powder.

Loteprednol etabonate is represented by the following structural formula:



C24H31CIO7

Mol. Wt. 466.96

Chemical name:

Chloromethyl  $17\alpha$ -[(ethoxycarbonyi)oxy]-11 $\beta$ -hydroxy-3-oxoandrosta-1,4-diene-17 $\beta$ -carboxylate.

Each mL contains: ACTIVE: Loteprednol Etabonate 2 mg (0.2%);

INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water, and Tyloxapol. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.3 - 5.6. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg. PRESERVATIVE ADDED: Benzalkonium Chloride 0.01%.

### CLINICAL PHARMACOLOGY:

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A<sub>2</sub> 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 A<sub>2</sub>. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes

\\BLPLM1\VOL2\RA\7114\LEA\353INSmar98.rtf Revised: 03/06/98

DOCKE

RM

Page 1 of 5

in the treatment of the signs and symptoms of seasonal allergic conjunctivitis. ALREX provided reduction in bulbar conjunctival injection and itching, beginning approximately 2 hours after instillation of the first dose and throughout the first 14 days of treatment.

### **INDICATIONS AND USAGE:**

ALREX<sup>™</sup> Ophthalmic Suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

### **CONTRAINDICATIONS:**

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

### WARNINGS:

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

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

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

#### **PRECAUTIONS:**

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

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

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

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term

\\BLPLM1\VOL2\RA\7114\LEA\353INSmar98.rtf Revised: 03/06/98

Page 2 of 5



Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

they insert their contact lenses.

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

**Pregnancy:** Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (85 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (15 times the maximum daily clinical dose). Oral treatment of rats during organogenesis with 0.5 to 100 mg/kg/day resulted in embryotoxicity (increased post-implantation losses at 100 mg/kg/day, and decreased fetal body weight and skeletal ossification with  $\geq$ 50 mg/kg/day) and teratogenicity (absent innominate artery at  $\geq$ 5 mg/kg/day doses, and cleft palate and umbilical hernia at  $\geq$ 50 mg/kg/day). Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of  $\geq$ 5 mg/kg/day.

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

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

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

H:\RA\7114\LEA\353INSmar98.rtf Revised: 03/09/98

Page 3 of 5

Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

underlying ocular disease being studied.

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

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure ( $\geq$  10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo. Among the smaller group of patients who were studied with ALREX, the incidence of clinically significant increases in IOP ( $\geq$ 10 mm Hg) was 1% (1/133) with ALREX and 1% (1/135) with placebo.

### **DOSAGE AND ADMINISTRATION:**

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

### **HOW SUPPLIED:**

ALREX<sup>™</sup> (loteprednol etabonate ophthalmic suspension, 0.2%) is supplied in a plastic bottle with a controlled drop tip in the following sizes: 2.5 mL bottle (NDC 24208-353-25) - AB35304 5 mL bottle (NDC 24208-353-05) - AB35307 10 mL bottle (NDC 24208-353-10) - AB35309

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

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

KEEP OUT OF REACH OF CHILDREN.

Rx only

### Manufactured by:

Bausch & Lomb Pharmaceuticals, Inc., Tampa, Florida 33637 under Agreement with Pharmos Corporation. U.S. Patent No. 4,996,335 U.S. Patent No. 5,540,930

\\BLPLM1\VOL2\RA\7114\LEA\353INSmar98.rtf Revised: 03/06/98

Page 4 of 5



Find authenticated court documents without watermarks at docketalarm.com.

\\BLPLM1\VOL2\RA\7114\LEA\353INSmar98.rtf Revised: 03/06/98

• •

Page 5 of 5



Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

# DOCKET



## Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## **Real-Time Litigation Alerts**



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## **Advanced Docket Research**



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## **Analytics At Your Fingertips**



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

### API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

### LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

### **FINANCIAL INSTITUTIONS**

Litigation and bankruptcy checks for companies and debtors.

### **E-DISCOVERY AND LEGAL VENDORS**

Sync your system to PACER to automate legal marketing.

