LOTEMAX® SM
(loteprednol etabonate ophthalmic gel) 0.38%

LOTEMAX SM for the management of pain following intravitreal injections

Sponsored by Bausch + Lomb

This supplement captures perspectives from a roundtable discussion held in October 2019 at the American Academy of Ophthalmology (AAO) Meeting in San Francisco, California

Participants:

- Sumit Sharma, MD (moderator)
- Mark R. Barakat, MD
- Kevin J. Blinder, MD
- David A. Eichenbaum, MD
- George Fivgas, MD
- Victor H. Gonzalez, MD
- Christopher D. Riemann, MD
- Gaurav K. Shah, MD

The participants are paid consultants for Bausch + Lomb.

Intravitreal injections are frequently performed surgical procedures but may be painful for patients

Intravitreal injections (IVIs) have become a primary method for the treatment of a variety of posterior segment diseases, including age-related macular degeneration, diabetic macular edema, retinal vein occlusion, and noninfectious posterior uveitis.[1] The number of IVIs has increased considerably over time, with an estimated 5.9 million procedures performed in the US in 2016.[1]

Due to the short half-life of intravitreally delivered drugs and a high rate of disease recurrences, multiple IVIs are often required to manage these conditions.[2] Patients have reported pain and discomfort during and after these procedures, potentially affecting patient compliance.[2-6] Additionally, it has been reported that healthcare professionals may underestimate the severity of pain in their patients.[7]

In preparation for an IVI, patients are typically administered a topical antiseptic and a topical anesthetic.[1] Povidone-iodine is a topical antiseptic that is widely used due to its broad-spectrum microbicidal activity, but has also been associated with ocular surface irritation.[1,8] "In my experience, povidone-iodine has irritated the eyes of multiple patients for up to 12 hours, even if it is washed out," says Dr. David Eichenbaum. Dr. Victor Gonzalez agrees, adding that many of his patients are older and have reduced tear production. "Administering anesthetic drops will further decrease their reflex tearing.[9] If these patients are not injected right away, they are waiting with povidone-iodine in their eye and are not producing enough tears," says Dr. Gonzalez. "It is not surprising that a large percentage of these patients are going to have irritation just from all the chemicals that are administered prior to an IVI."

Indication

LOTEMAX SM (loteprednol etabonate ophthalmic gel) 0.38% is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information

- LOTEMAX SM, 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.

Please see additional Important Safety Information throughout and full Prescribing Information pages 5-6.

Pain during an IVI is typically managed with a topical anesthetic such as proparacaine or lidocaine.[1] Topical anesthesia does not completely eliminate pain, as one study has reported that 58% (n=132/229) of patients experienced mild pain during an injection.[5] Smaller gauge needles have been associated with less pain during the injection and less vitreous reflux.[10] However, low vitreous reflux coupled with the volume expansion from the injection may cause an immediate increase in IOP and contribute to ocular pain.[1]

"Our practice cannot seem to eliminate pain, but we have reduced it," says Dr. Eichenbaum. "I use a 33-gauge steeply beveled needle with a spring-loaded guard. I use topical pledget for anesthesia and I do not use a lid speculum." Dr. Christopher Riemann adds, "Some patients can just feel the needle entering and find it painful. For these patients I use subconjunctival lidocaine and find that it helps mitigate much of that pain."

In a study of 40 patients undergoing anti-VEGF injections for the treatment of neovascular age-related macular degeneration, the average duration of postinjection pain was 5 days, with some patients reporting pain for up to 7 days (Figure 1).[6] One study demonstrated that a majority of patients undergoing repeated injections have reported comparable levels of postinjection pain with their second injection as with their first injection.[2] Many of these patients require repeated IVIs to manage their ocular conditions; thus, management of postinjection pain is important to maintain patient comfort. "It doesn't have to be severe pain for it to be important," says Dr. Gaurav Shah. "For example, if you can make your patient more comfortable, by going from 3 to a 0 on the pain scale, that is significant."

