PRODUCT MONOGRAPH

[Pr]LOTEMAX® OINTMENT

(loteprednol etabonate ophthalmic ointment 0.5 % w/w)

Professed Standard

Corticosteroid

Bausch & Lomb Incorporated
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Date of Revision:
March 14, 2014

Distributed in Canada by:
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Submission Control No: 163703

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Ointment, 0.5% w/w	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Lotemax® (loteprednol etabonate) Ointment 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® Ointment should not be used in pediatric patients. The safety and effectiveness of Lotemax® Ointment have not been established in pediatric patients.

CONTRAINDICATIONS

- Patients with suspected or confirmed infection of the eye such as viral disease of the corena 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 corticosetorids. 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® Ointment is indicated as a short-term treatment only (up to 14 days). The initial prescription and renewal of Lotemax® Ointment 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® Ointment 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® Ointment 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® Ointment should not be used in cases of existing (suspected or confirmed) ocular viral, fungal, or mycobacterial infections. Lotemax® Ointment may suppress the host response and thus increase the hazard of secondary ocular infections. The use of Lotemax® Ointment in patients with a history of herpes simplex requires great caution and close monitoring. See **WARNINGS and PRECAUTIONS – Ophthalmologic**.

Lotemax® Ointment has not been studied in pregnant or nursing women, but has been found to be teratogenic in animals. Lotemax® Ointment 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 lypokalemia and may exaggerate the hypokaliemic 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® Ointment 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® Ointment as directed, these possible effects are not likely. **See ACTION and CLINICAL PHARMACOLOGY**.

Ophthalmologic

Lotemax® Ointment should be used as a short-term treatment. If Lotemax® Ointment is used for 10 days or longer, intraocular pressure should be closely monitored. The initial prescription and renewal of Lotemax® Ointment 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® Ointment 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® Ointment.

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

Sexual Function/Reproduction
The effect of Lotemax® Ointment 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® Ointment 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® Ointment clinical dose. **See WARNING and PRECAUTIONS – Special Populations – Pregnant Women**.

Special Populations

Pregnant Women:
Lotemax® Ointment 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® Ointment clinical dose. At lower doses (approximately 4 times the Lotemax® Ointment 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® Ointment should not be used in lactacting 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® Ointment should not be used in pediatric patients. The safety and efficacy of Lotemax® 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® Ointment 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® Ointment, 405 patients received Lotemax® Ointment for approximately 14 days and 400 patients received placebo for approximately 9 days – shorter duration due to need for rescue medication – following cataract surgery. Adverse events related to Lotemax® Ointment were generally mild to moderate, non-serious and did not interrupt continuation in the studies. The most frequent ocular event reported as related to therapy was anterior chamber inflammation: 10.1% (41/405), as compared to 19.5% (78/400), in the placebo treated patients.

The incidence of all events in the Lotemax® Ointment group was similar or less than that of the placebo control group. Conjunctival hyperaemia and blurred vision were reported as related to therapy in 1.7% and 1.5% respectively of the Lotemax® Ointment treated eyes. Eye pain, ciliary hyperaemia, photophobia and uveitis, were each reported as related to therapy for 0.7% of patients. The most frequent non-ocular event reported as related to therapy was headache, reported for 0.5% of the Lotemax® Ointment treated patients.

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® Ointment in the treatment of inflammation following cataract surgery with intraocular lens (IOL) implantation.[1] Both studies were randomized, double-masked, placebo controlled, multi-centre parallel group. Patients with a combined anterior chamber rating of cell and flare ≥ 3 (scale 0-4, respectively) were enrolled in Study A (N=400) or Study B (N=405). Patients with history of intraocular or laser surgery on the eye three months prior to enrollment or elevated intraocular pressure ≥21mm Hg or the presence of any severe/serious ocular condition or unstable medical condition were excluded from the studies. During these studies, 405 patients were exposed to Lotemax® Ointment four-times daily for up to 14 days.

