

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210565Orig1s000**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use INVELTYS™ safely and effectively. See full prescribing information for INVELTYS.

**INVELTYS (loteprednol etabonate ophthalmic suspension) 1%, for topical ophthalmic use**

**Initial U.S. Approval:** 1998

—————**INDICATIONS AND USAGE**—————

INVELTYS is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery. (1)

—————**DOSAGE AND ADMINISTRATION**—————

Shake for one to two seconds before using. (2)

Instill one to two drops of INVELTYS into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period. (2)

—————**DOSAGE FORMS AND STRENGTHS**—————

INVELTYS is a sterile preserved ophthalmic suspension containing 10 mg/mL of loteprednol etabonate. (3)

—————**CONTRAINDICATIONS**—————

INVELTYS 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. (4)

—————**WARNINGS AND PRECAUTIONS**—————

- Intraocular pressure (IOP) increase – prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored. (5.1)

- Cataracts – Use of corticosteroids may result in posterior subcapsular cataract formation. (5.2)
- Delayed healing – Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order 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. (5.3)
- Bacterial infections – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. (5.4)
- Viral infections – Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). (5.5)
- Fungal Infections – Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. (5.6)

—————**ADVERSE REACTIONS**—————

The most common adverse drug reactions were eye pain (1%) and posterior capsular opacification (1%). These reactions may have been the consequence of the surgical procedure. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Kala Pharmaceuticals, Inc. at 1-833-287-KALA (1-833-287-5252) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2018

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\*Sections or subsections omitted from the full prescribing information are not listed.

## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

**INVELTYS** is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

### **2 DOSAGE AND ADMINISTRATION**

Shake for one to two seconds before using.

Instill one to two drops of **INVELTYS** into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

### **3 DOSAGE FORMS AND STRENGTHS**

**INVELTYS** (loteprednol etabonate ophthalmic suspension) 1% is a sterile preserved ophthalmic suspension containing 10 mg/mL of loteprednol etabonate.

### **4 CONTRAINDICATIONS**

**INVELTYS** 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.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Intraocular Pressure (IOP) Increase**

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

#### **5.2 Cataracts**

Use of corticosteroids may result in posterior subcapsular cataract formation.

#### **5.3 Delayed Healing**

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order 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.

#### **5.4 Bacterial Infections**

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

#### **5.5 Viral Infections**

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

#### **5.6 Fungal Infections**

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

#### **5.7 Contact Lens Wear**

The preservative in **INVELTYS** may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **INVELTYS** and may be reinserted 15 minutes following administration.

### **6 ADVERSE REACTIONS**

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

#### **6.1 Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse drug reactions in the clinical trials with **INVELTYS** were eye pain and posterior capsular opacification, both reported in 1% of patients. These reactions may have been the consequence of the surgical procedure.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

INVELTYS is not absorbed systemically following topical ophthalmic administration and maternal use is not expected to result in fetal exposure to the drug.

### 8.2 Lactation

#### Risk Summary

INVELTYS is not absorbed systemically by the mother following topical ophthalmic administration, and breastfeeding is not expected to result in exposure of the child to INVELTYS.

### 8.3 Pediatric Use

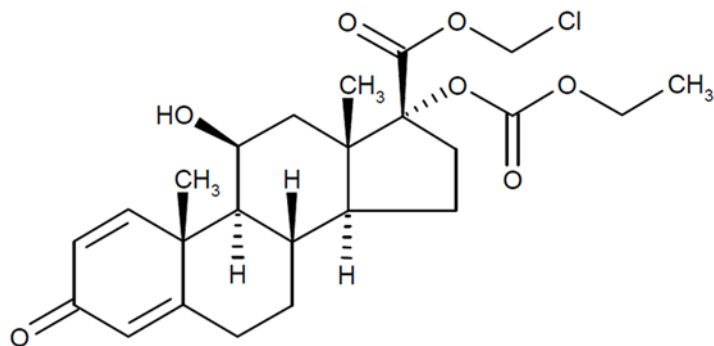
Safety and effectiveness in pediatric patients have not been established.