> "It doesn't have to be severe pain for it to be important. For example, if you can make your patient more comfortable, by going from 3 to a 0 on the pain scale, that is significant." — ***Dr. Shah***

The retina specialists agreed that postinjection pain experienced by the patient has resulted in a significant number of callbacks in their practices. "A vast majority of the phone calls I receive are about postinjection pain," says Dr. Mark R. Barakat. Dr. Gonzalez agrees, adding, "I do not want my patients calling me about postinjection pain, which happens often. I began prescribing an ophthalmic corticosteroid, and I have noticed that the frequency of calls has decreased." Dr. Sumit Sharma adds, "I have patients who have complained about pain from a prior injection and patients who have called our office and complained about pain. In these instances, I prescribe an ophthalmic corticosteroid for the treatment of pain following an ocular injection."

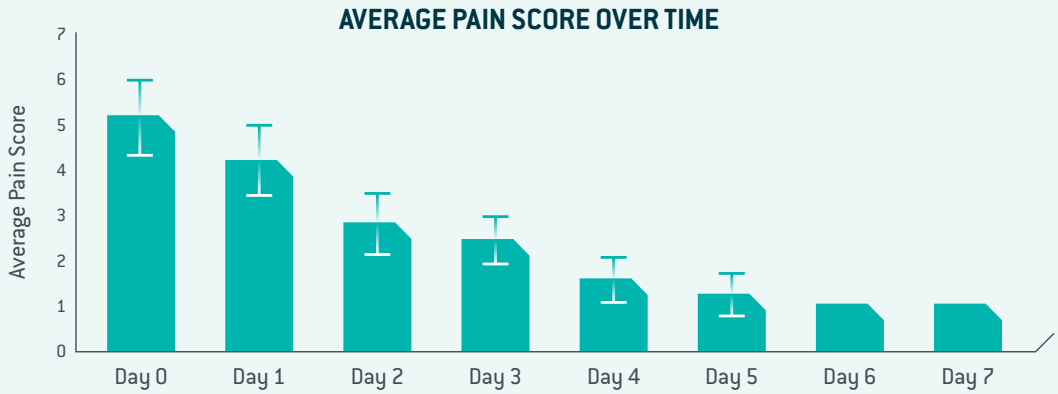

Figure 1. Patient-reported pain following an anti-VEGF injection. The average pain score was measured using the Visual Analogue Pain Scale (scale of 0-10) in 15 patients receiving anti-VEGF injections. At Day 0, the day of injection, patients experienced moderate pain, and some patients continued to experience mild pain up to 7 days following an intravitreal injection.[6]

Important Safety Information (cont.)

- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If LOTEMAX SM is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.

Please see additional Important Safety Information throughout and full Prescribing Information on pages 5-6.

Consider LOTEMAX SM to manage postoperative pain following an intravitreal injection

"Corticosteroids act to reduce inflammation after any type of physical trauma to the eye from ocular surgery.[11] Certain types of surgeries will inflict more trauma than others. In my experience, intravitreal injections are where most patients really complain about pain, much more than with other surgeries such as vitrectomy, where patients expect pain," says Dr. Sharma.

> "I have transitioned to LOTEMAX SM and use it exclusively as my corticosteroid of choice following a vitrectomy procedure." — ***Dr. Blinder***

LOTEMAX SM is indicated for the treatment of postoperative inflammation and pain following ocular surgery.[12] In clinical trials, 74% of patients achieved complete resolution of pain at Day 8 following cataract surgery.[13*†] Furthermore, 72% of patients achieved complete resolution of pain as early as 48 hours from the start of treatment.[13†] In these trials, patients treated with LOTEMAX SM had a low incidence of IOP elevation — only 1 of 369 patients (0.3%) experienced an IOP elevation ≥10 mm Hg.[13] Additionally, no single treatment-emergent adverse event was reported in >1% of subjects treated with LOTEMAX SM across both clinical trials.[12]

The LOTEMAX SM formulation was designed for patient comfort with a low concentration of preservative (0.003% benzalkonium chloride) and pH close to that of human tears (pH 6.5).[12,13] Additionally, LOTEMAX SM contains the moisturizing ingredients glycerin and propylene glycol.[12] LOTEMAX SM does not need to be shaken to resuspend the drug prior to administration, and each drop delivers a consistent concentration of loteprednol etabonate.[12,14] "I use LOTEMAX SM because patients do not need to shake the bottle," says Dr. Riemann. "Patients have a tendency to not shake their eye drops before instilling them."