Incidences 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 Events in ≥ 1% Study Eyes, Lotemax® Ointment Treatment Group, Integrated Analyses - Safety Population

	Lotemax® Ointment (N = 405)	Vehicle (N = 400)
Number of Patients with at Least 1 AE	191 (47.2%)	312 (78.0%)
SYSTEM ORGAN CLASS Preferred Term (PT)		
EYE DISORDERS	**189 (46.7%)**	**312 (78.0%)**
Anterior chamber inflammation	110 (27.2%)	200 (50.0%)
Photophobia	22 (5.4%)	31 (7.8%)
Corneal oedema	18 (4.4%)	23 (5.8%)
Conjunctival hyperaemia	16 (4.0%)	30 (7.5%)
Eye pain	15 (3.7%)	43 (10.8%)
Iritis	15 (3.7%)	31 (7.8%)
Ciliary hyperaemia	10 (2.5%)	23 (5.8%)
Anterior chamber cell	10 (2.5%)	16 (4.0%)
Lacrimation increased	8 (2.0%)	19 (4.8%)
Vision blurred	7 (1.7%)	7 (1.5%)
Eye pruritus	6 (1.5%)	19 (4.8%)
Anterior chamber flare	6 (1.5%)	14 (3.5%)
Foreign body sensation in eyes	6 (1.5%)	10 (2.5%)
Ocular hyperaemia	5 (1.2%)	11 (2.8%)
Visual acuity reduced	5 (1.2%)	10 (2.5%)
Uveitis	4 (1.0%)	11 (2.8%)
INVESTIGATIONS	**6 (1.5%)**	**11 (2.8%)**
Intraocular pressure increased	5 (1.2%)	10 (2.5%)

The protocol required the recording of an adverse event of Anterior chamber inflammation (ACI) prior to initiation of rescue therapy.
The only non-ocular adverse event reported at a rate of at least 1% was headache, which occurred in 1.5% and 1.3% of patients in the Lotemax® Ointment and placebo groups, respectively.

Five serious adverse events were reported for 4 patients receiving Lotemax® Ointment; non-ocular events (4) were considered to be unrelated to study drug, and ocular event (1) (i.e., moderate macular edema) was considered to be possibly drug related. In the placebo group, 9 serious adverse events were reported for 8 patients; 4 of them were ocular (i.e., mild cystoid macula edema (3), endophthalmitis (1)). One case of cystoid macula edema was considered possibly drug related and all other events were considered unrelated to study drug.

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 29 patients in the Lotemax® Ointment group and in 33 patients in the placebo group (see table below). Four patients, 3 Lotemax® Ointment and 1 placebo, had a change from baseline IOP ≥ 10 mm Hg with a maximum post-baseline IOP of 32 mmHg for an Lotemax® Ointment-treated patient at Visit 6 (Postoperative Day 15).

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 = 396	N = 320	N = 273	N = 212	N = 398
≥10 mm Hg					
LE Ointment	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Placebo	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)	1 (0.5%)
5 to 9 mm Hg					
LE Ointment	3 (1.5%)	8 (4.3%)	5 (2.8%)	5 (3.4%)	15 (7.5%)
Placebo	4 (2.0%)	5 (3.7%)	4 (4.3%)	2 (3.0%)	12 (6.1%)
Pivotal Study B	N = 401	N = 309	N = 257	N = 215	N = 402
≥10 mm Hg					
LE Ointment	1 (0.5%)	0 (0%)	2 (1.2%)	1 (0.7%)	3 (1.5%)
Placebo	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
5 to 9 mm Hg					
LE Ointment	4 (2.0%)	9 (5.0%)	8 (4.7%)	5 (3.4%)	14 (6.9%)
Placebo	7 (3.5%)	7 (5.4%)	7 (8.0%)	8 (11.8%)	21 (10.6%)

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Eye Disorders: dry eye, eye irritation, eye discharge, cystoid macular oedema.
Immune system disorders: dermatitis contact.

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® 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.

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Apply a small amount (approximately ½ inch ribbon) into the conjunctival sac(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative 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® Ointment should be stored between 15°– 25°C (59° - 77°F).

Do not use if tamper evident skirt is visible on bottom of cap.

Patients should be advised not to touch the eyelid or surrounding areas with the tip of the tube.

The cap should remain on the tube when not in use.

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

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

If pain, 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, no cases of overdosehave been reported.

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.

There is no generally accepted mechanism of action of ocular corticosteroids. They are thought to act by the induction of lipocortins; inhibitory proteins of phospholipase A2. Inhibition of phospholipase A2 prevents the membrane phospholipid release of arachidonic acid and the subsequent biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes.
Corticosteroids are capable of producing a rise in intraocular pressure; delay wound healing following surgery, increase susceptibility for posterior subcapsular cataract formation; and increase susceptibility to secondary infections.

