

PRODUCT MONOGRAPH

Pr Alex[®]

(loteprednol etabonate ophthalmic suspension 0.2% w/v)

Corticosteroid

Professed Standard

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Pr **Alrex[®]**

(loteprednol etabonate ophthalmic suspension 0.2% w/v)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Suspension, 0.2% w/v	Benzalkonium Chloride <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Alrex[®] (loteprednol etabonate) Ophthalmic Suspension is indicated for:

- temporary short-term relief of the signs and symptoms of seasonal allergic conjunctivitis

Pediatrics (< 18 years of age):

Alrex[®] should not be used in pediatric patients. The safety and efficacy of Alrex[®] have not been studied in pediatric patients.

Geriatrics (> 65 years of age):

Alrex[®] should not be used in geriatric patients. The safety and efficacy of Alrex[®] have not been established in patients > 65 years of age.

CONTRAINDICATIONS

- Suspected or confirmed infection of the eye: viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella; untreated ocular infection of the eye; mycobacterial infection of the eye and fungal diseases of ocular structures.
- Hypersensitivity to this drug or any ingredient in the formulation or container, or to other corticosteroids. For a complete listing, see the Dosage Forms, Composition and Packaging section.

WARNINGS AND PRECAUTIONS

General

For ophthalmic use only.

Alrex[®] is indicated as a short-term treatment only (up to 14 days). The initial prescription and renewal of Alrex[®] should be made by a prescribing 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 Alrex[®] 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. Alrex[®] 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**.

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

Alrex[®] contains benzalkonium chloride. See **DOSAGE and ADMINISTRATION section**.

Alrex[®] has not been studied in pregnant or nursing women, but has been found to be teratogenic in animals. Alrex[®] should not be used in pregnant or nursing women unless the benefits to the mother clearly outweigh the risk to the foetus 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**.

Ophthalmologic

Alrex[®] should be used as a brief temporary treatment. If Alrex[®] is used for 10 days or longer, intraocular pressure should be closely monitored. The initial prescription and renewal of Alrex[®] should be made by a prescribing 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.

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Alrex[®] 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.

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

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

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

Formulations with benzalkonium chloride should be used with caution in soft contact lens wearer. See **DOSAGE AND ADMINISTRATION – Administration**.

Sexual Function/Reproduction

The effects of Alrex[®] on sexual function and reproduction have not been studied in humans. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively (1000 and 500 times the Alrex[®] 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 females to become pregnant). However, these doses were highly toxic and had significant toxic effects on the pregnancies, and the survival and development of the offspring. Maternal toxicity, possible occurrence of abnormalities and growth retardation started at 10 times the Alrex[®] clinical dose. See **WARNINGS and PRECAUTIONS- Special Populations- Pregnant Women**.

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 Alrex[®] as directed, these possible effects are not likely. See **ACTION and CLINICAL PHARMACOLOGY**.

Endocrine and Metabolism

Glucocorticoids, mostly when systemic exposure occurs, decrease the hypoglycemic activity of insulin and oral hypoglycemics, so that a change in dose of the anti-diabetic drugs may 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 Alrex[®] 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, cicatrization.

Special Populations

Pregnant Women:

Alrex[®] should not be used in pregnant women, unless the benefit to the mother clearly outweighs the risks to the foetus. Studies in pregnant women have not been conducted. However, studies in animals have shown major reproductive and developmental toxicity when administered orally at ~100 times the Alrex[®] clinical dose. At lower doses (10 times the Alrex[®] 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 Toxicology**

Nursing Women:

Alrex[®] should not be used in lactating women, unless the 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:

Alrex[®] should not be used in pediatric patients. The safety and efficacy of Alrex[®] have not been studied in pediatric patients.

Geriatrics (> 65 years of age):

Alrex[®] should not be used in geriatric patients. The safety and efficacy of Alrex[®] have not been established in patients > 65 years of age.

Monitoring and Laboratory Tests

If Alrex[®] 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 nineteen clinical trials ranging from 1 to 42 days in length, 1,209 patients received various concentrations of loteprednol etabonate in topical ocular drops (0.005%, 0.05%, 0.1%, 0.2%, 0.5%). Adverse events related to loteprednol etabonate 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 increased IOP: 6% (77/1209) in patients receiving loteprednol etabonate, as compared to 3% (25/806) in the placebo treated patients.

