PRODUCT MONOGRAPH

[Pr]LOTEMAX® GEL

(loteprednol etabonate ophthalmic gel 0.5 % w/w)

Professed Standard

Corticosteroid

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Gel, 0.5% w/w	Benzalkonium Chloride 0.003% w/w *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Lotemax® (loteprednol etabonate) Gel is a corticosteroid indicated for:

- treatment of post-operative inflammation and pain following cataract surgery

Geriatrics (> 65 years of age):
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Pediatrics (< 18 years of age):
Lotemax® Gel should not be used in pediatric patients. The safety and effectiveness of Lotemax® Gel have not been established in pediatric patients.

CONTRAINDICATIONS

- Patients with suspected or confirmed infection of the eye such as viral disease of the cornea and conjunctiva, including epithelial herpes, simplex keratitis (dendritic keratitis), vaccinia, and varicella. Patients with untreated ocular infection of the eye such as mycobacterial infection of the eye and fungal disease of ocular structures.
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container, or to other corticosteroids. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General
For ophthalmic use only.

Lotemax® Gel is indicated as a short-term treatment only (up to 14 days). The initial prescription and renewal of Lotemax® Gel should be made by a doctor only after appropriate ophthalmologic examination is performed. If signs and symptoms fail to improve after two days, the patient should be re-evaluated. If Lotemax® Gel is used for 10 days or longer, intraocular pressure should be closely monitored. See **WARNINGS and PRECAUTIONS – Ophthalmologic**.

Prolonged use of corticosteroids may result in cataract and/or glaucoma formation. Lotemax® Gel should not be used in the presence of glaucoma or elevated intraocular pressure, unless absolutely necessary and close ophthalmologic monitoring is undertaken. Extreme caution should be exercised, and duration of treatment should be kept as short as possible. See **WARNINGS and PRECAUTIONS – Ophthalmologic**.

Lotemax® Gel should not be used in cases of existing (suspected or confirmed) ocular viral, fungal, or mycobacterial infections. Lotemax® Gel may suppress the host response and thus increase the hazard of secondary ocular infections. The use of Lotemax® Gel in patients with a history of herpes simplex requires great caution and close monitoring. See **WARNINGS and PRECAUTIONS – Ophthalmologic**.

Lotemax® Gel has not been studied in pregnant or nursing women, but has been found to be teratogenic in animals. Lotemax® Gel should not be used in pregnant or nursing women unless the benefits to the mother clearly outweigh the risk to the embryo or fetus, or the nursing child. See **WARNINGS AND PRECAUTIONS – Special Populations**.

Carcinogenesis and Mutagenesis
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. **See TOXICOLOGY**.

Endocrine and Metabolism
Glucocorticoids, mostly when systemic exposure occurs, decrease the hypoglycemic activity of insulin and oral hypoglycemic, so that a change in dose of the antidiabetic drugs many be necessitated. In high doses, glucocorticoids also decrease the response to somatotropin. The usual doses of mineralocorticoids and large doses of some glucocorticoids cause hypokalemia and may exaggerate the hypokalemic effects of thiazides and high-ceiling diuretics. In combination with amphotericin-B, they also may cause hypokalemia. Glucocorticoids appear to enhance the ulcerogenic effects of non-steroidal anti-inflammatory drugs. They decrease the plasma levels of salicylates, and salicylism may occur on discontinuing steroids. Glucocorticoids may increase or decrease the effects of prothrombopenic anticoagulants. Estrogens, phenobarbital, phenytoin and rifampin increase the metabolic clearance of adrenal steroids and hence necessitate dose adjustments. However, given the very low systemic

exposure to loteprednol etabonate when using Lotemax® Gel as directed, these possible effects are not likely. **See ACTION and CLINICAL PHARMACOLOGY**.

Immune

Cortisol and the synthetic analogs of cortisol have the capacity to prevent or suppress the development of the local heat, redness, swelling, and tenderness by which inflammation is recognized. At the microscopic level, they inhibit not only the early phenomena of the inflammatory process (edema, fibrin deposition, capillary dilation, migration of leukocytes into the inflamed area, and phagocytic activity) but also the later manifestations, such as capillary proliferation, fibroblast proliferation, deposition of collagen, and, still later, cicatrisation.

Neurologic

Disturbances and suppression of the Hypothalamic-Pituitary-Adrenal (HPA) axis can occur with systemic exposure to corticosteroids. However, given the very low systemic exposure to loteprednol etabonate when using Lotemax® Gel as directed, these possible effects are not likely. **See ACTION and CLINICAL PHARMACOLOGY**.

Ophthalmologic

Lotemax® Gel should be used as a short-term treatment. If Lotemax® Gel is used for 10 days or longer, intraocular pressure should be closely monitored. The initial prescription and renewal of Lotemax® Gel should be made by a doctor only after appropriate ophthalmologic examination is performed 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.

Intraocular Pressure (IOP) Increase:

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Lotemax® Gel should not be used in the presence of glaucoma or elevated intraocular pressure, unless absolutely necessary and careful and close appropriate ophthalmologic monitoring (including intraocular pressure and lens clarity) is undertaken.

Cataracts:

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing:

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. If bleb formation occurs, decrease or discontinue corticosteroid therapy. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids.

Bacterial infections:

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Viral infections:
Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

Fungal infections:
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 culture should be taken when appropriate.

Contact Lens Wear:
Patients should not wear contact lenses during their course of therapy with Lotemax® Gel.

Topical ophthalmic use only:
Lotemax® Gel is not indicated for intraocular administration.

Sexual Function/Reproduction
The effect of Lotemax® Gel on sexual function and reproduction have not been studies in humans. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (approximately 400 and 200 times the Lotemax® Gel clinical dose) prior to and during mating, was clearly harmful to the rats, but did not impair their copulation performance and fertility (i.e., ability of female rats to become pregnant). However, these doses were highly toxic and had major and significant toxic effects on the pregnancies, and the survival and development of the off spring. Maternal toxicity, possible occurrence of abnormalities and growth retardation started at approximately 4 times the Lotemax® Gel clinical dose. **See WARNING and PRECAUTIONS – Special Populations – Pregnant Women**.

Special Populations

Pregnant Women:
Lotemax® Gel should not be used in pregnant women, unless the potential benefit to the mother clearly outweighs the risks to the embryo or foetus. Studies in pregnant women have not been conducted. However, studies in animals have shown major reproductive and developmental toxicity when administered orally at approximately40 times the Lotemax® Gel clinical dose. At lower doses (approximately 4 times the Lotemax® Gel clinical dose), maternal toxicity was demonstrated and, although there were no major teratogenic effects, growth retardation and a possible increase in the occurrence of some abnormalities were noted. **See TOXICOLOGY – Developmental and Reproductive Toxicity**.

Nursing Women:
Lotemax® Gel should not be used in lactating women, unless the potential benefit to the mother clearly outweighs the risks to the nursing infant/child. Studies in lactating women have not been conducted. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects.

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

Pediatrics (< 18 years of age):
Lotemax® Gel should not be used in pediatric patients. The safety and efficacy of Lotemax® Gel have not been established in pediatric patients

Geriatrics (> 65 years of age):
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Monitoring and Laboratory Tests
If Lotemax® Gel is used for 10 days or longer, intraocular pressure should be monitored. See **WARNINGS AND PRECAUTIONS – General.**

ADVERSE REACTIONS

Adverse Drug Reaction Overview
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.

In two clinical trials with Lotemax® Gel, 409 patients received Lotemax® Gel for 14 days and 404 patients received placebo following cataract surgery. The incidence of all events in the Lotemax® Gel group was similar or less than that of the placebo control group. Ocular events and non-ocular events were reported respectively in 17.4% and 5.1% of the Lotemax® Gel treated patients. The corresponding rates for the placebo treated patients are 25.2% and 3.5% respectively.

Adverse events related to Lotemax® Gel were generally mild to moderate, nonserious and did not interrupt continuation in the studies. The most frequent ocular events reported as related to therapy in the Lotemax® Gel group were eye pain, anterior chamber inflammation and lacrimation increased, all reported with a frequency of 0.7%(3/409). In the placebo treated patients, these rates were respectively 1.5%, 0.7% and 0%.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Two phase 3 studies were conducted to assess the safety and efficacy of Lotemax® Gel in the treatment of inflammation and pain following cataract surgery with intraocular lens (IOL) implantation. Both studies were randomized, double-masked, placebo controlled, multi-centre parallel group. Patients having routine uncomplicated cataract surgery with at least Grade 2 (6-15 cells) anterior chamber cells were enrolled and randomized in Study A (N=406) and Study B (N=407). Patients expected to require concurrent anti-inflammatory drugs or having elevated intraocular pressure ≥21mm Hg at screening or having any severe/serious ocular condition or unstable medical condition were excluded from the studies. During these studies, 409 patients were exposed to Lotemax® Gel.[1,2]

Incidence of Ocular Events in the phase 3 studies are outlined in the table below, many of these events may have been the consequence of the surgical procedure.