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.

Pharmacokinetics

The systemic exposure to loteprednol etabonate following ocular administration of Lotemax® Ointment 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.

STORAGE AND STABILITY

Store between 15 - 25ºC (59-77ºF) for up to 14 days after first opening.

KEEP OUT OF REACH OF CHILDREN.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for Lotemax® Ointment.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Lotemax® Ointment (loteprednol etabonate 0.5% w/w (5mg/g)) is a sterile ointment supplied in a tin tube with a pink polypropylene cap in the following size: 3.5 gram.

Non medicinal ingredients are as follows: mineral oil and white petrolatum.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

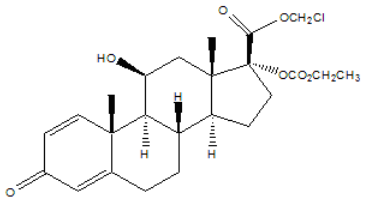
Drug Substance

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® Ointment (LE Ointment) 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 ointment to its vehicle for the treatment of inflammation and pain following cataract surgery[1].

Study demographics and trial design

The population for the two studies consisted of 805 adults (21-94 years of age) who underwent routine, uncomplicated cataract surgery. To be eligible for randomization, each subject had to have a sum of anterior chamber cell and flare measures (each measured on a 0-4 scale) of at least 3 at post-operative day 1 (Visit 3). The sum of anterior chamber cell and flare measures was also identified as anterior chamber reaction (ACR) in the study protocol. See table 3.

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	Randomized, double-masked, placebo controlled, parallel group Subjects included had a combined grade ≥ 3 for anterior chamber reaction (ACR) at postoperative Day 1	LE Ointment, 0.5% vehicle One-half inch long ribbon in study eye QID at ~4-hr intervals for 14 days	LE: 201/200 PL: 199/193	70 years (21 – 94)	163 M 237 F
Study B	Randomized, double-masked, placebo controlled, parallel group Subjects included had a combined grade ≥ 3 for anterior chamber reaction (ACR) at postoperative Day 1	LE Ointment, 0.5% vehicle One-half inch long ribbon in study eye QID at ~4-hr intervals for 14 days	LE: 203/200 PL: 202/200	70 years (38 – 90)	175 M 230 F

Study duration was approximately 4 weeks from screening to the last visit. Randomized subjects self-administered approximately a ½ inch (1.3 cm) ribbon 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 and flare at post-operative day 8 (Visit 5) followed by the proportion of subjects with Grade 0 (no) pain at post-operative day 8 (Visit 5). Secondary efficacy endpoints were the proportion of subjects with complete resolution of anterior chamber cells and flare (combined and separated) at each visit and the change from baseline to each follow-up visit in anterior chamber cells and flare. Safety endpoints included the incidence of adverse events (AEs), change in Intraocular Pressure (IOP), and ocular signs. Ocular symptoms were also considered a tolerability endpoint.

Treatment success in each study was defined as achieving complete resolution of cells and flare at post-operative day 8 (Visit 5), after approximately 7 days of QID dosing. For inclusion, subjects needed to have a sum of anterior chamber cell and flare measures of at least 3 (each measured on a 0-4 scale) at post-operative day 1. Any cell or flare score greater than 0 on Day 8 was judged as a treatment failure. Subjects with missing data on post-operative day 8 (Visit 5) or subjects who required rescue medication 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 post-operative day 8 (Visit 5), and any positive value, missing data, or use of rescue medicaiton was judged as a treatment failure for pain.