### 8.4 Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

## 11 DESCRIPTION

Loteprednol etabonate is a corticosteroid. Its chemical name is chloromethyl 17 $\alpha$ -[(ethoxycarbonyl)oxy]-11 $\beta$ -hydroxy-3-oxoandrosta-1,4-diene-17 $\beta$ -carboxylate. Its molecular formula is C<sub>24</sub>H<sub>31</sub>ClO<sub>7</sub> and its chemical structure is:



C<sub>24</sub>H<sub>31</sub>ClO<sub>7</sub>  
Mol. Wt. 467.0

INVELTYS (loteprednol etabonate ophthalmic suspension) 1% contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Each mL contains:

- ACTIVE: loteprednol etabonate 10 mg (1%)
- INACTIVES: glycerin, sodium citrate dihydrate, Poloxamer 407, sodium chloride, edetate disodium dihydrate, citric acid, and water for injection

- PRESERVATIVE: benzalkonium chloride 0.01%

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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. While glucocorticoids are known to bind to and activate the glucocorticoid receptor, the molecular mechanisms involved in glucocorticoid/glucocorticoid receptor-dependent modulation of inflammation are not clearly established. However, corticosteroids are thought to inhibit prostaglandin production through several independent mechanisms.

### 12.3 Pharmacokinetics

Loteprednol etabonate is lipid soluble and can penetrate 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, PJ-91 and PJ-90.

Following twice-daily unilateral topical ocular dosing of **INVELTYS** for 14 days in healthy subjects, the plasma concentrations of loteprednol etabonate were below the limit of quantitation (1 ng/mL) at all timepoints.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

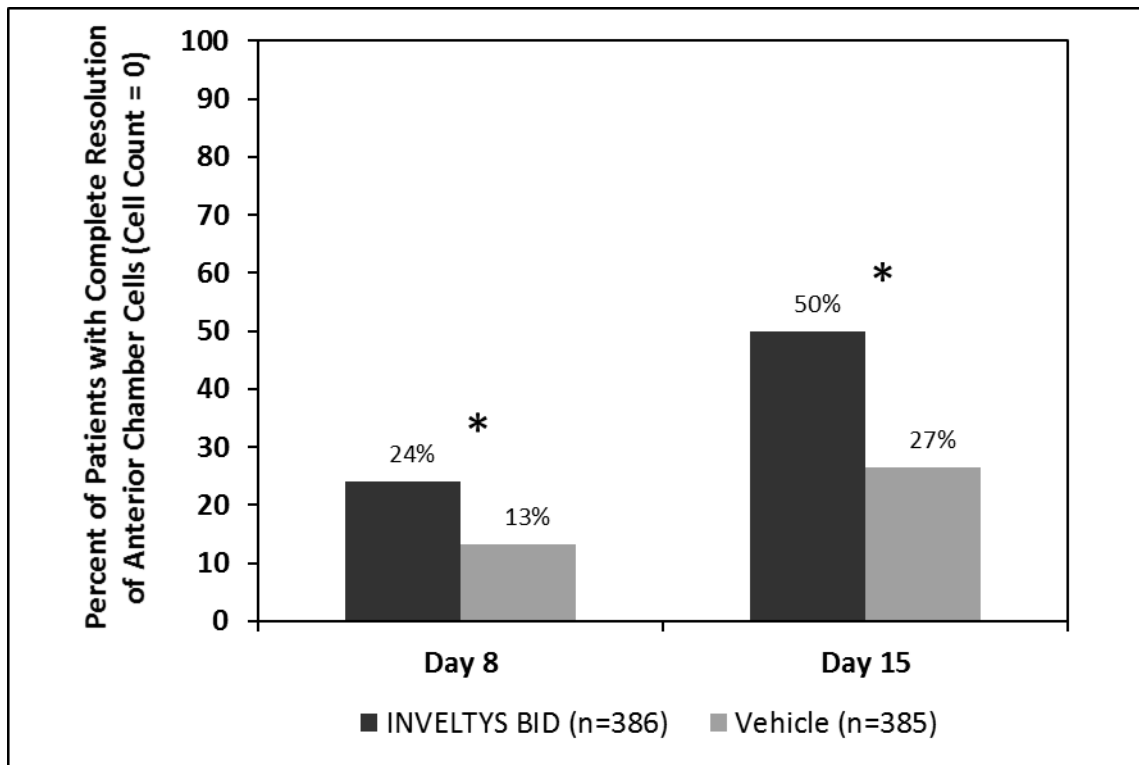
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay.