Table 1: Ocular TEAEs in ≥ 1% of Study Eyes, Either Treatment Group, Prior to Rescue Medication Use, Integrated Analyses - Safety Population

	LE Gel (N = 409)	**Vehicle (N = 404)**	**p-Value[1]**
Total Number of AEs	97	148	
Number of Subjects with at Least One AE	71 (17.4%)	102 (25.2%)	0.006
EYE DISORDERS	68 (16.6%)	94 (23.3%)	0.022
Anterior chamber inflammation	15 (3.7%)	24 (5.9%)	0.142
Eye pain	8 (2.0%)	18 (4.5%)	0.047
Photophobia	5 (1.2%)	12 (3.0%)	0.091
Foreign body sensation in eyes	8 (2.0%)	8 (2.0%)	>0.999
Iritis	4 (1.0%)	5 (1.2%)	0.751
Dry eye	3 (0.7%)	4 (1.0%)	0.724
Eye irritation	2 (0.5%)	5 (1.2%)	0.284
Myodesopsia	3 (0.7%)	4 (1.0%)	0.724
Vision blurred	2 (0.5%)	5 (1.2%)	0.284
Conjunctival hemorrhage	5 (1.2%)	1 (0.2%)	0.217
Lacrimation increased	6 (1.5%)	0 (0.0%)	0.031
Anterior chamber cells	1 (0.2%)	4 (1.0%)	0.215
INVESTIGATIONS			
Intraocular pressure increased[2]	4 (1.0%)	10 (2.5%)	0.113

[1] p-Value based on Fisher's Exact test.
[2] Includes also non-TEAEs (2 LE patients and 1 vehicle patient had IOP increased as TEAE, 11 patients had IOP increase reported just before treatment instillation and event ended the same day).
Note: A subject was counted at most once for a given preferred term (except for total number of AEs).

Occurrence of non-ocular adverse event was low. Headache was reported at a rate of 0.7% (3 patients) in both the Lotemax® Gel and placebo groups, nausea was reported at a rate of 0.7% in the Lotemax® Gel group and 0.5% in the placebo group.

A total of 9 treatment-emergent serious adverse events were reported for 7 patients (4 receiving Lotemax® Gel and 3 receiving placebo), all these events were considered to be unlikely related or unrelated to study drug. In the Lotemax® Gel group, each of the 4 patients experienced one

serious adverse event: moderate cystoid macula edema, severe diverticulitis, severe cholecystitis, and severe myocardial infarction. In the placebo group, 5 serious adverse events were reported for 3 patients: mild cystoid macula edema, severe bronchitis with severe exacerbated systolic congestive heart failure, moderate dehydration with moderate hypokalemia.

Intraocular Pressure
Elevated IOP is associated with the application of topical corticosteroids. IOP was closely monitored in the phase 3 studies.

In the phase 3 studies, IOP increases of 5 to 9 mm Hg were seen in 42 patients in the Lotemax® Gel group and in 25 patients in the placebo group (see table below). Three patients, 2 Lotemax® Gel and 1 placebo, had a change from baseline IOP ≥ 10 mm Hg with a maximum post-baseline IOP of 42 mmHg for a Lotemax® Gel-treated patient at Visit 6 and Visit 7 (Postoperative Day 15 and 18).

Table 2: Incidence of IOP increases from baseline (number of patients and percentages)

	Visit 4 Day 3 n (%)	**Visit 5 Day 8 n (%)**	**Visit 6 Day 15 n (%)**	**Visit 7 Day 18 n (%)**	**Any Visit n (%)**
Pivotal Study A	N = 403	N = 317	N = 261	N = 189	N = 403
≥10 mm Hg					
LE Gel	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)
Placebo	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	1 (0.5%)
5 to 9 mm Hg					
LE Gel	9 (4.5%)	11 (6.0%)	11 (6.7%)	8 (6.2%)	25 (12.4%)
Placebo	5 (2.5%)	3 (2.2%)	2 (2.1%)	3 (5.0%)	10 (5.0%)
Pivotal Study B	N = 406	N = 350	N = 296	N = 250	N = 406
≥10 mm Hg					
LE Gel	0 (0%)	0 (0%)	1 (0.5%)	1 (0.6%)	1 (0.5%)
Placebo	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
5 to 9 mm Hg					
LE Gel	4 (1.9%)	8 (4.0%)	10 (5.5%)	6 (3.6%)	17 (8.3%)
Placebo	6 (3.0%)	5 (3.3%)	8 (7.0%)	3 (3.5%)	15 (7.5%)

Loteprednol etabonate 0.5% has been reported to have less effect on IOP elevation when compared to prednisolone acetate 1.0% in one of the studies performed with loteprednol etabonate 0.5% suspension. This investigation was conducted in subjects known to respond to ocular corticosteroid administration with elevated IOP. Nineteen subjects with known IOP response to ocular corticosteroids were randomly assigned to receive either Lotemax® suspension (LE) 0.5% or prednisolone acetate 1.0% (PA; PredForte®, Allergan) QID for up to 42 days.[3]

The proportion of subjects in the PA group with a significant elevation in IOP (≥ 10 mm Hg) was 55% (5/9), much greater than that in the LE group (1/10, 10%). At the end of the exposure period, the mean IOP was approximately 20 mm Hg in the LE group and 27 mm Hg in the PA group.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Eye Disorders: dry eye, myodesopsia, corneal edema, punctate keratitis, posterior capsule

opacification

Abnormal Hematologic and Clinical Chemistry Findings
Not applicable.

Adverse Reactions reported in phase 3 controlled randomized studies with loteprednol etabonate suspension 0.5%
In seven clinical trials ranging from 14 to 42 days in length, 746 patients received loteprednol etabonate (LE) ophthalmic suspension 0.5% in topical ocular drops. Most events were less frequent or similar in frequency between the LE suspension and control groups. The ocular event reported more frequently in the LE suspension group compared to the placebo groups was increased intraocular pressure: 12.7% in patients receiving LE suspension, as compared to 6.1% in the placebo population.

Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate (LE) suspension (0.5%) in clinical studies included: abnormal vision/blurring, itching, IOP increase, epiphora, injection, eye discomfort, photophobia, eye discharge, foreign body sensation. Non-ocular adverse reactions occurred in less than 15% of patients taking loteprednol etabonate suspension (0.5%), included: headache, rhinitis, and pharyngitis.

Post-Market Adverse Drug Reactions
Since the launch of Lotemax® Gel in 2012 in the US, there has been no serious adverse drug reaction reported.

Since the launch of Lotemax® Ointment, more than 306,000 units have been shipped in the United States from April 15 2011 to July 2012. Overall, there has been no serious adverse drug reaction reported.

In more than a decade of post-marketing experience with loteprednol etabonate (LE) suspension products (0.5%, 0.2% and combination of 0.5% with tobramycin 0.3%), more than 38 million units have been shipped globally from April 1998 to July 2012. Overall, 37 cases with adverse events that qualified as serious were reported, 22 cases were unexpected and 15 cases were expected (visual field defect, IOP increase, corneal disorder, glaucoma, cataract, keratitis herpetic, corneal infection, corneal epithelium defect, ulcerative keratitis, corneal perforation, uveitis, ocular hypertension). The unexpected SAEs include severe corneal disorders, corneal decompensation, corneal scar, endophthalmitis, Toxic Anterior Segment Syndrome, retinal vein occlusion & macular oedema, anterior chamber inflammation, atrophy of globe & iris coloboma, visual acuity decreased, ocular toxicity & toxicity to various agents, chemical burns of eye, eye injury, & hypersensitivity, transplant rejection, staphylococcal infection, hypertension, , atrial fibrillation, atrioventricular block & bradycardia, blood glucose decreased, headache, sudden hearing loss, spontaneous abortion, throat tightness, paranoia, insomnia, suicide attempt/ideation, pneumothorax, and VIIth nerve paralysis.

DRUG INTERACTIONS

Overview

No specific interaction studies have been conducted. There are no known drug interactions.