With the exception of elevations in IOP, the incidence of events in the LE group was similar to, or less than that of the placebo control groups. Itching was reported as related to therapy in 3% of the loteprednol treated eyes, injection, epiphora, burning/stinging other than at instillation, foreign body sensation, and burning/stinging at instillation were each reported for 2% of eyes. The most frequent non-ocular event reported as related to therapy was headache, reported for 1.2% of the loteprednol treated subjects and 0.6% of the placebo treated subjects.

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 III studies were designed to assess the safety and efficacy of Alex[®] in Seasonal Allergic Conjunctivitis (SAC). Both studies were randomized, double-masked, placebo controlled, multi-centre (3 and 4) parallel group studies. Patients with an IOP \leq 21 mm Hg and no glaucoma were enrolled in study A (N=133) and study B (N=135). During these studies, 133 patients were exposed to Alex[®].^{1,2}

Possibly or probably related adverse events are listed below.

	Alrex[®] 0.2%, N=133	Placebo, N = 135
Special senses (Eye disorders)		
Intraocular Pressure elevation of 6 to 9 mmHg*	2% to 12%*	0% to 6%*
elevation of ≥ 10 mmHg	1 (1%)	1 (1%)
Chemosis	6 (5%)	7 (5%)
Vision, Abnormal or Blurred	4 (3%)	5 (4%)
Burning/Stinging On instillation	3 (2%)	6 (4%)
Itching, Eye	3 (2%)	3 (2%)
Dry Eyes	2 (2%)	4 (3%)
Burning/Stinging, not on instillation	2 (2%)	2 (1%)
Epiphora	1 (1%)	9 (7%)
Discharge	1 (1%)	3 (2%)
Foreign Body Sensation	1 (1%)	1 (1%)
Discomfort, eye	1 (1%)	0 (0%)
Injection	1 (1%)	0 (0%)
Eye Pain	1 (1%)	0 (0%)
Sticky Eye	0 (0%)	7 (5%)
Erythema, Eyelids	0 (0%)	2 (1%)
Eye Disorder	0 (0%)	2 (1%)
Body As A Whole		
Face Edema (Head)	1 (1%)	0 (0%)
Allergic Reaction	1 (1%)	0 (0%)
Musculoskeletal System		
Twitching	0 (0%)	1 (1%)

*: for IOP increase of 6 to 9 mm Hg, please see below

One patient in the Alrex[®] group and one patient in the placebo group experienced increases in IOP of ≥ 10 mm Hg. Among these, one in each group had an IOP increase of ≥ 15 mm Hg, reaching IOP values over 30 mm Hg.

In both studies, there were more patients with IOP increases of 6 to 9 mm Hg in the Alrex[®] group than in the placebo group (see table below). In study A, among the patients with IOP increases of 6 to 9 mm Hg, four reached an IOP value of 22 to 23 mm Hg, and one patient reached 29 mm Hg and was discontinued (clinically significant increase in IOP). All these five patients were from the Alrex[®] groups.

Incidence of IOP increases of 6 to 9 mm Hg from baseline
(number of patients and percentages)

	Duration of treatment		
	Day 7	Day 14	Day 28
Alrex[®]			
Study-A	6(9%)	6(9%)	8(12%)
Study-B	3(5%)	1(2%)	4 (6%)
Placebo			
Study-A	0(0%)	4(6%)	1(2%)
Study-B	0(%)	0(%)	0(%)

Due to the sample size for each arm of the two phase III studies in SAC, all events captured are greater than 1% of n.

Adverse Reactions reported in other controlled randomized trials

In nineteen clinical trials ranging from 1 to 42 days in length, 1,209 patients received various concentrations of loteprednol etabonate in topical ocular drops (0.005%, 0.05%, 0.1%, 0.2%, 0.5%), the most frequent ocular event reported as related to therapy was increased intraocular pressure: 6% (77/1209) in patients receiving loteprednol etabonate, as compared to 3% (25/806) in the placebo population.