Study results

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

	Study A			Study B		
	LE Ointment (N = 201)	**Vehicle (N = 199)**	**Difference (95% CI) [b] / p-Value [c]**	**LE Ointment (N = 203)**	**Vehicle (N = 202)**	**Difference (95% CI) [b] / p-Value [c]**
Complete resolution of anterior chamber cells and flare at Visit 5 (Postoperative Day 8) [a]						
Yes	48 (23.9%)	27 (13.6%)	10.3% (2.2%, 18.4%)	64 (31.5%)	23 (11.4%)	20.1% (11.9%, 28.4%)
No	153 (76.1%)	172 (86.4%)		139 (68.5%)	179 (88.6%)	
Subjects without Rescue Medication Use	139	109	0.0082/0.0022	114	108	< 0.0001/ < 0.0001
Subjects with Rescue Medication Use	12	59		23	70	
Subjects with Missing Data	2	4		2	1	
Grade 0 (no) pain at Visit 5 (Postoperative Day 8) [a]						
Yes	156 (77.6%)	90 (45.2%)	32.4% (22.9%, 41.9%)	149 (73.4%)	83 (41.1%)	32.3% (22.7%, 41.9%)
No	45 (22.4%)	109 (54.8%)		54 (26.6%)	119 (58.9%)	
Subjects without Rescue Medication Use	31	46	< 0.0001/ < 0.0001	29	48	< 0.0001/ < 0.0001
Subjects with Rescue Medication Use	12	59		23	70	
Subjects with Missing Data	2	4		2	1	

[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/Cochran Mantel-Haenszel (CMH) controlling for site, and the Pearson value was the primary outcome. Grade 0 (no) pain was only tested if complete resolution of cells and flare were significant (at 0.05 level for Pearson Chi-squared).

In the two studies, Lotemax® Ointment had statistically significant higher incidence of complete clearing of anterior chamber cells and flare at post-operative day 8 (24-32% vs. 11-14%) and also had a statistically significant higher incidence of subjects that were pain free at post-operative day 8 (73-78% vs. 41-45%).

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® Ointment was superior to vehicle in the treatment of postoperative inflammation as judged by the complete resolution of anterior chamber cells and flare at post-operative day 8 (Visit 5). Additionally, Lotemax® Ointment was superior to vehicle in the treatment of pain as judged by Grade 0 (no) pain at post-operative day 8. Both tests of the primary efficacy endpoints proved successful in the intent-to-treat (ITT) and per protocol (PP) populations at post-operative day 8 (Visit 5)

(subjects with missing values and subjects requiring rescue medication were considered treatment failures).

Table 5 - Primary Efficacy Analysis, Integrated ITT Population

	LE Ointment (N = 404)	Vehicle (N = 401)	Difference (95% CI) [b] / p-Value [c]
Complete resolution of anterior chamber cells and flare at Visit 5 (Postoperative Day 8) [a]			
Yes	112 (27.7%)	50 (12.5%)	15.3%
No	292 (72.3%)	351 (87.5%)	(9.6%, 20.9%)
Subjects without Rescue Medication Use	253	217	<0.0001/<0.0001
Subjects with Rescue Medication Use	35	129	
Subjects with Missing Data	4	5	
Grade 0 (no) pain at Visit 5 (Postoperative Day 8) [a]			
Yes	305 (75.5%)	173 (43.1%)	32.4%
No	99 (24.5%)	228 (56.9%)	(25.7%, 39.0%)
Subjects without Rescue Medication Use	60	94	<0.0001/<0.0001
Subjects with Rescue Medication Use	35	129	
Subjects with Missing Data	4	5	