Numerous concomitant medications were used during the Lotemax® Gel clinical studies as the majority of the population studied was above 65 years of age. The most frequent non-ocular drugs included those prescribed for the cardiovascular system: HMG CoA reductase inhibitors, platelet aggregation inhibitors, ACE inhibitors and beta blocking agents. Most ocular drugs were prescribed for the underlying condition (post cataract surgery) such as topical antibiotics or in a few cases, ocular hypotensive agents. None of the events reported were associated with a deleterious effect of the combination of study and non-study drugs, and no drug interactions were noted. Similarly, in the LE suspension and ointment studies, no deleterious drug interaction was reported.

Drug-drug, drug-food, drug-herb, and drug-laboratory interactions have not been studied.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Invert closed bottle and shake once to fill tip before instilling drops. No shaking is required to resuspend as the drug is distributed uniformly in the gel formulation and does not settle.

Apply one to two drops of Lotemax® Gel into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

Missed Dose

If a dose is missed, the patient should be instructed to take the next dose as scheduled then continue as before. Do not double doses.

Administration

Lotemax® Gel

Lotemax® Gel should be stored upright between 15°– 25°C (59° - 77°F).

Use only if imprinted neckband is intact.

Patients should be advised to invert the closed bottle and shake once to fill tip before instilling drops.

Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel.

Patients should be advised to wash hands prior to using Lotemax® Gel.

Patients should also be advised not to wear contact lenses during their course of therapy.

If pain develops or if redness, itching or inflammation becomes aggravated, the patient should be advised to consult a doctor.

OVERDOSAGE

Based on postmarketing safety data collected through July 2012 for loteprednol etabonate as an active substance (including Lotemax® suspension, Alrex®, Zylet® and Lotemax® Ointment), no cases of overdose have been reported.

Acute overdosage is unlikely to occur via the ophthalmic route, particularly with use of topical gel.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Corticosteroids elicit numerous potent anti-inflammatory effects.

They suppress cellular infiltration, capillary dilation, the proliferation of fibroblasts, collagen deposition, and eventually scar formation; they stabilise intracellular and extracellular membranes; and they increase the synthesis of lipocortins that block phospholipase A2 and inhibit histamine synthesis in the mast cells. Inhibition of phospholipase A2 prevents the conversion of phospholipids to arachidonic acid, a critical step in the inflammatory cascade. Corticosteroids also increase the enzyme histaminase and modulate transcription factors present in mast cell nuclei. Corticosteroids mediate their anti-inflammatory effects primarily through the modulation of the cytosolic glucocorticoid receptor (GR) and the corticosteroid-GR complex is involved in different pathways. There is further research into the mechanisms of action.[4]

Pharmacodynamics

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.

Loteprednol etabonate was derived from an inactive metabolite of prednisolone, cortienic acid, based on the 'inactive metabolite' approach[5,6]. Specifically, LE was designed with a 17-β-chloromethyl ester, but without the ketone group which is present at position 20 for other corticosteroids, such as prednisolone. The biologically labile 17-β-chloromethyl ester function, together with a labile 17-α-ethylcarbonate function result in metabolism of loteprednol etabonate to the 17-β-carboxylate form (PJ-91, Δ_1-cortienic acid etabonate) and subsequently to PJ-90 (Δ_1-cortienic acid)

Pharmacokinetics

The systemic exposure to loteprednol etabonate following ocular administration of Lotemax® Gel has not been studied in humans. However, results from a bioavailability study with Lotemax® suspension in normal volunteers established that plasma concentrations 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 of 0.5% loteprednol etabonate suspension in each eye of 10 patients, 8 times daily for 2 days or 4 times daily for 42 days.

The maximum systemic exposure to loteprednol following administration of the gel product dosed four times daily is not expected to exceed exposures attained with Lotemax® suspension dosed up to two drops four times daily. [7]

STORAGE AND STABILITY

Store upright between 15 - 25ºC (59-77ºF) for up to 28 days after first opening.

KEEP OUT OF REACH OF CHILDREN.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for Lotemax® Gel.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Lotemax® Gel 0.5% is a sterile ophthalmic gel supplied in a white low density polyethylene plastic bottle with a white controlled drop tip and a pink polypropylene cap in the following size: 5 g in a 10 mL bottle.

Lotemax® Gel 0.5% is a gel at rest and a fluid upon instillation into the eye. Product does not settle.

Nonmedicinal ingredients are as follows: boric acid, edetate disodium dihydrate, glycerin, polycarbophil, propylene glycol, sodium chloride, tyloxapol, water for injection, and sodium

hydroxide to adjust to a pH of between 6 and 7. Preservative is benzalkonium chloride 0.003% w/w. Glycerin and propylene glycol are added as humectants/lubricants to provide enhanced comfort for the formulation

Lotemax® Gel, 0.5% is an aqueous continuous phase formulation containing a "gelling agent" (polycarbophil) which provides the semi-solid characteristics resulting in a solid material at rest and a fluid under shear stress. The formulation flows under these shear stresses.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

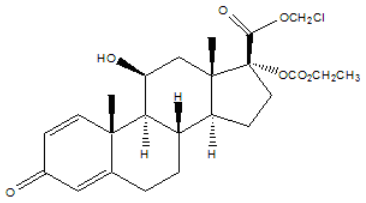
Drug Substance

Proper name: loteprednol etabonate

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

Molecular formula and molecular mass: $C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

Structural formula:



Physicochemical properties: Loteprednol etabonate (LE) is a white to off-white crystalline powder. LE is a corticosteroid and an analogue of prednisolone.

CLINICAL TRIALS

The clinical development program for Lotemax® Gel included 2 randomized, multicenter, double-masked, parallel-group safety and efficacy studies. The primary objective of these clinical studies was to compare the safety and efficacy of LE Gel to its vehicle for the treatment of inflammation and pain following cataract surgery.[1,2]

Study demographics and trial design

The population for the two studies consisted of 813 adults (30-91 years of age) who underwent routine, uncomplicated cataract surgery. To be eligible for randomization, each subject had to have anterior chamber cells (ACC) of at least Grade 2 (6-15 cells) on a 0-4 scale at Postoperative Day 1.

Prospective subjects were excluded from the study if they had elevated IOP (≥ 21 mm Hg), uncontrolled glaucoma, or were being treated for glaucoma in the study eye. Subjects who were expected to require concurrent ocular therapy (either eye) with nonsteroidal anti-inflammatory drugs (NSAIDs), mast cell stabilizers, antihistamines, or decongestants during the 18 days following cataract surgery or used any of the above within 2 days prior to surgery (intraoperative NSAIDs for mydriasis were permitted) were also excluded. Subjects who were expected to require treatment with systemic or ocular (either eye) corticosteroids during the 18 days following cataract surgery or those who used any systemic or ocular corticosteroids within 14 days prior to cataract surgery were excluded.

Table 3 - Summary of study population demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number) Enrolled/ Completed	Mean age (Range)	Gender
Study A	Multicenter, randomized, double-masked, placebo (vehicle) controlled, parallel group Subjects included had at least Grade 2 for ACC at baseline (postoperative Day 1)	LE Gel 0.5% vehicle 1 to 2 drops in study eye QID at ~4-hr intervals for 14 days	LE Gel: 203/199 Placebo: 203/198	71 years (36 – 91)	175 M 231 F
Study B	Multicenter, randomized, double-masked, placebo (vehicle) controlled, parallel group Subjects included had at least Grade 2 for ACC at baseline (postoperative Day 1)	LE Gel, 0.5% vehicle 1 to 2 drops in study eye QID at ~4-hr intervals for 14 days	LE Gel: 206/204 Placebo: 201/196	70 years (30 – 89)	174 M 233 F

Study duration was approximately 4 weeks from screening to the last visit. Randomized subjects self-administered 1 or 2 drops of study drug to the lower cul-de-sac of the study eye, QID, at approximately 4 hour intervals. Study treatment lasted approximately 14 days.

The hierarchal primary efficacy endpoints for each study were the proportion of subjects with complete resolution of anterior chamber cells at Visit 5 (Postoperative Day 8) followed by the proportion of subjects with no (Grade 0) pain at Visit 5 (Postoperative Day 8). Secondary efficacy endpoints were the proportion of subjects with complete resolution of anterior chamber cells and/or flare at each visit and the change from baseline to each follow-up visit in anterior chamber cells (ACC) and flare, and no (Grade 0) pain at each visit. Safety endpoints included the incidence of adverse events (AEs), change from baseline in Intraocular Pressure (IOP), and visual acuity, funduscopy, and the absence/presence of ocular signs and symptoms. Ocular symptoms were considered both a safety and efficacy measure.