Dr. George Fivgas adds, "I have used the LOTEMAX brand franchise since its inception, all the way up to the latest submicron formulation. I just find LOTEMAX SM to be very consistent. Patients take it easily, and I have not experienced problems with intraocular pressure." It should be noted that if LOTEMAX SM is used for 10 days of longer, IOP should be monitored. Dr. Kevin Blinder also adds, "LOTEMAX SM contains a lower concentration of loteprednol etabonate and exhibits better penetration to the aqueous humor compared to LOTEMAX Gel due to the submicron technology of LOTEMAX SM."[15]

Eligible patients can save on their prescription of LOTEMAX SM by taking a coupon to participating pharmacies. Visit **lotemaxsm.com/patient-access** for more information how patients can save.

Although the safety and efficacy of LOTEMAX SM were studied in the context of postoperative pain and inflammation following cataract surgery, it is important to note that LOTEMAX SM is indicated for the treatment of postoperative inflammation and pain following ocular surgery.[12] Many retina specialists prescribe LOTEMAX SM to manage pain following these IVIs and pars plana vitrectomies. Dr. Blinder says, "I have transitioned to LOTEMAX SM and use it exclusively as my corticosteroid of choice following a vitrectomy procedure."

*Pooled analysis of Phase 3 clinical studies. Study 1: 73% LOTEMAX SM (N=171) vs 48% vehicle (N=172) at Day 8. Study 2: 76% LOTEMAX SM (N=200) vs 50% vehicle (N=199) at Day 8; $P<0.05$ for all.[12,16]

†**Study Design:** Two randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies in 742 subjects examined the safety and efficacy of LOTEMAX SM in the treatment of postoperative inflammation and pain following cataract surgery. Primary efficacy endpoints were resolution of anterior chamber cells and grade (0) no pain at Day 8. Secondary efficacy endpoints included inflammation and grade (0) no pain at different visits (eg, Day 3).[12,13]

Important Safety Information (cont.)

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those with 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 infections.

Please see additional Important Safety Information throughout and full Prescribing Information on pages 5-6.

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"In my experience, some pars plana vitrectomy procedures such as macular puckers, membrane peels, and floaterectomies use smaller gauge needles and bring less trauma to the eye," says Dr. Sharma. "Other procedures such as removal of lens material, correcting tractional retinal detachments, and removal of intraocular foreign bodies will be more complex in nature and influence how inflammation and pain is managed postoperatively." Dr. Riemann adds, "I use corticosteroids following vitrectomy procedures that cause greater trauma to the eye. I have used LOTEMAX SM to manage pain and inflammation following retinal detachment." Dr. Fivgas agrees, adding, "I will sometimes use LOTEMAX SM in complex cases, such as diabetic tractional retinal detachments."

LOTEMAX SM has also been used to manage postoperative pain following an IVI. "The treatment regimen I follow for IVIs is to ensure that I rinse the eye well to prevent excessive exposure to povidone-iodine," says Dr. Gonzalez. "I also give my patients artificial tears, particularly for the evening of the injection. Finally, I instruct them to administer LOTEMAX SM at home."

Considering that many patients require routine IVIs to manage their ocular conditions, it is important to take into account patient comfort for patient compliance.[3,4] "I believe that there is genuine treatable pain following an IVI," says Dr. Eichenbaum. "In my experience those first 24 hours can be really unpleasant, which is why I'm treating more and more patients with corticosteroids, specifically with a corticosteroid like LOTEMAX SM that has affordable access. I think LOTEMAX SM works well for postinjection pain." The retina specialists agree that clinical trials examining LOTEMAX SM in the mitigation of postoperative pain following IVIs would be beneficial to reaffirm what they see in their clinics.

Consider Lotemax SM for postoperative pain following injections

Important Safety Information (cont.)

- Employment 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. Fungal cultures should be taken when appropriate.
- Contact lenses should not be worn when the eyes are inflamed.
- There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

Please see additional Important Safety Information throughout and full Prescribing Information on pages 5-6.

