Lotemax® (loteprednol etabonate ophthalmic suspension) contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use.

Loteprednol etabonate is represented by the following structural formula:

\[
\text{CLo}_2\text{H}_2\text{CO}_2\text{H} + \text{CH}_2\text{C(O)}\text{H}_3\text{CO}_2\text{H} \rightarrow \text{C}_2\text{H}_3\text{ClO}_3\text{H}_2\text{O} + \text{CO}_2
\]

Med. Wt. 466.96

Chemical Name:

chloremethyl 17α[(ethoxymethyl)oxy]-11β-Hydroxy-3-oxandrost-1,4-diene-17β-carboxylate

Each ml contains:

ACTIVE: Loteprednol Etabonate 5 mg (0.5%);

INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water and Tyloxapol. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsm/kg.

STEROID PREPARATIONS: Loteprednol etabonate is represented by the following structural formula:

\[
\text{C}_2\text{H}_3\text{ClO}_3\text{H}_2\text{O} + \text{CO}_2
\]

Med. Wt. 466.96

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 ketone in the molecule 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 extensive metabolism to inactive carboxylic acid metabolites. Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ1 corticosteroid acid etabonate (99:1), its primary, inactive metabolite, were below the limit of quantitation (1 ng/ml) at all sampling times. The results were obtained following the oral administration of a single dose in each eye of 0.5% loteprednol etabonate 5 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/ml) systemic absorption occurs with LOTEMAX.

Clinical Studies

Post-Operative Inflammation: Placebo-controlled clinical studies demonstrated that LOTEMAX is effective for the treatment of anterior chamber inflammation as measured by cell and flare.

Giant Papillary Conjunctivitis: Placebo-controlled clinical studies demonstrated that LOTEMAX was effective in reducing the signs and symptoms of giant papillary conjunctivitis after 1 week of treatment and continuing for up to 6 weeks while on treatment.

Seasonal Allergic Conjunctivitis: A placebo-controlled clinical study demonstrated that LOTEMAX was effective in reducing the signs and symptoms of allergic conjunctivitis during peak periods of pollen exposure.

Precautions

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, fluorescent fundus examination.

If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored even though it may be difficult in children and uncooperative patients (see PRECAUTIONS).

Information for Patients

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using LOTEMAX®.
Carcinogenesis, Mutagenesis, 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, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

Pregnancy

Teratogenic effects

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 (35 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 (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≤15 mg/kg/day doses, and cleft palate and umbilical hernia ≤30 mg/kg/day) and embryotoxicity (increased post-implantation losses at 150 mg/kg/day and decreased fetal body weight and skeletal ossification with ≤50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≤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 unknown 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 LOTEMAX is administered to a nursing woman.

Pediatric use

Safety and effectiveness in pediatric patients have not been established.

Adverse Reactions

Reactions associated with topical steroid therapy include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular adverse reactions occurring in 5%-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2%-0.5%) in clinical studies included abnormal visual/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, keratocongestions, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being treated.

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 (>10 mmHg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (1/16) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo.

In a summation of randomized, double-masked clinical studies of 30 days duration, adverse events were similar to the underlying ocular disease being studied.

Adverse reactions associated with ocular corticosteroids include increased intraocular pressure, which may be associated with optic nerve damage.

Post-Operative Inflammation

Adverse reactions associated with topical corticosteroids in the postoperative period include increased intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, cataract formation, secondary ocular infection, increased inflammation, and retinal detachment.

Dosage and Administration

SHARE VIGOROUSLY BEFORE USING.

Shake Sterile Ophthalmic Solution Thoroughly. Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily.

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

DO NOT USE IF NECKBAND IMPRINTED WITH “Protective Seal” AND YELLOW IS NOT INTACT.

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

KEEP OUT OF REACH OF CHILDREN.

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