Treatment success in each study was defined as achieving complete resolution of ACC at Visit 5 (Postoperative Day 8), after approximately 7 days of QID dosing. Any cell score greater than 0 on Day 8 was judged as a treatment failure. Subjects with missing data on Visit 5 (Postoperative Day 8) or subjects who required rescue medication (RM) prior to Visit 5 were also judged as failures. Treatment success and failure for the relief of postoperative ocular pain were defined similarly. Pain was judged on a 0-5 scale, and there was no minimum level of baseline pain required for inclusion in the analysis. Treatment success required a subject to have Grade 0 (no pain) on Visit 5 (Postoperative Day 8), and any positive value, missing data, or use of RM was judged as a treatment failure for pain.

Study results

Table 4: Primary Efficacy Analysis, By Study - ITT Population

	Study A			Study B		
	LE Gel (N = 203)	**Vehicle (N = 203)**	**Difference (95% CI) [b] / p-Value [c]**	**LE Gel (N = 206)**	**Vehicle (N = 201)**	**Difference (95% CI) [b] / p-Value [c]**
Complete resolution of anterior chamber cells at Visit 5 (Postoperative Day 8) [a]						
Yes	62 (30.5%)	33 (16.3%)	14.3%	64 (31.1%)	28 (13.9%)	17.1%
No	141 (69.5%)	170 (83.7%)	(5.7%, 22.9%)	142 (68.9%)	173 (86.1%)	(8.7%, 25.6%)
Subjects without Rescue Medication Use	122	100	<0.001	134	124	< 0.001
Subjects with Rescue Medication Use	17	70		6	47	
Subjects with Missing Data	2	0		2	2	
Grade 0 (no) pain at Visit 5 (Postoperative Day 8) [a]						
Yes	148 (72.9%)	85 (41.9%)	31.0%	156 (75.7%)	92 (45.8%)	30.0%
No	55 (27.1%)	118 (58.1%)	(21.4%, 40.7%)	50 (24.3%)	109 (54.2%)	(20.4%, 39.5%)
Subjects without Rescue Medication Use	36	48	< 0.001	42	60	< 0.001
Subjects with Rescue Medication Use	17	70		6	47	

Subjects with Missing Data	2	0		2	2	

[a] Subjects who had missing data or took rescue medication prior to Visit 5 were imputed as 'No'.
[b] Difference in percentages; 95% Confidence Interval (CI) based on asymptotic normal approximations.
[c] p-Values from Pearson chi-squared statistic. The Pearson value was the primary outcome. Grade 0 (no) pain was only tested if complete resolution of cells was significant at the 0.05 level.

In the two studies, Lotemax® Gel had statistically significant higher incidence of complete clearing of anterior chamber cells at post-operative day 8 (30.5-31.1% vs. 16.3-13.9%) and also had a statistically significant higher incidence of subjects that were pain free at post-operative day 8 (72.9-75.7% vs. 41.9-45.8%). [1,2]

An integrated analysis of efficacy data collected from the two studies was also performed.

The primary efficacy endpoints for these studies were identical, and the efficacy data from the integrated analysis confirmed the results of each of the 2 pivotal studies. Lotemax® Gel was superior to vehicle in the treatment of postoperative inflammation as judged by the complete resolution of anterior chamber cells at Visit 5 (Postoperative Day 8). Additionally, Lotemax® Gel was superior to vehicle in the treatment of pain as judged by Grade 0 (no) pain at Day 8. Both tests of the primary efficacy endpoints proved successful in the ITT and PP populations at Visit 5, (subjects with missing values and subjects requiring RM were considered treatment failures).

Table 5 - Primary Efficacy Analysis, Integrated ITT Population

	LE Gel (N = 409)	**Vehicle (N = 404)**	**Difference (95% CI) [b] / p-Value [c]**
Complete resolution of anterior chamber cells at Visit 5 (Postoperative Day 8) [a]			
Yes	126 (30.8%)	61 (15.1%)	15.7%
No	283 (69.2%)	343 (84.9%)	(9.8%, 21.6%)
Subjects without Rescue Medication Use	256	224	<0.001
Subjects with Rescue Medication Use	23	117	
Subjects with Missing Data	4	2	
Grade 0 (no) pain at Visit 5 (Postoperative Day 8) [a]			
Yes	304 (74.3%)	177 (43.8%)	30.5%
No	105 (25.7%)	227 (56.2%)	(23.8%, 37.2%)
Subjects without Rescue Medication Use	78	108	<0.001
Subjects with Rescue Medication Use	23	117	
Subjects with Missing Data	4	2	

[a] Subjects who had missing data or took rescue medication prior to Visit 5 were imputed as 'No'.
[b] Difference in percentages; 95% CI based on asymptotic normal approximations.
[c] p-Values from Pearson chi-squared statistic. The Pearson value was the primary outcome and Grade 0 (no) pain was only tested if complete resolution of cells was significant at the 0.05 level.

Results of the secondary outcome measures were in agreement with primary outcome measures. Significantly more subjects randomized to Lotemax® Gel compared with subjects randomized to placebo (vehicle) had complete resolution of ACCs at all postoperative visits except Visit 4,

Postoperative Day 3. Complete resolution of anterior chamber flare was significantly better with Lotemax® Gel than with placebo at all postoperative visits; and complete resolution of ACCs and anterior chamber flare taken together was significantly better with Lotemax® Gel than with placebo at all postoperative visits except Visit 4, Postoperative Day 3. Efficacy for the treatment of ocular pain was significantly better than that of placebo at all postoperative visits. Baseline mean (SD) ACC score was 2.3 (0.48) and 2.3 (0.46) in the Lotemax® Gel and placebo treatment groups, respectively. Mean change from baseline ACC scores showed an improvement in both groups with a mean (SD) change of -0.8 (0.73), -1.3 (0.89), -1.6 (0.94) and -1.6 (0.96) for the Lotemax® Gel group and a mean change of -0.4 (0.87), -0.6 (1.05), -0.8 (1.14) and -0.8 (1.17) for the placebo group at visits 4-7, respectively. Mean changes were consistently and significantly greater in the Lotemax® Gel treatment group at each of these visits ($P < 0.001$).

Tolerability of the study medications was judged from assessment of the following ocular symptoms at baseline and at each visit: discharge, dryness, itching, pain, photophobia, and tearing. Ocular pain was assessed and rated on a 0 to 5 scale (0 = none to 5 = severe) while photophobia, itching, tearing, dryness and discharge were individually rated on a 0 to 3 scale (0 = absent to 3 = severe). Ocular symptoms were compared between treatments both as symptom severity and as change from baseline scores. For these analyses, subjects who used rescue medication prior to the visit being summarized were excluded.

Regarding ocular discharge, dryness and itching, a majority of patients (more than 89%, more than 96% and at least 96% respectively) had no symptoms or mild symptoms at baseline (Visit 3) and these symptoms were improved or did not change from baseline at follow-up visits without any significant differences between treatment groups in most cases, with the following exceptions: at Visit 5 (Postoperative Day 8), there was a significant difference between treatments in the severity level of ocular discharge that favored vehicle ($p = 0.012$). At Visits 4-6, itching was unchanged or improved from baseline in significantly more subjects in the Lotemax® Gel group than in the placebo (vehicle) group.

At baseline, some ocular pain (mostly minimal or mild) was reported by 52.8% and 51.2% of patients in the Lotemax® Gel and vehicle groups, respectively. There was a significant difference between treatment groups at Visits 4-6 (Postoperative Days 3, 8 and 15) both in the severity level of ocular pain and their change from baseline scores that favored Lotemax® Gel. Ocular pain either improved or did not change from baseline for 90.2% versus 74.1% of patients at Visit 4, $p < 0.001$, for 90.8% versus 78.2% of patients at Visit 5, $p < 0.001$, and for 96.5% versus 88.7% of patients at Visit 6, $p<0.001$ in the Lotemax® Gel and vehicle groups, respectively.

At baseline, photophobia and tearing were absent or mild in more than 75% and more than 87% of patients respectively. At Visits 4-6 (Postoperative Days 3, 8 and 15), there was a significant difference between treatment groups both in the severity level of photophobia and change from baseline scores that favored Lotemax® Gel. Similar results were observed for tearing except at Visit 6 (Day 15) for the change from baseline scores as the level of statistical significance was not reached in spite of a strong trend ($p = 0.054$).

Fewer Lotemax® Gel-treated patients required rescue medication (36.2% versus 66.6%) and fewer had an ocular adverse event (17.4% versus 25.2%; $P < 0.006$) while on study treatment. The most common ocular adverse events with Lotemax® Gel was anterior chamber inflammation (3.7% versus 5.9% in the Lotemax® Gel and vehicle groups, respectively, p = 0.142). The only ocular Treatment Emergent Adverse Events that occurred at statistically different rates between treatment groups included eye pain 2.0% versus 4.5%, p = 0.047 and increased lacrimation 1.5% versus 0.0%, p = 0.031. Eye pain was reported less frequently and increased lacrimation more frequently in the Lotemax® Gel group than in the vehicle group.