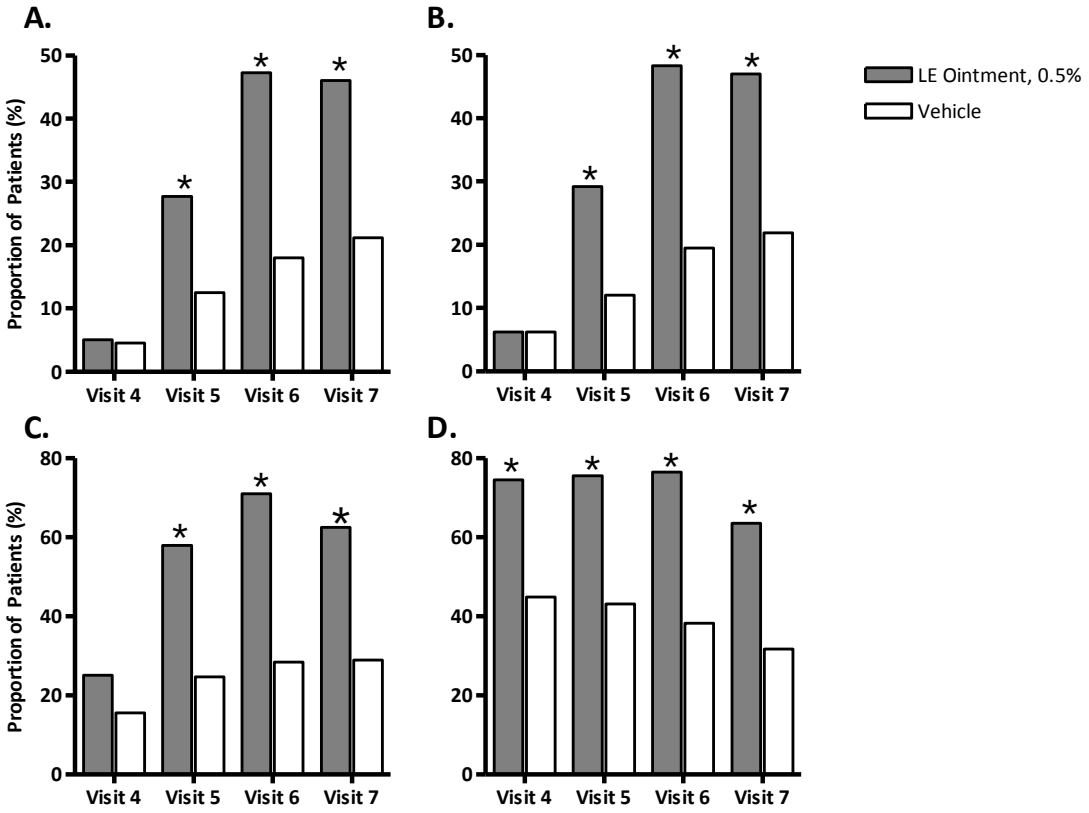
[a] Subjects who had missing data or took rescue medication prior to post-operative day 8 (Visit 5) were imputed as 'No'.

[b] Difference in percentages; 95% CI based on asymptotic normal approximations.

[c] p-Values from Pearson chi-squared statistic/Cochran Mantel-Haenszel (CMH) controlling for site, and the Pearson value was the primary outcome. Grade 0 (no) pain was only tested if complete resolution of cells and flare were significant (at 0.05 level for Pearson Chi-squared).

Results of the secondary outcome measures were in agreement with primary outcome measures. Significantly more patients randomized to Lotemax® Ointment compared with patients randomized to vehicle had complete resolution of anterior chamber inflammation and anterior chamber cells at post-oparatve days 8-18 (Visits 5-7); and anterior chamber flare as well as no (Grade 0) pain at post-operative days 3-18 (Visits 4-7) (Figure 1). Baseline mean (SD) anterior chamber inflammation severity was 3.7 (0.75) and 3.7 (0.82) in the Lotemax® Ointment and vehicle treatment groups, respectively. Mean change from baseline anterior chamber inflammation showed an improvement in both groups with a mean (SD) change of -1.1 (1.14), -2.2 (1.41), -2.6 (1.48) and -2.6 (1.52) for the LE Ointment group and a mean change of -0.5 (1.45), -0.7 (1.81), -1.0 (1.95) and -1.1 (1.98) for the vehicle group at post-operative days 3-18 (Visits 4-7), respectively. Mean changes were consistently and significantly lower in the Lotemax® Ointment treatment group at each of these visits ($P < 0.0001$).

Figure 1 – Proportion of patients with complete resolution of anterior chamber inflammation: A), complete resolution of anterior chamber cells; B), complete resolution of anterior chamber flare; C), and no (Grade 0) pain; D) at each study visit.



Notes: Visit 4 = post-operative day 3 (±1 day); visit 5 = post-operative day 8 (±1 day); visit 6 = post-operative day 15 (±1 day); visit 7 = post-operative day 18 (±1 day). *P < 0.0001

Tolerability of the study medications was judged from assessment of ocular symptoms at baseline and at each visit. At baseline post-operative day 1 (visit 3), less than 5% of subjects had symptoms of ocular discharge, dryness, or itching. The proportion of subjects with these symptoms and their change from baseline at postoperative days 3-18 (visits 4–7) were similar between treatment groups, with the exception of ocular discharge at post-operative day 18 (Visit 7), which favoured vehicle (4.8% versus 0.7%; *P* = 0.0306), and dryness at post-operative day 8 (visit 5), which favoured Lotemax® Ointment (13.7% versus 20.6%, *P* = 0.0213). Of the subjects who had discharge at post-operative day 18 (visit 7), all had mild discharge, and all but one either had discharge that was resolved previously and reported again or had discharge reported for the first time at post-operative day 18 (visit 7). The proportions of patients in the Lotemax® Ointment group and vehicle group with ocular pain, photophobia, and tearing at baseline were 44.1% versus 46.6%, 57.9% versus 55.9%, and 37.1% versus 35.7%, respectively. There were fewer subjects in the Lotemax® Ointment group compared with the vehicle group having pain at post-operative day 3 (visit 4) (24.9% versus 54.5%) and post-operative day 8

