

LOTEPREDNOL ETABONATE- loteprednol etabonate suspension/ drops
Amneal Pharmaceuticals NY LLC

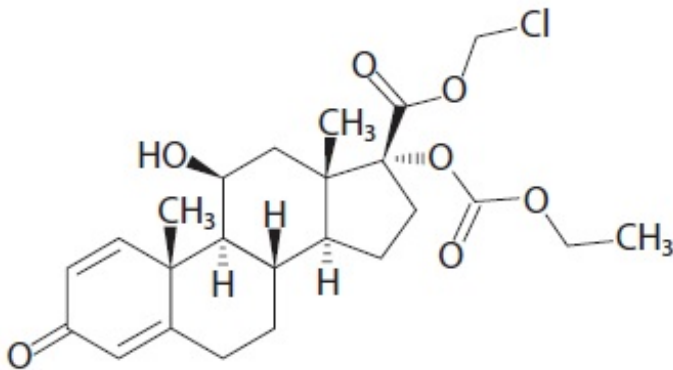
Loteprednol Etabonate Ophthalmic Suspension, 0.2%
Sterile
Rx only

DESCRIPTION

Loteprednol etabonate ophthalmic suspension contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use.

Loteprednol etabonate is a micronized sterile white to off-white crystalline powder. It is practically insoluble in water and sparingly soluble in alcohol.

Loteprednol etabonate is represented by the following structural formula:



Molecular formula: C₂₄H₃₁ClO₇

Molecular weight: 466.95 g/mol

Chemical name: Chloromethyl 11β, 17-dihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate, 17-(ethyl carbonate).

Each mL of Loteprednol etabonate ophthalmic suspension, 0.2% contains:

ACTIVE: Loteprednol etabonate, 2 mg (0.2%)

PRESERVATIVE ADDED: Benzalkonium chloride, 0.01%

INACTIVES: Edetate disodium, glycerin, povidone K90, tyloxapol and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH between 5.3 to 5.6. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg.

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 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.

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 extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers 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. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (< 1 ng/ml) systemic absorption occurs with loteprednol etabonate ophthalmic suspension.

Clinical Studies

In two double-masked, placebo-controlled six-week environmental studies of 268 patients with seasonal allergic conjunctivitis, loteprednol etabonate ophthalmic suspension, when dosed four times per day was superior to placebo in the treatment of the signs and symptoms of seasonal allergic conjunctivitis. Loteprednol etabonate ophthalmic suspension 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

Loteprednol etabonate ophthalmic suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

CONTRAINDICATIONS

Loteprednol etabonate, 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. Loteprednol etabonate ophthalmic suspension 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 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.

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 redness or itching becomes aggravated, the patient should be advised to consult a physician.

Patients should be advised not to wear a contact lens if their eye is red. Loteprednol etabonate ophthalmic suspension should not be used to treat contact lens related irritation. The preservative in loteprednol etabonate ophthalmic suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses **and whose eyes are not red**, should be instructed to wait at least ten minutes after instilling loteprednol etabonate ophthalmic suspension before 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, (1,500 and 750 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 (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 ≥ 50 mg/kg/day) and teratogenicity (absent innominate artery at ≥ 5 mg/kg/day doses and cleft palate and umbilical hernia at ≥ 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 ≥ 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 loteprednol etabonate ophthalmic suspension is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

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.

Ocular adverse reactions occurring in 5% to 15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2% to 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 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 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 loteprednol etabonate ophthalmic suspension, the incidence of clinically significant increases in IOP (≥ 10 mm Hg) was 1% (1/133) with loteprednol etabonate ophthalmic suspension and 1% (1/135) with placebo.

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals LLC at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION

SHAKE VIGOROUSLY BEFORE USING.

One drop instilled into the affected eye(s) four times daily.

HOW SUPPLIED

Loteprednol etabonate ophthalmic suspension, **0.2%** is a sterile, white to off-white uniform suspension essentially free from foreign particles filled in 10 mL low density polyethylene white opaque bottle with low density polyethylene white opaque nozzle and high density polyethylene pink cap.

It is available as follows:

5 mL in 10 mL Bottle (Filled to 1/2 Capacity): NDC 60219-1366-3

10 mL in 10 mL Bottle: NDC 60219-1367-6

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

KEEP OUT OF REACH OF CHILDREN.

DO NOT USE IF PINK PLASTIC BAND UNDER CAP IS BROKEN OR MISSING.