Mean Intraocular Pressure (IOP) for all study eyes was consistently slightly lower than baseline values at all follow-up visits in both treatment groups. Three patients had increased IOP ≥ 10 mm Hg (3 Lotemax® Gel; 1 vehicle) prior to rescue medication. Visual acuity (VA) and dilated fundoscopy results were similar between treatment groups. **See Clinical Trial Adverse Drug Reactions.**

DETAILED PHARMACOLOGY

The drug substance loteprednol etabonate (LE) is an analog of prednisolone that was developed for use in ocular inflammatory conditions. LE was designed according to the retrometabolic drug design concept from an inactive metabolite of prednisolone, Δ_1-cortienic acid. Specifically, LE was designed with a 17-β-chloromethyl ester, but without the ketone group which is present at position 20 for other corticosteroids. LE is the only clinically used corticosteroid that lacks a ketone in the 20_{th} carbon position. The biologically labile 17-β-chloromethyl ester function, together with a labile 17-α-ethylcarbonate function, result in metabolism of LE to the 17-β-carboxylate form (PJ-91, Δ_1-cortienic acid etabonate) and subsequently to PJ-90 (Δ_1-cortienic acid). The PJ-91 and PJ-90 metabolites are inactive, as they do not bind to the glucocorticoid receptor. The metabolism of LE by enzymes located throughout the body, including the blood and/or liver, minimizes systemic exposure to LE, thereby decreasing the likelihood of systemic side effects. Furthermore, the local metabolism of LE by esterases located in the eye is a probable explanation of why LE has a lower propensity than other steroids to elevate IOP.[6,8,9]

Results from competitive binding studies indicate that LE has a binding affinity for glucocorticoid (Type II) receptors that is 4.3-times greater than that of dexamethasone and that LE binds competitively to the corticosteroid binding globulin, transcortin. In contrast, the LE metabolites, PJ-90 and PJ-91, do not bind to the glucocorticoid receptor.

The primary anti-inflammatory activity of LE has been demonstrated in several *in vivo* systems. Studies in three models of anterior ocular inflammation (*i.e.*, paracentesis-induced breakdown of the blood-aqueous-barrier, acute and chronic uveitis, and corneal inflammation) were conducted to evaluate the anti-inflammatory properties of LE when administered topically to the eye. Results from these studies support the classification of LE as a topical anti-inflammatory steroid when administered directly to the site of inflammation. In addition, LE was effective in nonocular inflammation models (*e.g.*, croton oil ear edema, carrageenan paw swelling, histamine

induce vascular permeability, cotton pellet granuloma, and homologous passive cutaneous anaphylaxis).

Primary Pharmacodynamics – Ocular

LE demonstrated anti-inflammatory activity in multiple ocular models of inflammation in rabbits; however, the magnitude of the effect varied depending on the model used and endpoints measured. At the specific doses tested, the anti-inflammatory effects of LE were similar to or less than the effects of the comparator compounds evaluated. In general, these studies were intended to provide proof-of-concept information, and did not include complete dose-vs-response profiles for LE or the comparator compounds that were tested and do not provide definitive information regarding the relative potency of LE vs other anti-inflammatory drugs. A summary of the ocular inflammation models used is shown below.

Ocular Inflammation Models in Rabbits

i) Paracentesis, nitrogen mustard, *Shigella* endotoxin, and immune uveitis models

Summary: LE (0.5%) inhibited an increase in protein levels in the aqueous humor in all models, with similar efficacy to dexamethasone (0.1%) and flurbiprofen (0.03%).

ii) Intravitreal endotoxin-induced (*E. coli*) ocular inflammation model

Summary: LE (1%) demonstrated anti-inflammatory effects that were similar to, or less than those observed with prednisolone (1%). Both agents reduced leukocyte infiltration into aqueous humor. Prednisolone, but not LE, also reduced myeloperoxidase (MPO) activity in iris/ciliary body as compared to placebo.

iii) Acute (endotoxin-induced) uveitis model

Summary: LE (0.5%) demonstrated anti-inflammatory activity, as assessed by conjunctival injection, anterior chamber flare, fibrin, and iris hyperemia, with no significant effect on anterior chamber cells and aqueous protein levels in this model. By several of these measures, anti-inflammatory activity of LE was less than that observed for dexamethasone (0.1%) and/or fluorometholone (0.1%).

iv) Chronic adjuvant-induced immune uveitis model

Summary: Anti-inflammatory effects of LE (1%) was similar to dexamethasone (0.1%), but less than fluorometholone (0.1%) based on conjunctival injection, cornea edema, cornea neovascularization, anterior chamber cells and flare, iris hyperemia, and aqueous protein levels.

v) Clove oil-induced corneal inflammation model

Summary: Following inoculation of clove oil into the cornea stroma, 0.5% LE was the minimum effective dose in this model, with no anti-inflammatory effects observed at lower doses (0.05% and 0.1%). Higher LE doses (1% and 2%) resulted in maximal anti-inflammatory effects in this model, with LE, 0.5% and 1%, producing equivalent efficacy to prednisolone, 0.125% and 1%, respectively.

Primary Pharmacodynamics – Non-Ocular

The anti-inflammatory effects of LE were also studied in multiple non-ocular models of inflammation in rats and mice.

Non-Ocular Inflammation Models

Model	Species	Compounds and Doses Tested
Croton oil-induced ear edema	Rat, Mouse	LE (0.1%) betamethasone (0.12%) hydrocortisone (0.1%)
DNFB-induced dermatitis	Rat	LE (0.1%) hydrocortisone (0.1%)
Cotton pellet granuloma assay	Rat	LE hydrocortisone betamethasone *(dose of ≤ 10 mg/pellet for each compound)*
Histamine-induced vascular permeability	Rat	LE (0.1%) dexamethasone (0.1%) hydrocortisone (0.1%)
Carrageenan-induced skin and paw edema	Rat	LE (0.1%) dexamethasone (0.1%) hydrocortisone (0.1%)
Adjuvant-induced arthritis	Rat	LE (0.1%) dexamethasone (0.1%)

Results from these studies support the classification of LE as a topical anti-inflammatory steroid when administered directly to the site of inflammation. Depending on the model, the effects of LE similar to or less than the effects of the other corticosteroids tested following direct application to the inflamed site. LE did not elicit a significant response in the DNFB-induced dermatitis model, and anti-inflammatory effects were not observed in the 2 models where systemic absorption and subsequent distribution to the inflamed site was required (adjuvant-induced arthritis model and carrageenan–induced skin and paw edema model), likely due to the high systemic clearance of LE resulting in low systemic availability in rats.

Secondary Pharmacodynamics

Secondary pharmacology effects demonstrated the reduced potential for LE to induce adverse effects when administered locally. In these studies, LE was evaluated for a potential effect on wound healing (skin and corneal) and scar formation (*in vitro* and *in vivo*), intraocular pressure (*in vivo*), skin thickness and thymus weight (*in vivo*). In the corneal wound healing model, as with other corticosteroids, LE decreased scar formation, inhibited inflammatory cell infiltration, inhibited fibroblast proliferation. LE also decreased tensile strength of the resulting scar, to a similar extent as prednisolone, but to a lesser extent that that observed with dexamethasone. In the skin wound healing model, LE did not reduce the rate of wound healing, while two steroids, BMV and prednicarbate did. No clear effect on intraocular pressure was noted with LE. Topical

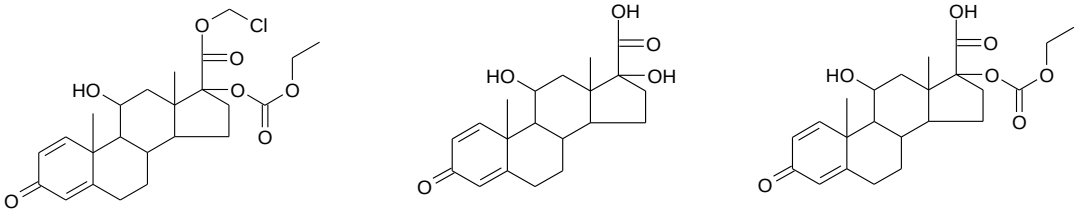
ocular treatment of normotensive rabbits with LE (0.1%, 1 dose per hour for 7 hours on two consecutive days) did not result in a sustained rise in IOP during the 55-h interval following the first administration. In contrast, treatment with dexamethasone (0.1%) with the same dosing regimen produced a statistically significant rise (3-5 mmHg) in IOP, which persisted for 48 hours after the initial dose. Topical dermal administration of LE led to a decrease in skin weight, but did not affect thymus weight, in contrast to both hydrocortisone-17-butyrate and betamethasone-17-valerate, which affected both tissues.