## 14 CLINICAL STUDIES

Clinical efficacy was evaluated in 2 multi-centered, randomized, double-masked, placebo-controlled trials in which patients with an anterior cell grade greater than or equal to “2” (a cell count of 6 or higher using a slit-lamp biomicroscope) after cataract surgery were assigned to **INVELTYS** or placebo (vehicle) following surgery (NCT # 02163824 and NCT # 02793817). One to two drops of **INVELTYS** or vehicle was self-administered twice a day for 14 days, beginning the day after surgery. Complete resolution of inflammation (a cell count of 0 maintained through day 15 without rescue medication) and complete resolution of pain (a

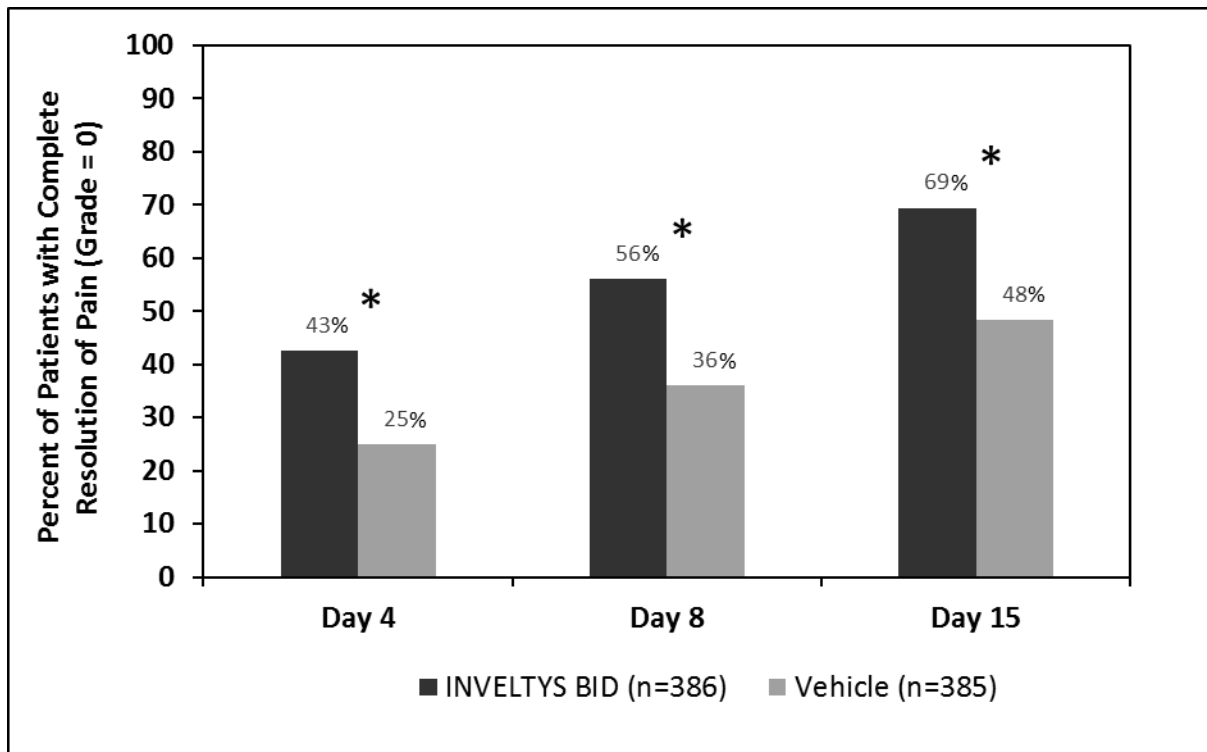
patient-reported pain grade of 0 maintained through day 15 without rescue medication) was assessed 4, 8, and 15 days post-surgery. In the intent-to-treat analysis of both studies, a significant benefit was seen in the **INVELTYS**-treated group for complete resolution of ocular inflammation at Days 8 and 15, and complete resolution of pain at Days 4, 8, and 15, when compared with placebo. The consolidated clinical trial results are provided below.

