Supplement to June 2019 Sponsored by Kala Pharmaceuticals

CRST
Cataract & Refractive Surgery Today

INTRODUCING INVELTYS (LOTEPREDNOL ETABONATE OPHTHALMIC SUSPENSION) 1% POWERED BY AMPPLIFY

Four surgeons discuss how **INVELTYS from Kala Pharmaceuticals** treats inflammation and pain following ocular surgery.

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Important Safety Information Continued

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.

See Important Safety Information throughout and full Prescribing Information.

INTRODUCING A NEW OCULAR CORTICOSTEROID POWERED BY AMPPLIFY TECHNOLOGY

Four surgeons discuss how INVELTYS (loteprednol etabonate ophthalmic suspension) 1% from Kala Pharmaceuticals treats inflammation and pain following ocular surgery.

Robert J. Weinstock, MD: As surgeons with a wide breadth of experience in both standard and refractive cataract surgery, we are all continually striving to optimize outcomes for our patients. Steroids are part of that effort. We're going to take a deep dive into the importance of steroids and the features we look for in treating patients' inflammation and pain.

To begin, Dr. Rowen, what do you see as the important reasons to treat postoperative inflammation and pain? What problems would we see in our patients if we didn't address these issues?

Sheri L. Rowen, MD, FACS: Inflammation is a risk with any ocular surgery. Even with the best surgical technique, the blood-aqueous barrier is compromised, which may lead to inflammation in the aqueous humor. Uncontrolled, this could lead to complications such as cystoid macular edema and permanent vision loss. To help prevent these complications, we need to treat postoperatively with a steroid.[1]

In addition to having a quiet eye, we also want patients to be pain-free after surgery. If we didn't treat proactively for postoperative inflammation and pain, they would certainly experience pain. When patients ask us before surgery, "Will this be painful?" we can safely say that with the treatments we have to offer, there should be little to no pain. That immediately removes the fear of pain that our patients may be experiencing when they think about eye surgery. We let patients know that it's not normal to have pain, and therefore if they do experience pain after surgery, they should tell us.

Dr. Weinstock: Dr. Sood, what medications are you and most eye doctors these days using to treat inflammation and pain after cataract surgery? Are they effective?

Priyanka Sood, MD: We typically put patients on a nonsteroidal anti-inflammatory drug (NSAID) as well as a steroid after surgery. The combination of those two drugs has been shown to decrease complications that we fear in cataract surgery.[1]

In fact, I think we often don't take into account that these drugs are the reason complications occur less frequently. We may credit the advanced technologies available for cataract surgery and the fact that we have become so skilled at performing the procedure. It may seem like we don't have to worry about complications. But as soon as we scale back on postoperative medications, the complications may start to arise again.

Using the combination of NSAID and steroid helps us deliver the positive experience that patients would like after cataract surgery. Patients become concerned when they experience postoperative pain and discomfort. That's why it's gratifying to have medications that can decrease not just the inflammation, but also the pain symptoms for our patients.

Dr. Weinstock: There is always a risk-benefit balance to everything we do. Do you see any downsides or negative consequences of using steroids after cataract surgery?

William Trattler, MD: Drs. Rowen and Sood offered a great overview of the benefits of controlling inflammation with topical steroids. The challenge is that there are some risks associated with steroids, the biggest concern being elevated eye pressure. On one hand, steroids such as prednisolone acetate or difluprednate will decrease inflammation.[2] However, these benefits can come with the potential risk of increased IOP, which can be serious in some cases.[3,4]

Dr. Weinstock: What is your current steroid treatment regimen before and after cataract surgery?

Dr. Rowen: We can't discuss presurgery protocols because the indication is only for 2 weeks postsurgery. Previously, our

only dosing option for steroids was four times daily (QID). Patients continue on the drops for 2 weeks after surgery. I can make an adjustment if I still see cells circulating in the anterior chamber at week 1.

Dr. Weinstock: If the sky is the limit and we're trying a steroid drop to control pain and inflammation, what features would you want in that drop?

Dr. Rowen: I'd like an option that not only has excellent penetration into the aqueous humor to powerfully treat inflammation, but also has little effect on intraocular pressure. If this steroid could come with less frequent dosing, that could be another big advantage.