Overall, the results from these studies support the classification of LE as a topical anti-inflammatory steroid. Depending on the model, the anti-inflammatory effects of LE were similar to or less than the effects of the other corticosteroids tested following direct application to the inflamed site.

Pharmacokinetics

The chemical structure of LE and the two metabolites evaluated in pharmacokinetic studies are shown in the figure below.

Chemical Structure of Loteprednol Etabonate, PJ-90, and PJ-91



Loteprednol Etabonate PJ-90 PJ-91

Ocular Pharmacokinetics in Rabbits

The ocular and systemic pharmacokinetics of LE and its metabolites, PJ-91 and PJ-90, were evaluated in Fauve de Bourgogne rabbits with clove oil-induced corneal inflammation following a single, topical ocular administration of Lotemax® Ointment. Quantifiable levels of LE were observed in ocular tissues for at least 24 h after dosing, and in plasma for 8 h after dosing. The metabolites of LE were also observed in ocular tissues, but the levels were lower than the levels of LE. Neither metabolite was detected in plasma after topical ocular administration. See the table below for details.

Mean pharmacokinetic parameters of LE and metabolites in ocular tissues and plasma following a single topical ocular administration of Lotemax® Ointment to Fauve de Bourgogne rabbits with clove oil-induced corneal inflammation

Tissue	PK Parameters	LE	PJ-91	PJ-90
Conjunctiva	Cmax (µg/g)	2.06 ± 2.51	0.0159 ± 0.0193	NC
	Tmax (h)	0.25	0.25	NC
	AUC(0-24h) (µg*h/g)	5.78	0.0115	NC
Cornea	Cmax (µg/g)	1.16 ± 0.505	0.0715 ± 0.159	0.0144 ± 0.0318
	Tmax (h)	0.5	0.083	0.083
	AUC(0-24h) (µg*h/g)	4.70	0.115	0.0107
Aqueous humor	Cmax (µg/mL)	0.0724 ± 0.102	0.00267 ± 0.00104	NC
	Tmax (h)	0.083	1.5	NC
	AUC(0-24h) (µg*h/mL)	0.164	0.00852	NC
Plasma	Cmax (ng/mL)	0.103 ± 0.0423	NC	NC
	Tmax (h)	1	NC	NC
	AUC(0-24h) (ng*h/mL)	0.000600	NC	NC

NC – Not calculated; too few measurable values to derive accurate PK estimates.

The ocular and systemic pharmacokinetics of LE and its metabolites, PJ-91 and PJ-90, were evaluated in Fauve de Bourgogne rabbits with clove oil-induced corneal inflammation following a single, topical ocular administration of Lotemax® suspension. Quantifiable levels of LE were observed in ocular tissues throughout the 24-h sampling period and in plasma for 8 h after dosing. The metabolites of LE were also observed in ocular tissues, but the levels were lower than the levels of LE. With the exception of one rabbit that had a measurable concentration of PJ-91 2 h after dosing, concentrations of the metabolites were not detected in the plasma following topical ocular administration. See the table below for details.

Mean pharmacokinetic parameters of LE and metabolites in ocular tissues and plasma following a single topical ocular administration of Lotemax® suspension to Fauve de Bourgogne rabbits

Tissue	PK Parameters	LE	PJ-91	PJ-90
Conjunctiva	Cmax (µg/g)	3.62 ± 5.47	0.0466 ± 0.0574	0.00634 ± 0.00593
	Tmax (h)	1.5	0.083	0.083
	AUC(0-24h) (µg*h/g)	6.10	0.0268	0.00400
Cornea	Cmax (µg/g)	1.40 ± 1.45	0.457 ± 0.252	0.0925 ± 0.0528
	Tmax (h)	1	0.083	0.083
	AUC(0-24h) (µg*h/g)	3.30	0.397	0.0758
Aqueous humor	Cmax (µg/mL)	0.0293 ± 0.00805	0.0541 ± 0.0208	0.0199 ± 0.00753
	Tmax (h)	0.5	0.25	0.25
	AUC(0-24h) (µg*h/mL)	0.0838	0.0628	0.0222
Plasma	Cmax (ng/mL)	0.354 ± 0.0326	NC	NC
	Tmax (h)	0.25	NC	NC
	AUC(0-24h) (ng*h/mL)	0.800	NC	NC

NC – Not calculated; too few measurable values to derive useful PK estimates.

Consistent with other polycarbophil-based formulations, LE was retained on the ocular surface through 24 hours following administration of Lotemax® Gel[12,13,14]. The ocular pharmacokinetics of LE was assessed following a single topical ocular administration of Lotemax® Gel to rabbits. The results indicate that the ocular exposure to LE is similar or somewhat greater than that observed with the Lotemax® suspension [10].

Pharmacokinetic parameter values for LE following single topical ocular administration of Lotemax® Gel (0.5%) to pigmented rabbits

Tissue	Cmax[a] (µg/g)	Tmax (h)	AUC(0-t) (µg*h/g)
Tear Fluid	1560 ± 1420	0.25	872
Conjunctiva	4.03 ± 2.42	0.0833	18.2
Cornea	2.18 ± 0.685	0.0833	5.44
Aqueous Humor[b]	0.0138 ± 0.00604	0.5	0.0157
Iris/Ciliary Body	0.162 ± 0.0384	0.5	0.282
Plasma	7.30 ± 6.79 (ng/mL)	1.5	6.77 ± 4.62 (ng*h/mL)

[a] Cmax values represent maximum mean ± SD LE concentration

[b] Relevant units for aqueous humor are µg/mL for Cmax and µg*h/mL for AUC(0-t)

The effect of concomitant administration of Lotemax® Gel and other ophthalmic drugs has not been investigated. The administration of other concomitant ophthalmic drugs during the 30 min prior to or after Lotemax® suspension administration did not result in meaningful changes in ocular tissue levels of LE.

Systemic Pharmacokinetics in Rats and Dogs

The systemic pharmacokinetics of LE were assessed following intravenous and oral administration (5 mg/kg) to four mongrel dogs. Blood levels of LE declined rapidly following intravenous administration, showing a biexponential plasma concentration profile. LE was eliminated from the plasma with a total body clearance of 22 L/h and a half-life of 2.8 h. LE had a large volume of distribution (37 L), characteristic of lipophilic drugs of this class. No LE was detected in the plasma after oral administration or in the urine after either intravenous or oral administration.

In Sprague-Dawley (SD) rats (5 males/group), following oral administration of [^{14}C]LE (5 mg/kg), levels of [^{14}C]LE in blood were relatively low and constant (20-33 ng/mL) throughout the 5-h sampling period. Of the tissues analyzed in this study, LE and PJ-91 levels were highest in liver, with maximal concentrations of approximately 1.9 µg/g for LE and 1.3 µg/g for PJ-91. LE levels in liver tended to be higher than PJ-91 levels; however, for other tissues, LE levels tended to be lower than (blood and kidney) or roughly similar to (heart and lung) PJ-91 levels.

Following intravenous administration to SD rats (3/group), LE was rapidly cleared from plasma in a biphasic manner, with half-life estimates of approximately 16-49 min, depending on the dose (see table below). Total clearance of LE from plasma was dose-dependent and decreased with increasing dosage. During the 4-h collection interval following dosing, approximately 9% of the administered dose was recovered in bile in the form of PJ-91 and PJ-90. Measurable levels of LE and PJ-91, but not PJ-90, were observed in urine, with <4% of the administered dose recovered as intact LE during the 2.5-h interval after dosing. These results suggest that the liver is an important site for the metabolism of LE and that biliary excretion of the metabolites of LE is a significant route of elimination.

Pharmacokinetic parameter values for LE in plasma following intravenous administration to rats

Dose (mg/kg)	AUC (µg•min/mL)	CL (mL/min/kg)	T½ (min)	MRT (min)
1	9.2 ± 0.4	108.53 ± 4.47	15.92 ± 1.23	17.59 ± 0.95
2	16.0 ± 1.1	125.76 ± 9.01	17.22 ± 1.71	18.34 ± 0.80
5	56.1 ± 6.2	90.28 ± 9.98	29.49 ± 0.00	31.98 ± 0.78
10	159.2 ± 31.3	67.35 ± 11.62	43.41 ± 7.58	48.72 ± 8.95
20	333.2 ± 17.9	60.35 ± 3.09	48.82 ± 1.52	51.79 ± 1.70

Abbreviations: AUC: Area under the concentration-time curve, CL: systemic clearance; T½: apparent terminal phase half-life; MRT: mean residence time.