References: 1. Grzybowski A, Told R, Sacu S, et al. 2018 Update on Intravitreal Injections: Euretina Expert Consensus Recommendations. *Ophthalmologica.* 2018;239(4):181–193. **2.** Shin SH, Park SP, Kim YK. Factors Associated with Pain Following Intravitreal Injections. *Korean J Ophthalmol.* 2018;32(3):196–203. **3.** Haas P, Falkner-Radler C, Wimpissinger B, Malina M, Binder S. Needle size in intravitreal injections - pain evaluation of a randomized clinical trial. *Acta Ophthalmol.* 2016;94(2):198–202. **4.** Moisseiev E, Regenbogen M, Bartfeld Y, Barak A. Evaluation of pain in intravitreal bevacizumab injections. *Curr Eye Res.* 2012;37(9):813–817. **5.** Nguyen NCI, Fabro F, Ambresin A, et al. Factors associated with pain during intravitreal injection of anti-vascular endothelial growth factor. *Eye (Lond).* 2018;32(9):1544–1546. **6.** Rifkin L, Schaal S. Shortening ocular pain duration following intravitreal injections. *Eur J Ophthalmol.* 2012;22(6):1008–1012. **7.** Prkachin KM, Solomon PE, Ross J. Underestimation of pain by health-care providers: towards a model of the process of inferring pain in others. *Can J Nurs Res.* 2007;39(2):88–106. **8.** Saedon H, Nosek J, Phillips J, Narendran N, Yang YC. Ocular surface effects of repeated application of povidone iodine in patients receiving frequent intravitreal injections. *Cutan Ocul Toxicol.* 2017;36(4):343–346. **9.** Jordan A, Baum J. Basic tear flow. Does it exist? *Ophthalmology.* 1980;87(9):920–930. **10.** Rodrigues EB, Grumann A Jr, Penha FM, et al. Effect of needle type and injection technique on pain level and vitreal reflux in intravitreal injection. *J Ocul Pharmacol Ther.* 2011;27(2):197–203. **11.** Dua HS, Attre R. Treatment of post-operative inflammation following cataract surgery-a review. *European Ophthalmic Review.* 2012;6(2):98–103. **12.** LOTEMAX SM Prescribing Information. Bausch & Lomb Incorporated. **13.** Fong R, Cavet ME, DeCory HH, Vittitow JL. Loteprednol etabonate (submicron) ophthalmic gel 0.38% dosed three times daily following cataract surgery: integrated analysis of two Phase III clinical studies. *Clin Ophthalmol.* 2019;13:1427–1438. **14.** Marlowe ZT, Davio SR. Dose uniformity of loteprednol etabonate ophthalmic gel (0.5%) compared with branded and generic prednisolone acetate ophthalmic suspension (1%). *Clin Ophthalmol.* 2014;8:23–29. **15.** Cavet ME, Glogowski S, Lowe ER, Phillips E. Rheological Properties, Dissolution Kinetics, and Ocular Pharmacokinetics of Loteprednol Etabonate (Submicron) Ophthalmic Gel 0.38. *J Ocul Pharmacol Ther.* 2019;35(5):291–300. **16.** Data on file. Bausch & Lomb Incorporated.

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LOTEMAX® SM
(loteprednol etabonate ophthalmic gel) 0.38%

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LOTEMAX® SM safely and effectively. See full prescribing information for LOTEMAX® SM.

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38%, for topical ophthalmic use

Initial U.S. Approval: 1998

---------- INDICATIONS AND USAGE ----------

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

---------- DOSAGE AND ADMINISTRATION ----------

Invert closed bottle and shake once to fill tip before instilling drops. (2)

Apply one drop of LOTEMAX® SM into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

LOTEMAX® SM is a sterile preserved ophthalmic gel containing 3.8 mg of loteprednol etabonate per gram of gel. (3)

---------- CONTRAINDICATIONS ----------

LOTEMAX® SM, 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. (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 – The 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 – Employment 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 ----------

There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC, at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

2 DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops. Apply one drop of LOTEMAX® SM into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

3 DOSAGE FORMS AND STRENGTHS

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% is a sterile preserved ophthalmic gel containing 3.8 mg of loteprednol etabonate per gram of gel.

4 CONTRAINDICATIONS

LOTEMAX® SM, 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, 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, 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

The 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

Employment 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).

5.6 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

Contact lenses should not be worn when the eyes are inflamed.

6 ADVERSE REACTIONS

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.

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.