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

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

In a summary of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥ 10 mmHg) was 2% (15/901) among patients receiving loteprednol etabonate and 0.5% (3/583) among patients receiving placebo.

Post-Market Adverse Drug Reactions

In over a decade of post-marketing experience, more than 8 million units of Alex[®] have been shipped globally. During that time four (4) adverse event reports that qualified as serious were received. The table below summarizes these events.

Alex[®] Serious Adverse Events Since 1998		
Sex	Age	Event
M	12	Corneal perforation
M	58	Corneal disorder, Intraocular pressure increased
F	60	Visual field defect, Glaucoma
M	74	Corneal ulcer, Keratitis bacterial, Drug maladministration

One case of mild cataract has been reported during this time.

DRUG INTERACTIONS

Overview

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

Alex[®] contains benzalkonium chloride which interacts with soft contact lens. See **DOSAGE AND ADMINISTRATION - Administration.**

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

One drop instilled into the affected eye(s) four times daily for up to 14 days.

Missed Dose

If scheduled dose is missed, patient should be advised to wait until the next dose and then continue as before.

Administration

SHAKE VIGOROUSLY BEFORE USING. Instill one drop into the affected eye(s) four times daily.

Alex[®] should be stored upright between 15°–25°C for up to 28 days after first opening.

The preservative in Alrex[®], benzalkonium chloride, may be absorbed by soft contact lenses, and can discolour soft contact lenses. Therefore, Alrex[®] should not be used while the patient is wearing soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red should wait ten to fifteen minutes after instilling Alrex[®] before they insert their contact lenses.

Patients should be advised not to wear a contact lens if their eye is red. Alrex[®] should not be used to treat contact lens related irritation.

OVERDOSAGE

For management of suspected accidental oral ingestion or drug overdose, consult your regional poison control centre.

No cases of overdose have been reported.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂. Corticosteroids are capable of producing a rise in intraocular pressure.

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

Results from a bioavailability study in normal volunteers (8 females, 2 males; age range of 19-44 years) established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times.³ The results were obtained following the ocular administration of one drop of 0.5% loteprednol etabonate ophthalmic suspension in each eye 8 times daily for 2 days or 4 times daily for 42 days.

STORAGE AND STABILITY

Store upright between 15°–25°C (59°–77°F). DO NOT FREEZE.
KEEP OUT OF REACH OF CHILDREN.

SPECIAL HANDLING INSTRUCTIONS

There is no special handling instruction for Alex[®].

DOSAGE FORMS, COMPOSITION AND PACKAGING

Alex[®] (loteprednol etabonate ophthalmic suspension 0.2% w/v) is supplied in a white low density polyethylene plastic bottle with a white controlled drop tip and a pink polypropylene cap in the following sizes:

5 mL in a 7.5 mL bottle

Nonmedicinal ingredients are as follows: benzalkonium chloride, edetate disodium, glycerin, povidone, purified water and tyloxapol.

Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.4-5.5.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

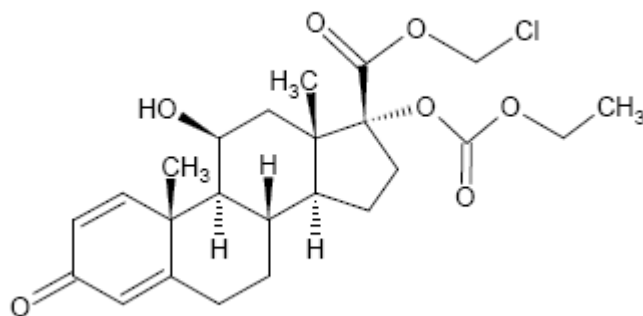
Drug Substance

Proper name: loteprednol etabonate

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

Molecular formula and molecular mass: C₂₄H₃₁ClO₇ Mol. Wt. 466.96

Loteprednol Etabonate formula:



Physicochemical properties: Loteprednol etabonate is a white to off-white powder. Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg. The pH is adjusted to 5.4-5.5.