Manufactured by:

**Amneal Pharmaceuticals Pvt. Ltd.
Parenteral Unit**

Ahmedabad 382213, INDIA

Distributed by:

Amneal Pharmaceuticals LLC

Bridgewater, NJ 08807

Rev. 12-2024-00

PRINCIPAL DISPLAY PANEL

NDC 60219-1366-3

Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Rx only

5 mL

Amneal Pharmaceuticals LLC

Unvarnished Area for, (6 x 18 mm)	NDC 60219-1366-3	Rx only
	Loteprednol Etabonate Ophthalmic Suspension	
	0.2%	
	Sterile	5 mL
	FOR EYE USE ONLY	
	SHAKE VIGOROUSLY BEFORE USING.	
	Usual Dosage: See Package Insert.	
	Storage: Store upright between 15° to 25°C (59° to 77°F). DO NOT FREEZE.	
	Note: Bottle filled to 1/2 Capacity.	
	Distributed by: Amneal Pharmaceuticals LLC	
	Mfg. Lic. No. G/28/1539	
	Made in INDIA.	
	Rev. 10-2023-00	
		
	N 3 60219 13663 2	
Unvarnished Area for, Lot. & Exp. (10 x 18 mm)		



NDC 60219-1367-6
Loteprednol Etabonate Ophthalmic Suspension, 0.2%
Rx only
10 mL
Amneal Pharmaceuticals LLC

NDC 60219-1367-6 Rx only

**Loteprednol Etabonate
Ophthalmic Suspension**

0.2%

Sterile 10 mL

FOR EYE USE ONLY

**SHAKE VIGOROUSLY
BEFORE USING.**

Usual Dosage: See Package Insert.

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

Distributed by: **Amneal Pharmaceuticals LLC**
Mfg. Lic. No. G/28/1539
Made in INDIA.
Rev. 10-2023-00



Unvarnished Area for, (6 x 18 mm)

Unvarnished Area for, Lot. & Exp. (10 x 18 mm)

Unvarnished area for Variable data of GTIN, Lot, Exp and unique serial no. on each carton with 2D data matrix shall be printed. 38 x 35 mm

Space for UPs No.

NDC 60219-1367-6 Rx only

**Loteprednol Etabonate
Ophthalmic Suspension**

0.2%

FOR EYE USE ONLY

Sterile 10 mL

amneal®

Sterile Ophthalmic Suspension.

Each mL contains:
ACTIVE: Loteprednol etabonate, 2 mg (0.2%)
PRESERVATIVE ADDED: Benzalkonium chloride, 0.01%
INACTIVES: Edetate disodium, glycerin, povidone K90, tyloxapol and water for injection. 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 mOsmol/kg.

Usual Dosage: See Package Insert.

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

**SHAKE VIGOROUSLY
BEFORE USING.**

NDC 60219-1367-6 Rx only

**Loteprednol Etabonate
Ophthalmic Suspension**

0.2%

FOR EYE USE ONLY

Sterile 10 mL

amneal®

DO NOT USE IF PINK PLASTIC BAND UNDER CAP IS BROKEN OR MISSING.

KEEP OUT OF REACH OF CHILDREN.

Mfg. Lic. No. G/28/1539

Manufactured by:
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Distributed by:
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Bridgewater, NJ 08807

Rev. 01-2024-00



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LOTEPREDNOL ETABONATE
loteprednol etabonate suspension/ drops

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:60219-1366
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LOTEPREDNOL ETABONATE (UNII: YEH1EZ96K6) (LOTEPREDNOL - UNII:Z8CBU6KR16)	LOTEPREDNOL ETABONATE	2 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
GLYCERIN (UNII: PDC6A3C0OX)	
POVIDONE K90 (UNII: RDH86HJV5Z)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
TYLOXAPOL (UNII: Y27PUL9H56)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	white (white to off-white uniform suspension)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:60219-1366-3	1 in 1 CARTON	12/18/2024	
1		5 mL in 1 BOTTLE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA216345	12/18/2024	

LOTEPREDNOL ETABONATE

loteprednol etabonate suspension/ drops

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:60219-1367
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LOTEPREDNOL ETABONATE (UNII: YEH1EZ96K6) (LOTEPREDNOL - UNII:Z8CBU6KR16)	LOTEPREDNOL ETABONATE	2 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
GLYCERIN (UNII: PDC6A3C0OX)	
POVIDONE K90 (UNII: RDH86HJV5Z)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
TYLOXAPOL (UNII: Y27PUL9H56)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	white (white to off-white uniform suspension)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:60219-1367-6	1 in 1 CARTON	12/18/2024	
1		10 mL in 1 BOTTLE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA216345	12/18/2024	

Labeler - Amneal Pharmaceuticals NY LLC (123797875)

Registrant - Amneal Pharmaceuticals of New York, LLC (123797875)

Establishment

Name	Address	ID/FEI	Business Operations
Amneal Pharmaceuticals Private Limited		860156658	analysis(60219-1366, 60219-1367) , manufacture(60219-1366, 60219-1367) , pack(60219-1366, 60219-1367) , sterilize(60219-1366, 60219-1367)

Revised: 12/2024

Amneal Pharmaceuticals NY LLC