There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses

in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 4.2 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 106 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 10.6 times the RHOD. Maternal toxicity was observed in rats at doses 1066 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 106 times the RHOD.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (4.2 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (17 times the RHOD). At 3 mg/kg (128 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (256 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day.

Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (106 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (1066 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (2133 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (10.6 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg.

A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (10.6 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (106 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (1066 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

8.2 Lactation

There are no data on the presence of loteprednol etabonate in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for LOTEMAX® SM and any potential adverse effects on the breastfed infant from LOTEMAX® SM.

8.4 Pediatric Use

Safety and effectiveness of LOTEMAX® SM in pediatric patients have not been established.

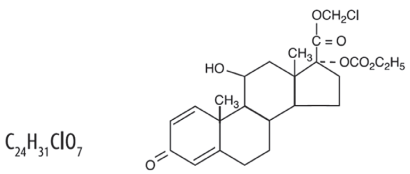
8.5 Geriatric Use

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

11 DESCRIPTION

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% contains a sterile, topical corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

Loteprednol etabonate is represented by the following structural formula:



$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

Chemical Name:

chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Each gram contains:

- Active: loteprednol etabonate 3.8 mg (0.38%);
- Inactives: boric acid, edetate disodium dihydrate, glycerin, hypromellose, poloxamer, polycarbophil, propylene glycol, sodium chloride, water for injection, and sodium hydroxide to adjust to a pH of between 6 and 7.
- Preservative: benzalkonium chloride 0.003%

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Loteprednol etabonate is a corticosteroid. Corticosteroids have been shown to inhibit the inflammatory response to a variety of inciting agents. 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

The pharmacokinetic exposure to loteprednol etabonate following topical bilateral ocular administration of one drop three times daily of LOTEMAX® SM for up to two weeks (Day 15) was evaluated in 18 healthy adult subjects. Plasma concentrations of loteprednol etabonate were analyzed using a validated LC/MS/MS method and the lower limit of quantitation for loteprednol etabonate was 0.05 ng/mL. The mean (± SD) C_{max} values for loteprednol etabonate in plasma were 0.13 (± 0.06) ng/mL on Day 1 after a single dose and 0.16 (± 0.06) ng/mL after the last dose on Day 15 of the study. The mean (± SD) AUC_t values for loteprednol etabonate in plasma were 0.15 (± 0.15) hr•ng/mL on Day 1 after a single dose and 0.35 (± 0.32) hr•ng/mL after the last dose on Day 15.

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 tk assay, or in the chromosomal aberration test in human lymphocytes, or *in vivo* in the mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (533 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (106 times the RHOD).

14 CLINICAL STUDIES

In two randomized, multicenter, double-masked, parallel group, vehicle-controlled trials in patients who underwent cataract extraction with intraocular lens implantation, LOTEMAX® SM administered three times daily to the affected eye beginning the day after cataract surgery was more effective compared to its vehicle in resolving anterior chamber inflammation and pain following surgery. In these studies, LOTEMAX® SM had statistically significantly higher rates of subjects with complete clearing of anterior chamber cells and of subjects who were pain free at post-operative Day 8 compared to vehicle. Results are shown in the following table.

Proportion of Subjects with Complete Clearing of Anterior Chamber Cells and Proportion of Subjects with Complete Resolution of Pain at Post-Operative Day 8.

	Study 1			Study 2		
Outcome	LOTEMAX® SM N=171 n (%)	Vehicle N=172 n (%)	Difference (95 CI) %	LOTEMAX® SM N=200 n (%)	Vehicle N=199 n (%)	Difference (95% CI) %
Cells	49 (29%)	16 (9%)	19 (11, 27)	61 (31%)	40 (20%)	10 (2, 19)
Pain	125 (73%)	82 (48%)	25 (15, 35)	151 (76%)	99 (50%)	26 (17, 35)

16 HOW SUPPLIED/STORAGE AND HANDLING

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% is a sterile ophthalmic submicron gel supplied in a white low-density polyethylene plastic bottle with a white controlled drop tip and a pink polypropylene cap in the following size: 5 g in a 10 mL bottle (NDC 24208-507-07)

Use only if imprinted neckband is intact.

Storage: Store upright at 15º to 25ºC (59º to 77ºF). After opening, LOTEMAX® SM can be used until the expiration date on the bottle.