Dr. Weinstock: Various companies have looked at different ways to address that penetration issue. We see a few medications on the market that are suspensions. Dr. Trattler, what are the pros and cons of suspensions and other different vehicles? And what is the ideal way to ensure penetration?

Dr. Trattler: The mucins in the tear film have a protective effect, eliminating pathogens and other insults. In doing so, they also may limit the penetration of traditional suspension eyedrops, as they too can be rapidly cleared. The traditional approach has been to increase penetration by developing formulations that adhere to the mucins longer in the hope for less rapid elimination and better penetration. A new drug delivery called AMPPLIFY Drug Delivery Technology (Kala Pharmaceuticals) has a completely different approach. In contrast to current suspension formulations that adhere to mucins, this technology allows more drug to penetrate through the mucins directly to the target ocular tissue.[5]

Dr. Weinstock: How does AMPPLIFY Drug Delivery Technology work?

Dr. Sood: AMPPLIFY uses mucus-penetrating particles, which are selectively-sized drug nanoparticles with a proprietary surface coating. The nanoparticles' tiny size allows them to penetrate into the mucus pores, while the coating keeps them from adhering to the mucins. Together, these attributes are designed to enhance penetration through the tear film's mucus barrier (Figure 1).[5] In nonclinical studies, AMPPLIFY delivered more than 3 times the drug concentration into the cornea and aqueous humor than loteprednol etabonate 0.5% suspension without AMPPLIFY.[5]

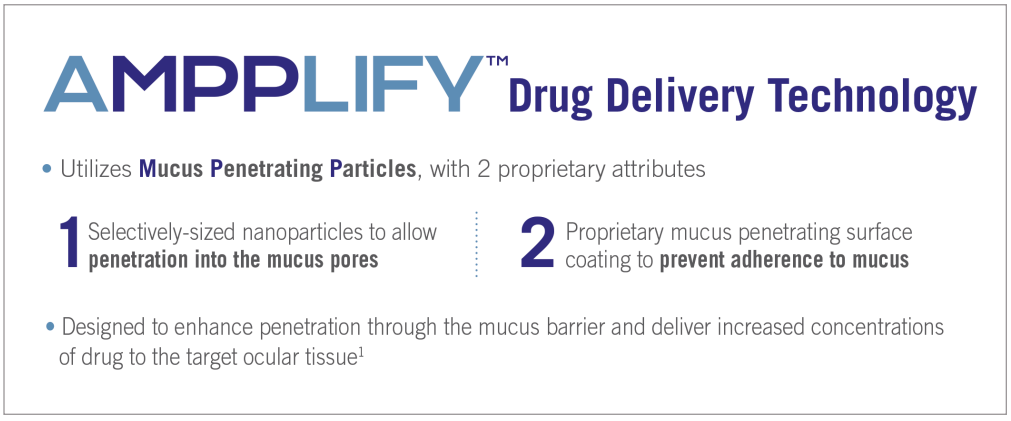

Figure 1. This technology allows more drug to penetrate through the mucins directly to the target ocular tissue.[5]

Dr. Weinstock: I'm concerned that sometimes patients may not even get the drops in their eyes. They could blink them away very quickly or miss entirely. Or they might instill the drop immediately after another drop. We can't really know how much of the medication we prescribe reaches the eye, so it would be nice to help make sure that any amount of the drop that hits the eye will have an opportunity to penetrate.

Dr. Rowen: We know that in most cases when patients instill a drop, and after blinking, tearing and drainage, they get only 5% to 7% of the dose.[6-9] This makes ocular penetration one of the most important features of any formulation.

Dr. Weinstock: What kind of steroid would you like to see formulated for better penetration? What features should the steroid have?

Dr. Trattler: Ideally, I would want a potent steroid that causes little to no increase in ocular pressure, and could deliver higher concentrations of drug to the ocular tissue. Loteprednol etabonate, in the right formulation and dosage, is quite powerful.

Dr. Weinstock: Please share your thoughts on why the loteprednol molecule has a low incidence of significant IOP and is an effective ocular steroid.