CLINICAL TRIALS

Study demographics and trial design

Two phase III studies were designed to assess the safety and efficacy of Alex[®] in the treatment of the signs and symptoms of Seasonal Allergic Conjunctivitis (SAC).^{1,2} Both studies were randomized, double-masked, placebo-controlled, multi-centre (3 and 4) parallel group studies. One hundred thirty three (133) patients with an IOP \leq 21 mm Hg and no glaucoma were enrolled in study A and 135 in study B. All had a positive skin

test or conjunctival injection at the time of enrolment. Patients were instructed to instill one drop into each eye four times daily for six weeks. Follow-up examinations occurred on Days 2 or 3, 7, 14, 28 and 42.

Daily pollen counts were recorded for each of the cities where the study sites were located. The active pollen season was defined *a priori* in the study protocol as the period when pollen counts were consistently greater than 100/m³. For the efficacy analysis, no visits within the first two weeks were disqualified. For Visits 5 and 6 (four and six weeks) only visits which met the pollen count criterion were used in the intent-to-treat analysis.

The primary outcome measures consisted of one sign (bulbar conjunctival injection) and one symptom (itching) and the primary analysis was a repeated measures analysis of change from baseline over the first 2 weeks (Visits 2, 3 and 4). The secondary analysis was a repeated measures analysis of change from baseline following the first dose (Visit 1, Hour 1 and Hour 2). The secondary outcome measure was the Investigator Global Assessment of the adequacy of treatment. A supportive analysis of treatment group difference was carried out for each visit. Itching was rated on a scale of 0 – 4 and bulbar conjunctival injection on a scale of 0 – 3. Other signs and symptoms were evaluated using scales of 0 – 3 at all visits and were analyzed as supportive outcome measures.

Summary of patient demographics for clinical trials in Seasonal Allergic Conjunctivitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range) yrs	Gender
A	Double-masked, placebo-controlled, parallel, multicenter	LE 0.2% vs. Placebo, ophthalmic QID for up to 42 days	133 (66 LE, 67 placebo)	41(20 – 73)	65M/68F
B	Double-masked, placebo-controlled, parallel, multicenter	LE 0.2% vs. Placebo, ophthalmic QID for up to 42 days	135 (67 LE, 68 placebo)	39(19 - 74)	62M/73F

Study results

In both studies, Alex[®] was significantly better than placebo in the reduction of itching and bulbar injection (primary efficacy over the first two weeks), and of secondary parameters and some of the supportive outcome measures. The results of the two studies were consistent.

For the primary outcome measures, bulbar injection and itching, patients from the intent to treat population were included in the analysis. The overall change from baseline for the first two weeks was analyzed by repeated measures analysis of covariance over Visit 2 (Day 2/3), Visit 3 (Day 7) and Visit 4 (Day 14). Estimates of the overall mean change from baseline and treatment effect were generated in the analysis.

Cure rate was defined as the proportion of patients with sign or symptom no longer present.

Results of studies in Seasonal Allergic Conjunctivitis

Primary efficacy measures - primary analysis : first two weeks

	Mean score ¹ change from baseline		Treatment effect ²		Cure rate ³	
	Alrex [®]	Placebo		<i>p</i>	Alrex [®]	Placebo
Study A						
Bulbar Injection	-1.32	-0.79	-0.54 (-0.71, -0.37)	< 0.001	31%	9%
Itching	-3.36	-2.72	-0.62 (-0.86, -0.37)	< 0.001	54%	38%
Study B						
Bulbar Injection	-1.41	-0.89	-0.52 (-0.67, -0.38)	< 0.001	36%	15%
Itching	-3.03	-2.63	-0.40 (-0.69, -0.11)	0.008	58%	38%

Secondary analysis – first two hours

	Mean score ¹ change from baseline		Treatment effect ²	
	Alrex [®]	Placebo		<i>p</i>
Study A				
Bulbar Injection	-0.78	-0.38	-0.40 (-0.56, -0.24)	< 0.001
Itching	-2.81	-2.78	-0.02 (-0.29, +0.24)	0.861
Study B				
Bulbar Injection	-0.66	-0.38	-0.29 (-0.43, -0.14)	<0.001
Itching	-2.44	-2.53	+0.09 (-0.23, +0.40)	0.592