17 PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

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

Contact Lens Wear

Advise patients contact lenses should not be worn when the eyes are inflamed.

Risk of Secondary Infection

Advise the patient to consult a physician if pain develops, redness, itching or inflammation becomes aggravated.

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Bridgewater, NJ 08807 USA

9669600-9669700

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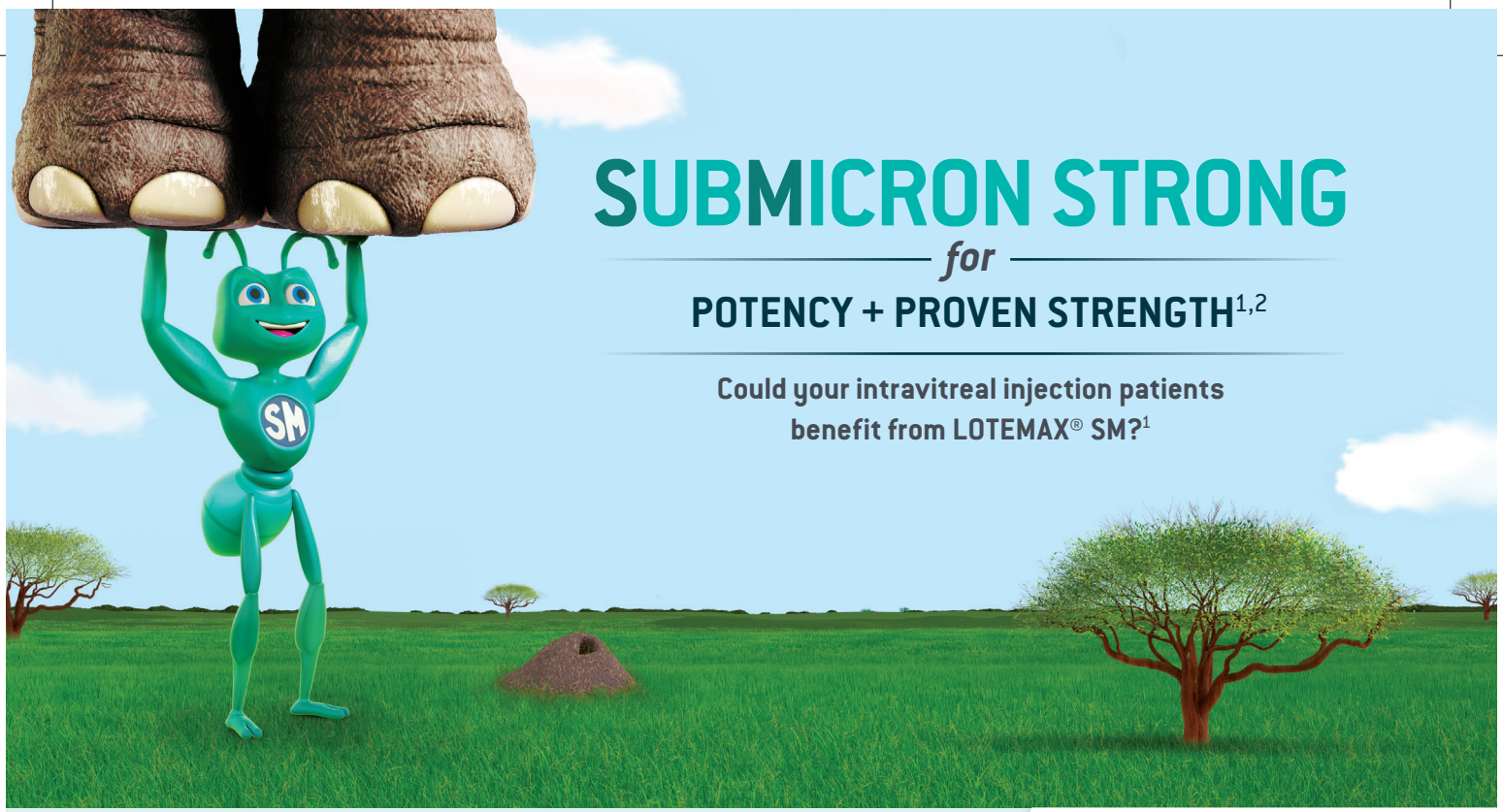

SUBMICRON STRONG

for

POTENCY + PROVEN STRENGTH[1,2]

Could your intravitreal injection patients benefit from LOTEMAX® SM?[1]

SM TECHNOLOGY™

- **Engineered with SM Technology™ for efficient penetration at a low BAK level (0.003%)[1,3]**
- **~2× greater penetration** to the aqueous humor than LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5%[3]*
- **2× greater inflammation clearance** as compared to vehicle[2†]

*Clinical significance of these preclinical data has not been established.