Dr. Rowen: Loteprednol etabonate is an ester of loteprednol. The therapeutic effect is followed by de-esterification to inactive carboxylic acid metabolites. Because it's hydrolyzed at the site of action, it doesn't hang around long enough to

Table. Efficacy of INVELTYS (loteprednol etabonate ophthalmic suspension) 1% for Postoperative Inflammation and Pain.[11]

In 2 clinical studies of cataract surgery patients (vs vehicle) with no concurrent NSAID use ($P<0.01$)*

ZERO Inflammation
in 50% of patients by Day 15

Complete resolution of inflammation (anterior chamber cell count=0), INVELTYS vs vehicle:

- **24% vs 13%** at Day 8 (93/386) (51/385)
- **50% vs 27%** at Day 15 (193/386) (102/385)

ZERO Pain
in nearly 70% of patients by Day 15

Complete resolution of pain (grade=0), INVELTYS vs vehicle:

- **43% vs 25%** at Day 4 (164/386) (96/385)
- **56% vs 36%** at Day 8 (216/386) (139/385)
- **69% vs 48%** at Day 15 (268/386) (186/385)

*Clinical efficacy and safety were evaluated in 2 multicentered, randomized, double-masked, placebo-controlled trials in which patients with an anterior cell grade ≥2 (ie, a cell count of 6 or higher using a slit-lamp biomicroscope) after cataract surgery were assigned to INVELTYS (n=386; Study 1, n=125; Study 2, n=261) or placebo (vehicle) (n=385; Study 1, n=126; Study 2, n=259) following surgery. One to 2 drops of INVELTYS or vehicle were 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 [rated via the Subject-Rated Ocular Pain Assessment, 0=none to 5=severe] maintained through Day 15 without rescue medication) were assessed 4, 8, and 15 days postsurgery. Consolidated clinical trial results provided above.

cause significantly increased IOP.[3,4] I think its safety profile is impressive.

Dr. Weinstock: All of these concepts have gone into the now FDA-approved INVELTYS, from Kala Pharmaceuticals. INVELTYS is approved for the treatment of postoperative inflammation and pain following ocular surgery and is the first product available with AMPPLIFY Drug Delivery Technology. In a preclinical study, AMPPLIFY delivered increased concentrations of loteprednol etabonate to target ocular tissue compared to an active comparator without AMPPLIFY. In the preclinical study, there was 3.7 times more loteprednol in the aqueous humor (Figure 4).[5,10,11]

Beyond the efficacy and safety of INVELTYS, how does its two times daily BID dosing help your patients? What are the functional or clinical benefits of going from a QID to BID?

Dr. Trattler: With INVELTYS BID dosing, I am confident that this shows the efficacy of the product, and with patients taking three medications before and after cataract surgery, the BID dosing makes me more confident in their adherence and compliance. INVELTYS also had low incidence of significant IOP elevations versus vehicle in the FDA clinical trials (Figure 2).[11]

Dr. Rowen: Another potential patient benefit of the INVELTYS formulation is that because the particles are so small,

Mean IOP (Integrated Safety Population)

	INVELTYS – BID Mean (SD) in mmHg	Vehicle Mean (SD) in mmHg
Baseline	15.7 (3.27); n=386	15.5 (3.02); n=325
Day 4	13.9 (3.13); n=380	13.3 (3.03); n=315
Day 8	14.3 (2.95); n=357	13.5 (3.08); n=253
Day 15	14.5 (2.77); n=322	14.1 (2.84); n=196

Number of Patients with IOP Increase ≥ 10 mm Leading to IOP ≥ 21 mm (Integrated Safety Population)

INVELTYS – BID N=386	Vehicle N=325
2 (0.5%)*	0

*Both occurred at Day 4 and were resolved at Day 8

Figure 2. This figure shows the INVELTYS effect on IOP versus the vehicle.[11]

Important Safety Information Continued

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.

Use of corticosteroids may result in posterior subcapsular cataract formation.

See Important Safety Information throughout and full Prescribing Information.