¹ Score for bulbar injection was 0 (absent) to 3 (severe), score for itching was 0 (absent) to 4 (severe)

² LE - Placebo: Difference in score change (95% confidence limits) over two weeks; negative numbers indicate LE favoured over placebo

³ Cure rate is defined as the proportion of patients with the sign or symptom no longer present at visit-4 (day-14)

Alrex[®] was more effective than placebo in the reduction of signs and symptoms of seasonal allergic conjunctivitis as demonstrated by statistically significant differences in primary efficacy parameters (itching and bulbar injection). This treatment effect in favour of Alrex[®] over placebo started two hours following dosing for the reduction of bulbar injection, and two to three days after for the reduction of itching.

A strong placebo response was observed, nevertheless the results seen in primary and secondary outcomes and in some supportive outcome measures were statistically significant in the Alex[®] group compared with placebo. Alex[®] had an acceptable safety profile compared with placebo with one patient in each treatment group demonstrating an IOP elevation of ≥ 10 mmHg during the first 6 weeks of treatment. More patients treated with Alex[®] had increased IOP of 6 to 9 mmHg than patients in the placebo group.

DETAILED PHARMACOLOGY

Results from a competitive binding study 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 transcortin. In contrast, the LE metabolites, PJ-90 and PJ-91, did 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 were 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%).

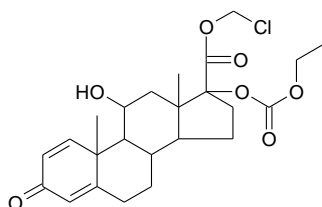
Intraocular Pressure: Topical ocular treatment of normotensive rabbits with LE (0.1%, 1 dose per hour for 7 hours on two consecutive days) did not result in a sustained rise in IOP during the 55-hr interval following the first administration. In contrast, treatment with dexamethasone (0.1%) with the 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.

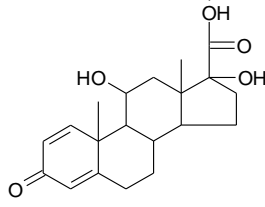
Pharmacokinetics

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

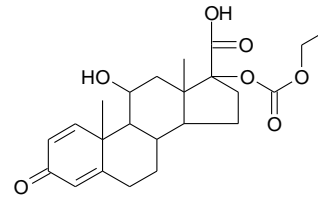
Chemical Structure of Loteprednol Etabonate, PJ-90, and PJ-91



Loteprednol Etabonate



PJ-90



PJ-91

Ocular Pharmacokinetics in Rabbits

The ocular pharmacokinetic properties of ¹⁴C-labeled LE (0.5%) were evaluated following topical ocular administration (3 drops per eye at 5-minute intervals) to New Zealand white rabbits. LE was absorbed into ocular tissues, and the presence of metabolites in these tissues suggests that LE is metabolized in ocular tissues following ocular dosing (see table below). Blood levels of LE and its metabolites were not detectable after topical ocular administration in this study.

Mean concentrations of LE and metabolites (nmoles/g) in ocular tissues following multiple topical ocular administration of [¹⁴C]LE to albino rabbits

Tissue	Analyte	Collection Time (hr)					
		0.5	1	2	4	6	8
Conjunctiva	LE	30.5	21.5	16.3	11.5	2.5	5.3
	M ^a	3.5	1.8	1.2	0.8	0.4	1.0
Cornea	LE	3.8	2.1	1.3	0.9	0.6	1.1
	M	4.9	4.1	3.2	2.2	1.8	2.2
Iris/Ciliary Body	LE	1.9	1.1	0.7	0.7	0.2	0.9
	M	0.4	0.3	0.2	0.3	0.1	0.2
Aqueous Humor	LE	0.027	0.016	0.007	0.003	0.002	0.002
	M	0.017	0.023	0.025	0.011	0.007	0.006

^a Metabolites. Includes all metabolites contained in aqueous phase following extraction of LE into organic solvent.