(visit 5) (16.4% versus 35.2%), and ocular pain either improved or did not change from baseline for 92.0% versus 66.2% of subjects, respectively, at post-operative day 3 (visit 4) and for 91.0% versus 78.7% of subjects, respectively, at post-operative day 8 (visit 5) ($P < 0.0001$ for all). Likewise, there were fewer subjects in the Lotemax® Ointment group compared to vehicle group with photophobia at post-operative day3 (Visit 4) (45.6% versus 64.9%) and post-operative day 8 (Visit 5) (40.0% versus 58.8%) and tearing at post-operative day 3 (Visit 4) (22.9% versus 34.6%) and post-operative day 8 (Visit 5) (16.4% versus 25.1%, $P < 0.01$ for all). Photophobia either improved or did not change from baseline for 88.5% versus 70.7% of subjects at post-operative day 3 (Visit) 4 and for 86.3% versus 71.2% of subjects at post-operative day 8 (Visit 5) ($P < 0.0001$ for both), while tearing improved or did not change from baseline in 91.8% versus 82.8% of subjects at post-operative day 3 (Visit 4) ($P = 0.003$) and for 92.1% versus 89.9 % at post-operative day 8 (Visit 5) ($P = 0.0287$) in the Lotemax® Ointment and vehicle groups, respectively. At post-operative day 15 (Visit 6), there was a significant difference in the proportion of eyes with stable or improved photophobia (90.8% versus 84.2%, respectively, $P = 0.0157$) but no difference in the presence of photophobia. Post-operative day 15 (Visit 6) tearing rate was significantly lower in the Lotemax® Ointment group when controlling for study centre ($P = 0.1216/0.0482$; Pearson/Cochran-Mantel-Haenszel).

Fewer subjects in the Lotemax® Ointmentgroup compared to vehicle group required rescue medication (27.7% versus 63.8%); and fewer had an ocular adverse event (47.2% versus 78.0%; $P < 0.0001$) while on study treatment. The most common ocular adverse events with Lotemax® Ointment were anterior chamber inflammation, photophobia, corneal edema, conjunctival hyperemia, eye pain, and iritis. Mean Intraocular Pressure (IOP) decreased in both treatment groups. Four patients had increased IOP ≥ 10 mm Hg (3 LE Ointment; 1 vehicle) prior to rescue medication. Visual acuity and dilated fundoscopy results were similar between treatment groups with the exception of visual acuity at post-operative days 8 and 15 (visits 5 and 6), which favoured Lotemax® Ointment. **See Clinical Trial Adverse Drug Reactions**

DETAILED PHARMACOLOGY

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.

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

Wound Healing and Scar Formation: The effect of LE on the wound healing and scarring process was assessed in several *in vivo* and *in vitro* studies. In rabbits, treatment (2 drops, TID for 15 days, single eye) of full-thickness corneal wounds with LE (0.1%) or dexamethasone (0.1%) resulted in decreased scar formation, inhibition of inflammatory cell infiltration, and inhibition of fibroblast proliferation compared with untreated eyes. The effect was most prominent after day 7, during the time when collagen deposition was evident in untreated eyes. A separate study examined the effect of LE on the corneal wound healing process in rabbits following corneal incision. BID treatment with LE (1%) or prednisolone (1%) for 9 days (17 doses) resulted in a significant decrease in the tensile strength of the resulting scar, which was less than that observed with dexamethasone (0.1%).

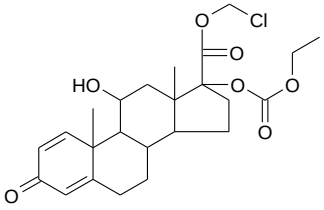
Intra-ocular Pressure: Topical ocular treatment of normotensive rabbits with LE (0.1%, 1 dose per hour for 7 hours on two consecutive days) did not result in a sustained rise in IOP during the 55-hr interval following the first administration. In contrast, treatment with dexamethasone (0.1%) with the same dosing regimen produced a statistically significant rise (3-5 mmHg) in IOP, which persisted for 48 hours after the initial dose.