**Figure 1 Consolidated Clinical Trial Data: Percent of Patients with Complete Resolution of Anterior Chamber Cells (Cell Count = 0) at Days 8 and 15**



\* p-values < 0.01 for treatment comparisons

**Figure 2 Consolidated Clinical Trial Data: Percent of Patients Who Were Pain Free at Days 4, 8, and 15**



\* p-values < 0.01 for treatment comparisons

## 16 HOW SUPPLIED/STORAGE AND HANDLING

INVELTYS (loteprednol etabonate ophthalmic suspension) 1% is a sterile ophthalmic suspension. It is supplied in a white low-density polyethylene plastic dropper bottle with a controlled-drop linear low-density polyethylene tip, a pink high-density polyethylene cap, and a white low-density polyethylene tamper-evident overcap in the following size:

2.8 mL in a 5 mL bottle (NDC 71571-121-28)

### Storage and Handling

Do not use if tamper-evident overcap seal is not intact.

Store upright at 15°C to 25°C (59°F to 77°F). Do not freeze.

## 17 PATIENT COUNSELING INFORMATION

### Administration

Instruct the patient to shake the bottle for one to two seconds before using.



### **Risk of Contamination**

Advise patients not to allow the dropper tip to touch any surface, as this may contaminate the suspension.

### **Risk of Secondary Infection**

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

### **Contact Lens Wear**

Advise patients that the preservative in **INVELTYS** may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **INVELTYS** and may be reinserted after 15 minutes following administration.

Manufactured for:

Kala Pharmaceuticals, Inc.  
Waltham, MA 02453

Marks designated by <sup>TM</sup> and <sup>®</sup> are owned by Kala Pharmaceuticals, Inc.

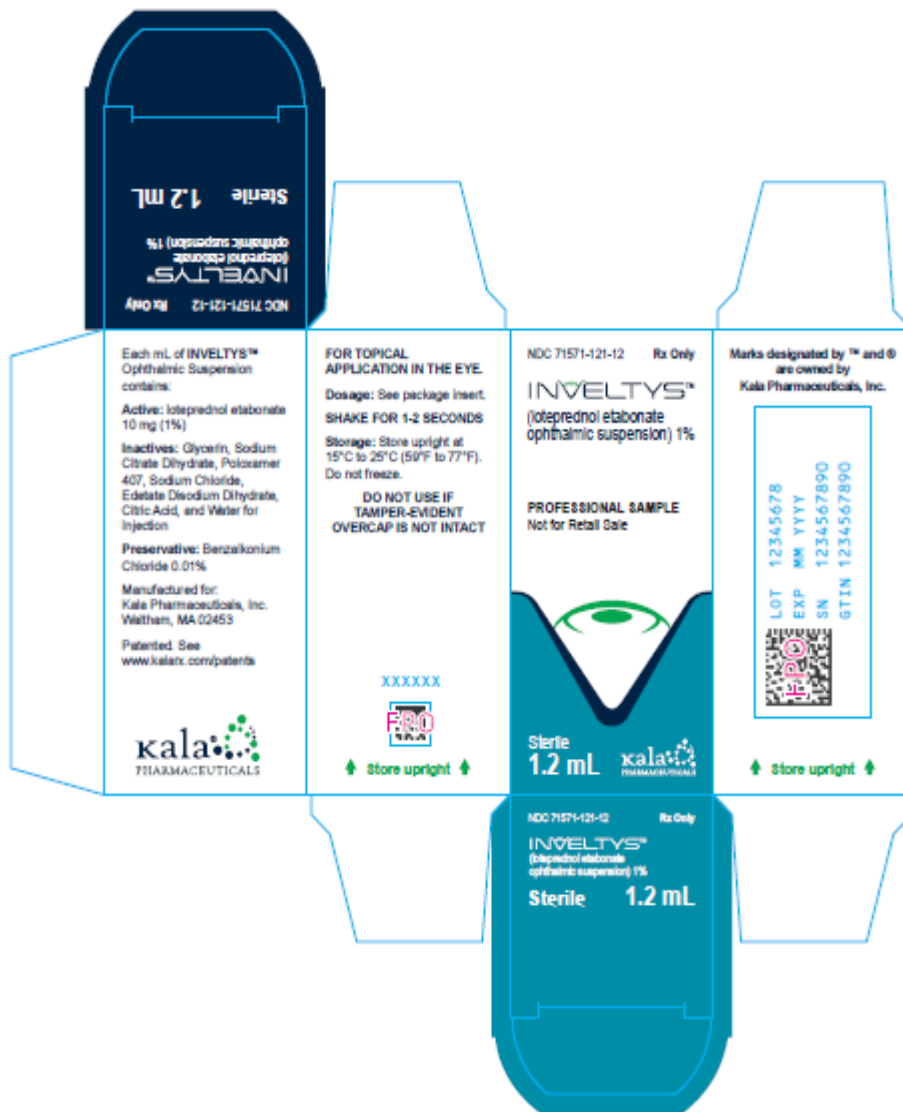
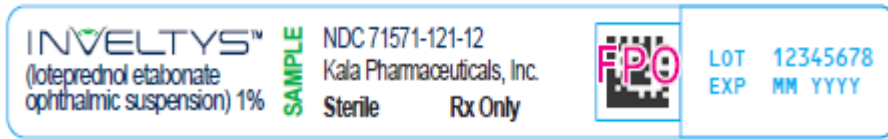
Patented. See [www.kalarx.com/patents](http://www.kalarx.com/patents)