The administration of other concomitant ophthalmic drugs during the 30 min prior to or after LE 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/hr and a half-life of 2.8 hr. 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 [¹⁴C]LE (5 mg/kg), levels of [¹⁴C]LE in blood were relatively low and constant (20-33 ng/mL) throughout the 5-hr 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-hr 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-hr 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 ($\mu\text{g}\cdot\text{min}/\text{mL}$)	CL (mL/min/kg)	T _{1/2} (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; T_{1/2}: 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 $\mu\text{g}/\text{mL}$) and the metabolite, PJ-91 (5-15 $\mu\text{g}/\text{mL}$), was investigated *in vitro* in dog blood. LE was highly bound to plasma proteins (mean \pm 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

This section is not applicable.

TOXICOLOGY

Single-dose toxicity

Acute oral toxicity studies in rats and mice indicate that the MTD for loteprednol etabonate (=LE) is greater than or in the region of 4000 mg/kg bodyweight, which is ~81,000 and ~41,000 times the Alex[®] 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. Combinations of 0.5% LE ophthalmic suspension with sulfacetamide (10% w/v) or Tobramycin (0.3% w/v) were not toxic by the oral route in rats or mice at a dose volume of 20 mL/kg bodyweight and the MTD of the possible secondary metabolite of loteprednol etabonate, PJ-90, 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 dosage level 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. This suggests that the observed biochemical changes represent a hypertrophic effect consistent with the liver being a significant site of metabolism of LE, as indicated by the presence of high concentrations of both metabolites of LE in bile fluid. 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 study mainly occurred at the high dose level which represented a multiple in excess of ~1000 times the anticipated human dose of Alex[®], although some evidence of hepatotoxicity was also apparent at the intermediate dose level (≥ 100 times the anticipated human dose of Alex[®]). In the rabbit study, hepatic effects were restricted to the high dosage group (i.e., ~100 times the equivalent human dose of Alex[®]). The low dose (0.5 mg/kg/day) in rats, which exceeded 10 times the equivalent human dose of Alex[®], was a no effect level. In rabbits, no significant toxicity was noted at the 0.7% dose, which is equivalent to ~ 14 times the human dose of Alex[®]. Complete systemic absorption of LE to the blood following Alex[®] 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 μ L) 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 ~12 times the Alex[®] human dose.

In a one-year study, dogs received 6 drops daily of dexamethasone 0.1%, LE 0.1%, or 0.5% - the latter high dose represents five times the human dose of Alex[®]. 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. On the other hand, the number of animals with IOP increase (≥ 5 mmHg) among those treated with dexamethasone 0.1% was larger and increased with time, and by week-52, almost all dogs treated with dexamethasone 0.1% experienced IOP increase. Also, in contrast to the LE groups, dogs treated with dexamethasone 0.1% 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 animal treated for 6 months with the equivalent of ~ 18 times the intended Alex[®] human dose.

Genotoxicity

Within the limitations imposed by the relative insolubility of LE, no evidence of mutagenic potential was apparent in the four *in vitro* tests conducted. 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 ~41,000 times the Alex[®] clinical dose.

Developmental and reproductive toxicology

In the fertility and general reproductive study in rats clear evidence of parental (F₀ 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 ~100 times the Alex[®] 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 F₁ generation foetuses and pups produced from F₀ animals of the intermediate and high dosage groups. With the exception of slight growth retardation, pups of F₀ parents receiving the low dose level (0.5 mg/kg/day) were unaffected by parental treatment (i.e., ~10 times the Alex[®] clinical dose). The mating performance of the F₁ generation and the F₂ generation was unaffected by F₀ treatment.

Maternal toxicity was demonstrated in the rabbit embryotoxicity study at 3 mg/kg/day LE (i.e., equivalent to ~120 times the Alex[®] 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 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 ~20 times the Alex[®] 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 ~100 times the Alex[®] 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 10 times the Alex[®] 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 test⁴ 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 ALREX[®]**

(loteprednol etabonate ophthalmic suspension 0.2% w/v)

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

ABOUT THIS MEDICATION**What the medication is used for:**

Alex[®] is used for the short-term relief of signs and symptoms (itching and redness in the eye) of seasonal allergic conjunctivitis due to pollens.

What it does:

Loteprednol etabonate is a corticosteroid. It acts by reducing inflammation and eases the symptoms (itching and redness) of allergic conjunctivitis due to pollens.