***In Vitro* Studies**

The *in vitro* metabolic stability of LE was investigated following incubation with rat, rabbit, and dog plasma, as well as human liver homogenate. LE was rapidly metabolized in rat plasma, with nearly 100% disappearance of intact LE within 30 min; however, no metabolism of LE was evident in rabbit, dog, or human plasma. In human liver homogenate, LE metabolism, while not complete, was more extensive than the other steroids tested.

Metabolic stability of LE and other steroids in human liver homogenate

Compound	% Remaining at 30 min
LE	73
Prednisolone	105
Dexamethasone	102
Betamethasone	89

Plasma protein binding and distribution into red blood cells of LE (6.2-18.5 µg/mL) and the metabolite, PJ-91 (5-15 µg/mL), was investigated *in vitro* in dog blood. LE was highly bound to plasma proteins (mean±SD of 95.3 ± 3.0% bound) over this concentration range. In contrast, PJ-91 was approximately 73% bound to plasma proteins. LE and PJ-91 distributed into red blood cells with a partition coefficient of 7.8 and 0.25, respectively.

Pharmacokinetic Summary

The available pharmacokinetic data from *in vivo* and *in vitro* studies indicate that LE is readily absorbed into ocular tissues, with low systemic exposure following topical ocular administration. To the extent that LE reaches the systemic circulation, data from rats suggest that it is extensively metabolized and subsequently excreted via bile and urine. LE is highly protein bound in plasma, and distributes preferentially into the cellular components of blood. Although LE is rapidly hydrolyzed in rat blood, systemic metabolism in humans likely occurs in the liver.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

A repeat ocular dose study was conducted to evaluate the ocular tolerance of LE, 0.4% and 0.7% in the gel formulation in New Zealand white rabbits following QID dosing for 28 days. No local ocular effects related to LE gel were observed at either dose. Systemic effects of LE included corticosteroid class effects of low body weight gains and adrenal cortical atrophy. Telogen atrophy of the eyelid hair follicle (but not eye lashes) was related to dermal exposure to LE.

Two repeat ocular dose studies were conducted to evaluate the ocular tolerance of LE, 0.5% in the ointment formulation (New Zealand white rabbit; Beagle dog) following QID dosing for 28 days. In general, no local ocular effects related to 0.5% LE ointment were observed in either study. However, conjunctival redness, chemosis, and discharge were observed in rabbits, and transient punctiform ocular surface opacities were observed daily following repeated treatments in beagle dogs; these events were considered to be associated with the ointment. Furthermore, no systemic effects of LE, as evaluated by clinical evaluations and necropsy (with organ weights), were observed in either study. The effect of supratherapeutic concentrations of Lotemax® Ointment was not studied.

Single-dose toxicity

Acute oral toxicity studies in rats and mice indicate that the maximum tolerated dose (MTD) for loteprednol etabonate (LE) is greater than or in the region of 4000 mg/kg bodyweight, which is ~27,000 and ~14,000 times the Lotemax® Ointment clinical dose, respectively. The MTD for both species by the subcutaneous route (rats and mice) was found to be >1333 mg/kg bodyweight (the maximum practical dose by this route). Apparent reductions in spleen size were noted in both species at necropsy following subcutaneous administration and may be treatment related. In an evaluation of a secondary metabolite of loteprednol etabonate, PJ-90, the MTD was shown to be >100 mg/kg bodyweight when administered subcutaneously in the rat. These data indicate that LE is of a low order of acute toxicity.

Repeat-dose toxicity – sub-chronic studies

Twenty-eight day toxicity studies conducted in the rat by the oral route (0.5, 5, or 50 mg/kg/day) and in the rabbit by ocular administration (0.1 ml/day of LE 0.1%, 0.7%, or 5%) identified the liver as a potential target organ for LE; increased ALT and glucose levels were identified at the high dose group in both studies, together with other, less consistent biochemical changes suggestive of hepatotoxic effects. No histological changes were seen in the liver in either species. Other changes observed in these studies were generally consistent with the effects which would be expected following administration of high doses of corticosteroids.
The hepatic effects observed in the rat oral study mainly occurred at the high dose level which represented a multiple in excess of approximately 400 times the anticipated human dose of

Lotemax® Ointment, although some evidence of hepatotoxicity was also apparent at the intermediate dose level (≥ 40 times the anticipated human dose of Lotemax® Ointment). The low dose (0.5 mg/kg/day) in rats, which exceeded 4 times the equivalent human dose of Lotemax® Ointment, was a no effect level. In the ocular rabbit study, hepatic effects were restricted to the high dosage group (i.e., approximately 40 times the equivalent human dose of Lotemax® Ointment). In rabbits, no significant toxicity was noted at the 0.7% mid dose, which is equivalent to approximately 6 times the human dose of Lotemax® Ointment. Complete systemic absorption of LE to the blood following Lotemax® Ointment administered by ocular route is not expected in humans. See **ACTION and CLINICAL PHARMACOLOGY.**

No adverse ocular effects were observed following administration of LE at concentrations of up to 5% in 2-hydroxypropyl-β -cyclodextrin, of LE, 0.5% in combination with Tobramycin, 0.3%, or of LE, 0.5% in combination with sulfacetamide sodium, 10% for 30 days. Similarly, no adverse effects were apparent following ocular administration of PJ-90, a possible secondary metabolite of LE, for 28 days. However, based on this single study and its limitations, no definitive conclusions can be drawn regarding the potential toxic effect of PJ-90.

Repeat-dose toxicity – chronic studies

In a six-month study, rabbits were exposed to loteprednol etabonate LE 0.5% ocular drops (30 µL) eight times daily for the first week, and then four times daily thereafter. No significant ocular signs were reported. The average adrenals' weight in the exposed group was significantly lower, but no corresponding microscopic modifications of the adrenals were observed. Thymus involution was observed more frequently in the treated females. The dose used in rabbits was equivalent to approximately5 times the Lotemax® Ointment human dose.

In a one-year study, dogs received 6 drops daily of dexamethasone 0.1%, LE 0.1%, or 0.5%. An increasing incidence of stromal anomalies ranging from fine haze to crystalline deposits in the cornea of the treated eye in animals receiving LE 0.5% was noted between Week 26 and Week 52. A few of those treated with LE 0.1%, had stromal anomalies, but only at Week 52. Some IOP increase (≥ 5 mmHg) was reported in few animals starting on week 13, however, no clear dose-response or time trend were present. There were no apparent toxic effects on the adrenal glands as confirmed by the histological reports. In contrast, the number of animals with IOP increase (≥ 5 mmHg) among those treated with dexamethasone 0.1% was higher and increased with time; by week 52, almost all dogs treated with dexamethasone 0.1% experienced IOP increase. The dexamethasone 0.1% treated dogs had a significant reduction of males' bodyweight and adrenals organ weights. The latter was confirmed by the presence of cortical atrophy of the adrenals in all animals treated with dexamethasone. Thymus involution was also more marked in the dexamethasone 0.1% group. Please note that corneal opacities were seen exclusively in dogs and not in any other studied animals (rats, rabbits).

In a six- month study, rabbits exposed to LE 0.5% ocular drops 6 times daily experienced no significant IOP increase, or corneal deposits. However, small adrenal glands were noted in 3/10 animals and were correlated by a lower average adrenals weight and corresponding histological changes (e.g., atrophy). These effects were seen mainly in animals treated for 6 months with the equivalent of approximately 7 times the intended Lotemax® Ointment human dose.

Genotoxicity

No evidence of mutagenic potential was apparent in the four *in vitro* tests conducted up to the limits of LE solubility. No evidence of mutagenicity was apparent in the micronucleus test at dose levels in the region of 4,000 mg/kg bodyweight which, although probably slightly less than the maximum tolerated dose by the oral route in the mouse, equates to an exposure equivalent to ~14,000 times the Lotemax® Ointment clinical dose.

Developmental and reproductive toxicology

In the fertility and general reproductive study in rats clear evidence of parental (F_0 generation) toxicity was demonstrated at the high dose levels of loteprednol etabonate (males, 50 mg/kg/day; females 25 mg/kg/day), and to a lesser extent at the intermediate 5 mg/kg/day level which is equivalent to approximately 40 times the Lotemax® Ointment clinical dose. The fertility and mating performance of the F0 generation was unaffected by treatment. However, pregnancies and pregnancy outcomes were significantly affected (e.g., longer gestation, marked decrease in live foetuses, and poor foetus and pups survival).