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Part # xxxxxx  
August 2018

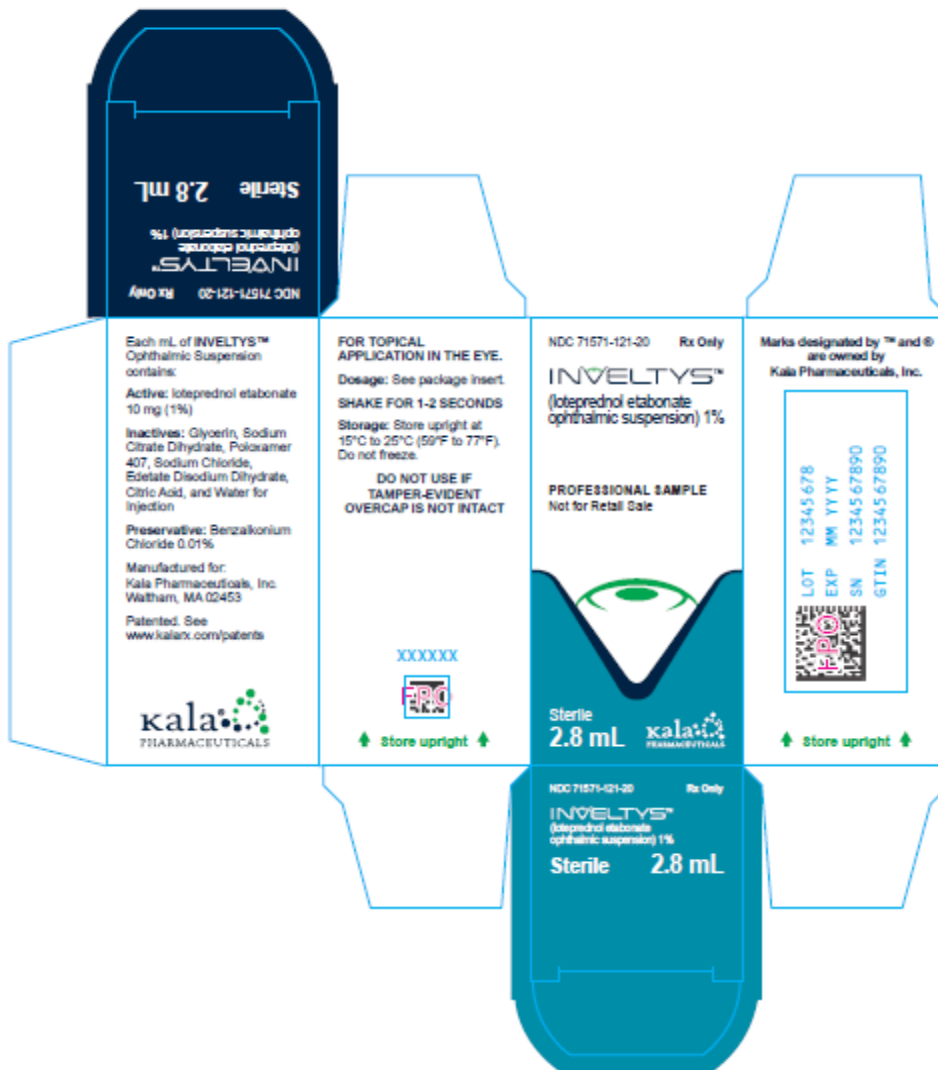
**Kala<sup>®</sup>**

**Carton and Container labeling for 1.2 mL Professional Sample**





**Carton and Container labeling for 2.8 mL Professional Sample**



<b>INVELTYS™</b> (loteprednol etabonate ophthalmic suspension) 1%	SAMPLE	NDC 71571-121-20 Kala Pharmaceuticals, Inc. Sterile Rx Only		LOT 12345678 EXP MM YYYY
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**Top Flap:** INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1% Sterile 2.8 mL NDC 71571-121-20 Rx Only

**Left Side Panel:**  
 Each mL of INVELTYS™ Ophthalmic Suspension contains:  
**Active:** loteprednol etabonate 10 mg (1%)  
**Inactives:** Glycerin, Sodium Citrate Dihydrate, Poloxamer 407, Sodium Chloride, Edetate Disodium Dihydrate, Citric Acid, and Water for Injection  
**Preservative:** Benzalkonium Chloride 0.01%  
 Manufactured for: Kala Pharmaceuticals, Inc. Waltham, MA 02453  
 Patented. See www.kala.com/patents  


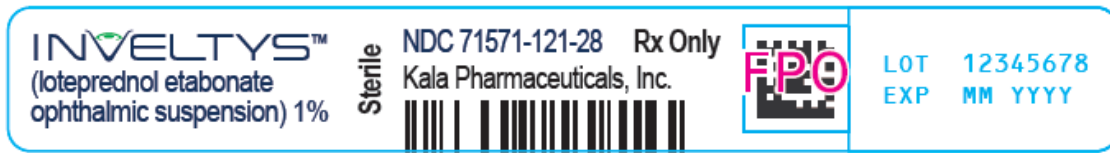