When it should not be used:**Do not use Alex[®]:**

- If you are allergic to loteprednol or any ingredient contained in Alex[®] (see What the nonmedicinal ingredients are), or if you are allergic to any other corticosteroid.
- If you have eye diseases 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 are pregnant, breastfeeding, under 18 years of age or have had glaucoma or increased pressure in the eye, see Warnings and Precautions.

What the medicinal ingredient is:

The medicinal ingredient is loteprednol etabonate. Each mL contains 2 mg (0.2% w/v) loteprednol etabonate

What the important nonmedicinal ingredients are:

Benzalkonium Chloride (0.01% w/v) as preservative.

Edetate Disodium, Glycerin, Povidone, Purified Water and Tyloxapol. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH.

What dosage forms it comes in:

Sterile ophthalmic suspension (eye drops) 0.2% w/v

WARNINGS AND PRECAUTIONS

BEFORE you use Alex[®] talk to your doctor or pharmacist if:

- Alex[®] should not be used if you are pregnant, breastfeeding or under 18 years of age.
- If you are pregnant or intend to become pregnant, or if you are breastfeeding as there might be a risk of harm to the embryo/foetus or nursing baby.
- If you have an eye disease/infection caused by viruses (such as herpes simplex, vaccinia, and varicella), or by bacteria or a fungus, or if you think you have any other eye infection.
- If you have glaucoma or have been told that you have increased pressure in the eye as Alex[®] 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. Your doctor may also check your lens as there is a small risk Alex[®] might induce cataract formation.
- If signs and symptoms fail to improve after two days of using Alex[®], consult your doctor.

Consult your doctor if the following occurs while taking Alex[®]:

- If you develop an eye infection or other new or worsening symptoms

The preservative in Alex[®], benzalkonium chloride, may be absorbed by soft contact lenses. After instilling Alex[®], you must wait at least 10 to 15 minutes before inserting your contact lenses. Do not wear a contact lens if your eye is red. Alex[®] should not be used to treat contact lens irritation.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Alex[®] include: medicines taken to control the ocular pressure. 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

This product is sterile when packaged.

For ophthalmic use only.

Usual dose:

For Adults only.

Do not use Alex[®] in children, or if you are pregnant or breastfeeding.

- Shake Alex[®] eye drops vigorously before using.
- Apply one drop of Alex[®] eye drops into the gap between your eyeball and eyelid, four times a day or as directed.
- You will only use Alex[®] for a short period of time, usually not more than two weeks, unless specifically instructed by your

doctor. Your doctor will tell you how long your treatment will last.

- If redness or itching become aggravated or if signs and symptoms fail to improve after two days, consult your doctor.
- Do not allow the tip of the dropper to touch any surface because this may contaminate the medicine.
- If you wear soft contact lenses, after instilling Alex[®], you must wait at least 10 to 15 minutes before inserting your contact lenses.
- If you are using another medicine in the eye, wait at least 10 minutes before applying.
- Alex should be stored upright between 15°–25°C for up to 28 days after first opening.

Overdose:

If you use more Alex[®] than you should, or there is accidental oral ingestion, you should immediately contact your doctor, or regional poison control centre.

Missed Dose:

If you forget to use Alex[®] eye drops, wait until the next dose and then continue as before. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Eye drops 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, Alex[®] can have unwanted effects. The most common side effects in patients treated with Alex[®] are:

- Increased pressure within the eye
- Blurred or abnormal vision
- Floaters in the eye
- Burning when putting drops in the eye or at any time while on the medication
- 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)

Other unwanted effects might include:

- Headache or migraine, cough or sore throat, runny nose, fatigue, nervousness, facial swelling, general pain, or rash.

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

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

HOW TO STORE IT

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

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345

By toll-free fax: 866-678-6789

Online: www.healthcanada.gc.ca/medeffect

By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:

Canada Vigilance National Office

**Marketed Health Products Safety and Effectiveness
Information Bureau**

Marketed Health Products Directorate

Health Products and Food Branch

Health Canada

Tunney's Pasture, AL 0701C

Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. 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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