent corticosteroid for their inflammatory condition.

LOTEMAX is also indicated for the treatment of post-operative inflammation following ocular surgery.

CONTRAINDICATIONS: -

LOTEMAX, as with other ophthalmic corticosteroids,

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. LOTE MAX 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. If this product is used for 10 days or longer, intraocular pressure should be routinely monitored. 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 (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: Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using LOTEMAX™.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Loteprednol etabonate was shown to be non-mutagenic in a series of *in vivo* and *in vitro* studies. Fertility was not affected in one study in rats using doses up to 40 times the human topical dose in males and 20 times the human topical dose in females. No studies have been conducted to evaluate the possibility of carcinogenicity with loteprednol etabonate.

Pregnancy: Pregnancy Category C. Loteprednol etabonate has been shown to be teratogenic in rabbits when administered orally on days 6 to 18 of gestation in doses of up to 30 times the human topical dose (3 mg/kg/day).

Fetal abnormalities included meningocele, abnormal left common carotid artery and limb flexures. There are no adequate and well controlled studies in pregnant women. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 which could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects.

Caution

should be exercised when LOTEMAX 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 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 1.7% (14/823) among patients receiving loteprednol etabonate, 6.3% among patients receiving 1% prednisolone acetate (5/79) and 0.5% among patients receiving placebo (3/583).

DOSAGE AND ADMINISTRATION:

SHAKE WELL BEFORE USING.

Steroid Responsive Disease Treatment: Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye(s) four times daily. During the initial treatment within the first week, the dosing may be increased, if necessary up to 1 drop every hour. Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after two days, the patient should be re-evaluated (See PRECAUTIONS).

Post-Operative Inflammation:

Apply one drop of LOTEMAX 0.5% Ophthalmic Suspension into the conjunctival sac of the affected eye(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

HOW SUPPLIED:

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

2.5 mL	(NDC 24208-299-25) - AB29904
5 mL	(NDC 24208-299-05) - AB29907
10 mL	(NDC 24208-299-10) - AB29909

15 mL (NDC 24208-299-15) - AB29911

DO NOT USE IF NECKBAND IMPRINTED WITH ??? IS NOT INTACT.

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

KEEP OUT OF REACH OF CHILDREN.

Caution: Federal law prohibits dispensing without prescription.

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

© Bausch & Lomb Pharmaceuticals, Inc.

XO50317 Rev. 3/97-7C

**APPEARS THIS WAY
ON ORIGINAL**

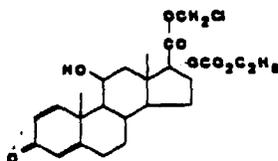
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Mol. Wt. 466.96

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Each mL contains: ACTIVE: Loteprednol Etabonate 5 mg (0.5%);
 INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water, 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 ???.
 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 and it is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a transformation to an inactive metabolite. Therefore, loteprednol etabonate is designed to exert

its effects and be hydrolyzed to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Clinical Pharmacology: 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 ~~no~~limited, systemic absorption occurs with LOTEMAX Ophthalmic Suspension.

Clinical Studies:

Post-operative Inflammation:

In two placebo controlled clinical studies of patients following cataract surgery, LOTEMAX was more effective than its vehicle in clearing post-operative inflammation as measured by cell and flare counts during the first two weeks of therapy.

Giant Papillary Conjunctivitis:

In two placebo controlled clinical studies, LOTEMAX was more effective than its vehicle in reducing the signs and symptoms of giant papillary conjunctivitis after 1 week of treatment and continuing for up to 6 weeks.

INDICATIONS AND USAGE:

LOTEMAX is indicated for the treatment of post-operative inflammation following ocular surgery and for the treatment of the signs and symptoms of giant papillary conjunctivitis.

CONTRAINDICATIONS:

LOTEMAX, 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. LOTEMAX 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. If this product is used for 10 days or longer, intraocular pressure should be routinely monitored. 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