LOTEMAX® SM
(loteprednol etabonate ophthalmic gel) 0.38%

SMALL & MIGHTY
SUBMICRON PARTICLES

†PROVEN STRENGTH

- **30% of LOTEMAX® SM patients had complete ACC resolution** vs vehicle (15%) at Day 8 post-cataract surgery (N=371, *P*<0.0001)[1,2†]
- **74% of LOTEMAX® SM patients were completely pain-free** vs vehicle (49%) at Day 8 post-cataract surgery (N=371, *P*<0.0001)[1,2§]

†Pooled analysis of Phase 3 clinical studies. **Study 1:** 29% LOTEMAX® SM (N=171) vs 9% vehicle (N=172). **Study 2:** 31% LOTEMAX® SM (N=200) vs 20% vehicle (N=199); *P*<0.001 for all.

§Pooled analysis of Phase 3 clinical studies. **Study 1:** 73% LOTEMAX® SM (N=171) vs 48% vehicle (N=172). **Study 2:** 76% LOTEMAX® SM (N=200) vs 50% vehicle (N=199); *P*<0.001 for all.

Indication

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information

- LOTEMAX® SM, 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.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If LOTEMAX® SM is used for 10 days or longer, IOP should be monitored.

Important Safety Information (cont.)

- Use of corticosteroids may result in posterior subcapsular cataract formation.
- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those with 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 infections.
- Employment 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. Fungal cultures should be taken when appropriate.
- Contact lenses should not be worn when the eyes are inflamed.
- There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

Please see brief summary of Prescribing Information on adjacent page.

References: 1. LOTEMAX SM Prescribing Information. Bausch & Lomb Incorporated. **2.** Fong R, Cavet ME, DeCory HH, Vittitow JL. Loteprednol etabonate (submicron) ophthalmic gel 0.38% dosed three times daily following cataract surgery: integrated analysis of two Phase III clinical studies. *Clin Ophthalmol.* 2019;13:1427-1438. **3.** Cavet ME, Glogowski S, Lowe ER, Phillips E. Rheological properties, dissolution kinetics, and ocular pharmacokinetics of loteprednol etabonate (submicron) ophthalmic gel 0.38%. *J Ocul Pharmacol Ther.* 2019. doi: 10.1089/jop.2019;35(5):291-300.

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www.LOTEMAXSM.com

LOTEMAX® SM
(loteprednol etabonate ophthalmic gel) 0.38%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use LOTEMAX® SM safely and effectively. See full prescribing information for LOTEMAX® SM.

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38%

For topical ophthalmic use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

LOTEMAX® SM is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops. Apply one drop of LOTEMAX® SM into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

LOTEMAX® SM, 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, 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, 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: The 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: Employment 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: 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: Contact lenses should not be worn when the eyes are inflamed.

ADVERSE REACTIONS

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. 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. There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

USE IN SPECIAL POPULATIONS

Pregnancy: Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 4.2 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 106 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 10.6 times the RHOD. Maternal toxicity was observed in rats at doses 1066 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 106 times the RHOD. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies. Data: *Animal Data.* Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (4.2 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (17 times the RHOD). At 3 mg/kg (128 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (256 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day. Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (106 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (1066 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (2133 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (10.6 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg. A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (10.6 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (106 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (1066 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

Lactation: There are no data on the presence of loteprednol etabonate in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for LOTEMAX® SM and any potential adverse effects on the breastfed infant from LOTEMAX® SM.

Pediatric Use: Safety and effectiveness of LOTEMAX® SM 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 tk assay, or in the chromosomal aberration test in human lymphocytes, or *in vivo* in the mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (533 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (106 times the RHOD).

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