AMPPLIFY IS DESIGNED TO ENHANCE PENETRATION TO THE TARGET OCULAR TISSUES

The mucus barrier is part of the tear film that offers a natural protective mechanism for the eye. This heterogeneous mesh of mucin fibers binds with drugs and other particulate matter to facilitate elimination by the tears.

INVELTYS (loteprednol etabonate ophthalmic suspension) 1% from Kala Pharmaceuticals utilizes AMPPLIFY mucus-penetrating particles (MPPs) to help loteprednol etabonate penetrate the mucus barrier and reach the target ocular tissues. AMPPLIFY drug nanoparticles are selectively sized to penetrate through mucus pores. The particles have a proprietary surface coating that prevents the particles from adhering to mucins, further improving their ability to pass through the mucus barrier (Figure 5).

This ability to penetrate the mucus barrier, delivering higher concentrations of a drug to the target ocular tissue, makes an AMPPLIFY formulation like INVELTYS very different from traditional ophthalmic suspensions. In nonclinical studies, loteprednol etabonate suspensions with AMPPLIFY delivered significantly higher steroid concentration into the cornea and aqueous humor than an active comparator formulated without AMPPLIFY (Figure 4).

When we further compare AMPPLIFY to MPP nanoparticles of the same size and composition without the AMPPLIFY coating, the difference was evident (Figure 3).[2]

When loteprednol etabonate suspension with AMPPLIFY was compared with loteprednol etabonate suspension 0.5%, they showed enhanced drug penetration (Figure 4).[1,2]

1. Schopf L, Enlow E, Popov A, et al. Ocular pharmacokinetics of a novel loteprednoletabonate 0.4% ophthalmic formulation. *Ophthalmol Ther.* 2014;3(1-2):63-72.
2. Kala Pharmaceuticals. Data on file.

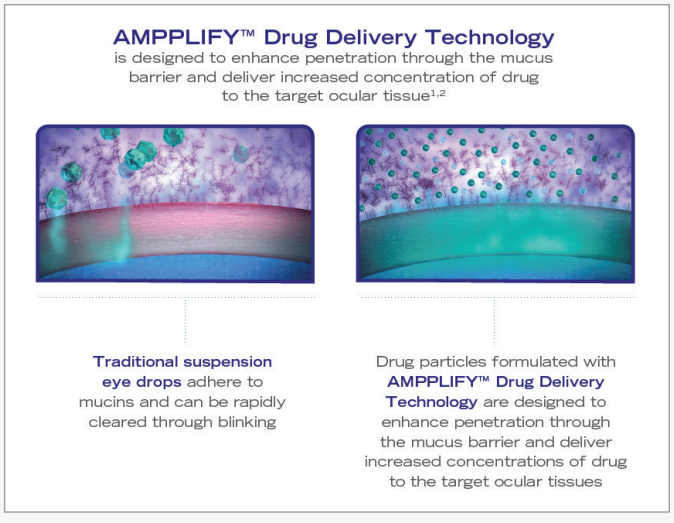

Figure 5. MPPs avoid clearance by tear film to increase drug delivery to target ocular tissues.

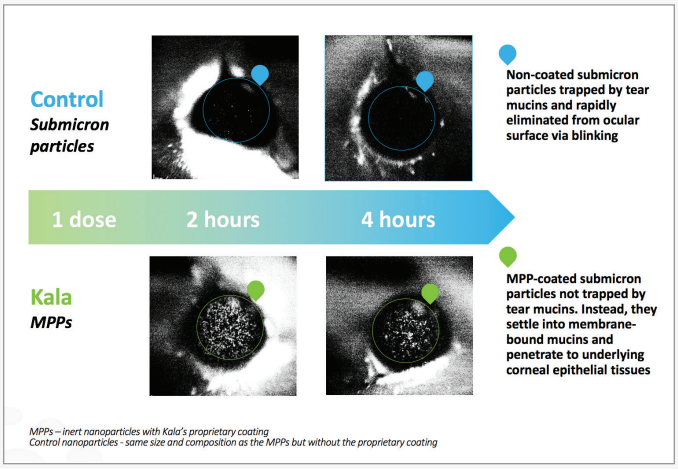

Figure 3. MPPs' impact on drug delivery to the ocular surface.[2]