**Center Panel (Top):**  
 FOR TOPICAL APPLICATION IN THE EYE.  
 Dosage: See package insert  
**SHAKE FOR 1-2 SECONDS**  
 Storage: Store upright at 15°C to 25°C (59°F to 77°F). Do not freeze.  
**DO NOT USE IF TAMPER-EVIDENT OVERCAP IS NOT INTACT**  
 XXXXXX  
  
 ↑ Store upright ↓

**Center Panel (Middle):**  
 NDC 71571-121-20 Rx Only  
**INVELTYS™**  
 (loteprednol etabonate ophthalmic suspension) 1%  
**PROFESSIONAL SAMPLE**  
 Not for Retail Sale  
  
 Sterile 2.8 mL   
 ↑ Store upright ↓

**Center Panel (Bottom):**  
 NDC 71571-121-20 Rx Only  
**INVELTYS™**  
 (loteprednol etabonate ophthalmic suspension) 1%  
**Sterile 2.8 mL**

**Right Side Panel:**  
 Marks designated by ™ and © are owned by Kala Pharmaceuticals, Inc.  
 LOT 12345678  
 EXP MM YYYY  
 SN 1234567890  
 GTIN 1234567890  
  
 ↑ Store upright ↓

### Carton and Container labeling for 2.8 mL Trade



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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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WILEY A CHAMBERS  
08/22/2018