Skin Atrophy and Thymus Changes: The potential effect of LE on skin atrophy and thymus changes were evaluated in rats following topical (dermal) administration at LE doses of 200 mg/rat/day for 14 days or 400 mg/rat/day for 7 days. Both hydrocortisone-17-butyrate and betamethasone-17-valerate caused decreased skin weight and/or skin thickness, as well as a significant decrease in thymus weight. In contrast, LE treatment resulted in a significant decrease in skin weight, but did not affect thymus weight in this study.

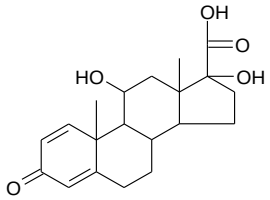
Pharmacokinetics

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

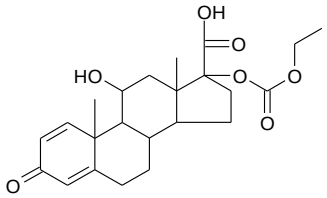
Chemical Structure of Loteprednol Etabonate, PJ-90, and PJ-91



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 effect of concomitant administration of Lotemax® Ointment 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
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® Ointmetnt 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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1. Comstock TL, Paterno MR, Singh A, Erb T, Davis E. Safety and efficacy of loteprednol etabonate ophthalmic ointment 0.5% for the treatment of inflammation and pain following cataract surgery. *Clin Ophthalmol*. 2011;5:177-186. Epub 2011 Feb 10. (Study #525 and #526)

PART III: CONSUMER INFORMATION

[Pr]Lotemax® Ointment
(loteprednol etabonate ophthalmic ointment 0.5% w/w)

This leaflet is part III of a three-part "Product Monograph" published when Lotemax® Ointment 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® Ointment. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

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

What it does:
Lotemax® Ointment 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® Ointment:

- **If you are allergic to loteprednol or any of the ingredients contained in Lotemax® Ointment (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 gram contains 5 mg (0.5% w/w) loteprednol etabonate.

What the important nonmedicinal ingredients are:
Mineral Oil, White Petrolatum.

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

WARNINGS AND PRECAUTIONS

BEFORE you use Lotemax® Ointment 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® Ointment 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® Ointment, consult your doctor**
- **If you are pregnant or planning to become pregnant. Lotemax® Ointment 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® Ointment 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® Ointment:

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

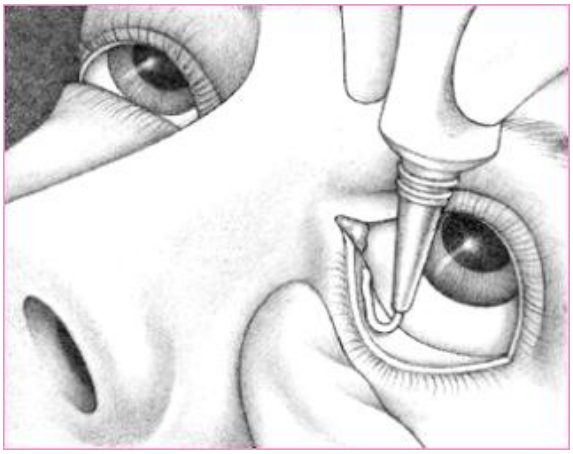
INTERACTIONS WITH THIS MEDICATION

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

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.
Apply a small amount (about½ inch ribbon) into the conjunctival sac(s) (see pictogram) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.



- Do not touch the eyelid or surrounding areas with the tip of the tube. The cap should remain on the tube when not in use.
- Wash hands prior to using Lotemax® Ointment.
- 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, 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 ointment 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® Ointment can have unwanted effects. The most common side effects in patients treated with Lotemax® Ointment 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, cold, cough, runny nose, or drug sensitivity.

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® Ointment, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15-25ºC (59-77ºF) for up to 14 days after first opening, then discard the tube.

KEEP OUT OF REACH 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

This leaflet was prepared by Bausch & Lomb Incorporated.

Last revised: March 14, 2014.