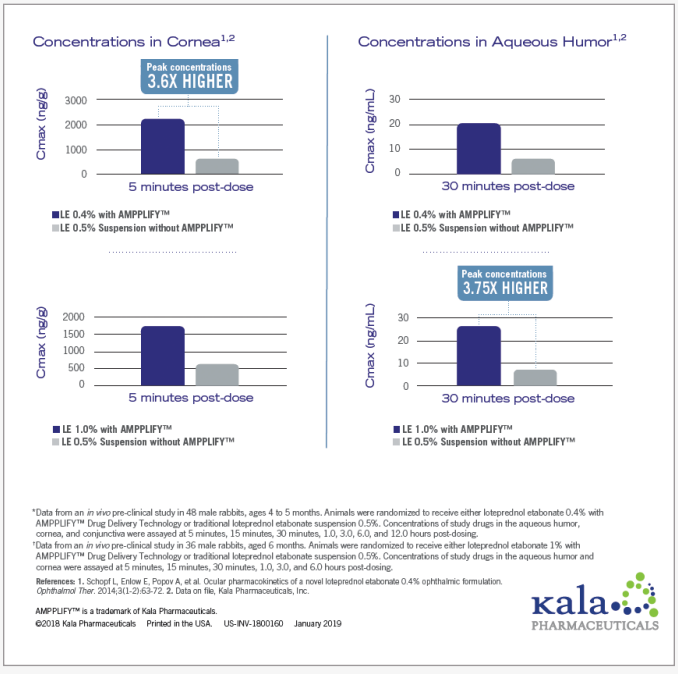

Figure 4. In preclinical studies, increased ocular exposure with AMPPLIFY drug delivery technology.

Important Safety Information Continued

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.

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).

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patients can shake for 1 to 2 seconds before use. In addition, it's a thin liquid, not thick and viscous.

Dr. Weinstock: Aside from BID dosing, what attributes of INVELTYS (loteprednol etabonate ophthalmic suspension) 1% from Kala Pharmaceuticals make it exciting to you? How do you think INVELTYS can be incorporated into a postoperative regimen?

Dr. Rowen: In my opinion, loteprednol is a fantastic steroid, and improvements in formulation and increased concentration or ease of use for the patient are icing on the cake. It has BID dosing and can be continued for 2 weeks as needed.

Dr. Sood: I am excited about the increased penetration into the ocular tissue, the opportunity to potentially have patients on the medicines for shorter duration postoperatively because no tapering is needed for INVELTYS, and the chance to improve my patients' outcomes and experience. I think it could be very easy to incorporate this treatment into a patient's regimen to help minimize the duration and frequency of postoperative management.

Dr. Trattler: I am excited about the significant increased penetration of loteprednol with this formulation.[5,10] The strong anti-inflammatory effect will be very beneficial to our patients, who are expecting a very rapid visual recovery.

INVELTYS will be easy to add into the postoperative care of patients following cataract surgery. The clinical data look very strong, allowing for BID dosing. Typically, we will also have an NSAID used once a day.

Dr. Weinstock: Thank you all very much for you thoughtful and valuable comments. I think we are all looking forward to using this newly approved FDA steroid drop with its novel features for improved postoperative care for our patients. ■

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IMPORTANT SAFETY INFORMATION

INDICATION

INVELTYS (loteprednol etabonate ophthalmic suspension) 1% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

IMPORTANT SAFETY INFORMATION

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.

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.

Use of corticosteroids may result in posterior subcapsular cataract formation.

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.

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.

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).

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.

In clinical trials, 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.

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

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

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

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.

WARNINGS AND PRECAUTIONS
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.

Cataracts—Use of corticosteroids may result in posterior subcapsular cataract formation.

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.

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.

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).

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.

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.

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.

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.

USE IN SPECIFIC POPULATIONS
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.

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.

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

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

NONCLINICAL TOXICOLOGY
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.

For a copy of the Full Prescribing Information, please visit www.INVELTYS.com.

Manufactured for:
Kala Pharmaceuticals, Inc. Waltham, MA 02453

US-INV-1900021 December 2018