Clear evidence of toxicity was observed for Fl generation foetuses and pups produced from F_0 animals of the intermediate and high dosage groups. With the exception of slight growth retardation, pups of F_0 parents receiving the low dose level (0.5 mg/kg/day) were unaffected by parental treatment (i.e., approximately 4 times the Lotemax® Ointment clinical dose). The mating performance of the F_1 generation and the F_2 generation was unaffected by F_0 treatment.

Maternal toxicity was demonstrated in the rabbit embryotoxicity study at 3 mg/kg/day LE (approximately50 times the Lotemax® Ointment clinical dose), together with clear evidence of embryotoxicity characterized by slight developmental retardation. There was also some evidence of teratogenicity as meningocele (major abnormality) in some foetuses and an increased incidence of abnormal left common carotid artery (minor abnormality) were noted. In the 0.5 mg/kg/day group, an increase in the occurrence of abnormal left common carotid artery was suggested, but there were no major adverse effects on embryonic or foetal development at 0.1 or 0.5 mg/kg/day LE. The 0.5 mg/kg/day dose is equivalent to approximately8 times the Lotemax® Ointment clinical dose.

In the rat embryotoxicity study, evidence of maternal toxicity was apparent at dose levels of 5, 50 and 100 mg/kg/day and clear evidence of embryotoxicity and teratogenicity was observed for groups receiving 50 and 100 mg/kg/day of loteprednol etabonate. These toxic effects included major abnormalities, such as cleft palate, umbilical hernia, and aortic arches abnormalities. No evidence of major embryotoxicity or teratogenicity was seen at dose levels of 0.5 or 5 mg/kg/day. The latter dose is equivalent to approximately40 times the Lotemax® Ointment clinical dose.

In the peri- and post-natal study in rats, maternal toxicity was demonstrated following treatment with loteprednol etabonate during late pregnancy and lactation at dose levels of 0.5, 5 and 50 mg/kg/day. However, no effects on the onset or progress of parturition were observed in any of the treated groups. Maternal treatment elicited clear toxic effects in the offspring at 50 mg/kg/day which included reduced bodyweight, developmental retardation, poor survival and clinical condition, and an increased incidence of umbilical hernia. At 5 mg/kg/day, effects on the offspring were limited to lower birth weight and possibly to the occurrence of umbilical hernia in one pup. There was no apparent toxicity in the offspring at 0.5 mg/kg, which is equivalent to 4 times the Lotemax® Ointment clinical dose.

Carcinogenicity

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.

Delayed contact hypersensitivity study

The sensitizing potential of LE was evaluated in the guinea-pig using a modification of the Buehler test[4] using a cream formulation which, presumably, differs in terms of excipients from the intended ophthalmic formulation**.** There was no evidence to suggest that LE, 0.5% cream had the potential to induce delayed contact hypersensitivity.

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PART III: CONSUMER INFORMATION

[Pr]Lotemax® Gel
(loteprednol etabonate ophthalmic gel 0.5% w/w)

This leaflet is part III of a three-part "Product Monograph" published when Lotemax® Gel was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Lotemax® Gel. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Lotemax® Gel is used for the treatment of post-operative inflammation and pain following cataract surgery.

What it does:
Lotemax® Gel is a corticosteroid and is believed to act by reducing the production of substances associated with inflammation, including prostaglandins and leukotrienes. By reducing these substances inflammation and pain are reduced..

When it should not be used:
Do not use Lotemax® Gel:

- **If you are allergic to loteprednol or any of the ingredients contained in Lotemax® Gel (see What the important nonmedicinal ingredients are) or if you are allergic to any other corticosteroid.**
- **If you have eye infections caused by viruses such as herpes simplex, vaccinia and varicella or caused by bacteria or a fungus or if you think you have any other eye infection.**

What the medicinal ingredient is:
The medicinal ingredient is loteprednol etabonate. Each mL contains 5 mg (0.5% w/w) loteprednol etabonate.

What the important nonmedicinal ingredients are:
Boric acid, edetate disodium dihydrate, glycerin, polycarbophil, propylene glycol, sodium chloride, tyloxapol, water for injection, and sodium hydroxide. The preservative is benzalkonium chloride 0.003% w/w.

What dosage forms it comes in:
Sterile ophthalmic gel 0.5% w/w.

WARNINGS AND PRECAUTIONS

BEFORE you use Lotemax® Gel talk to your doctor or pharmacist:

- **If you have an eye disease/infection caused by viruses such as herpes simplex, vaccinia and varicella or caused by bacteria or a fungus or if you think you have any other eye infection.**
- **If you had or have glaucoma or increased pressure in the eye as Lotemax® Gel might increase the pressure in the eye. Glaucoma, which occurs when the pressure in the eye increases for a period of time, can cause damage to the optic nerve, vision problems, and sometimes a loss of vision. Your doctor may monitor your intraocular pressure.**
- **If signs and symptoms fail to improve after two days of using Lotemax® Gel, consult your doctor**
- **If you are pregnant or planning to become pregnant. Lotemax® Gel should not be used in pregnant women unless the doctor determines this is appropriate for you as there might be a risk of harm to the embryo or fetus.**
- **If you are breastfeeding or planning to breastfeed. Lotemax® Gel should not be used in breastfeeding women unless the doctor determines that this is appropriate for the infant as there might be a risk of harm to the nursing baby.**
- **If you are under 18 years of age.**

Consult your doctor if the following occurs while taking Lotemax® Gel:

- **If you develop an eye infection or other new or worsening symptoms.**
- **If you develop a blister on the eye (a bleb).**

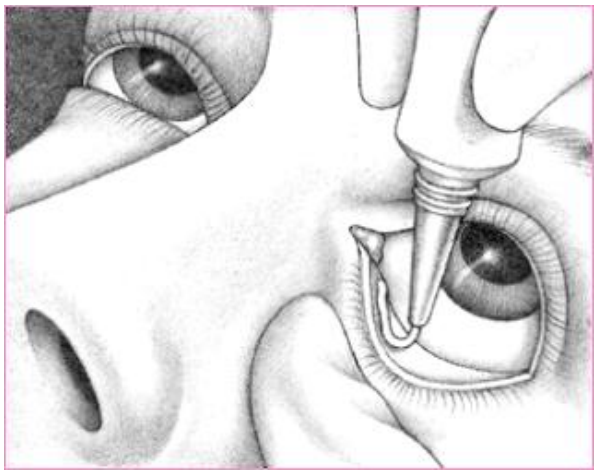
INTERACTIONS WITH THIS MEDICATION

Drug interaction studies have not been done for Lotemax® Gel.

Please inform your doctor or pharmacist if you are taking or have taken recently any other medicines, even those not prescribed.

PROPER USE OF THIS MEDICATION

Usual dose:
For adults only.
Invert closed bottle and shake once to fill tip before instilling drops.
Apply one or two drops of Lotemax® Gel into the conjunctival sac (see pictogram) of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the postoperative period.



- Do not allow the dropper tip to touch any surface as this may contaminate the gel. The cap should remain on the bottle when not in use.
- Use only if imprinted neckband is intact.
- Wash hands prior to using Lotemax® Gel.
- Do not wear contact lenses during the course of therapy.
- Do not use if tamper evident skirt is visible on bottom of cap.
- If pain develops, redness, itching or inflammation becomes aggravated, consult your doctor.
- If you are using another medication in the eye, wait at least 15 minutes before applying.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take the next dose as scheduled then continue as before. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Eye gel can cause your vision to be blurred. This usually passes quickly. Do not drive or use machines until your vision is clear. Like all medicines, Lotemax® Gel can have unwanted effects. The most common side effects in patients treated with Lotemax® Gel are:

- **Increased pressure within the eye**
- **Blurred or abnormal vision**
- **Swelling or discharge from the eyes**
- **Painful, dry or sticky eyes**
- **Tearing**
- **Sensation of having an object in your eye**
- **Itching in the eye or on the eyelid**
- **Redness in the eye or on the eyelid**
- **Photophobia (discomfort on exposure to light)**

Another unwanted effect might include headache, nausea, cold, sore throat, runny nose, dizziness or rash.

If you notice these or any other effects, tell your doctor or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking Lotemax® Gel, contact your doctor or pharmacist.

HOW TO STORE IT

Store upright between 15 - 25ºC (59-77ºF) for up to 28 days after first opening.

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701D
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.bausch.ca
or by contacting the sponsor, Bausch & Lomb Incorporated, at:
1-888-459-5000

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