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APPLICATION NUMBER:

208219Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208219
Supporting document/s:	SD 1 (new NDA, submitted 4/25/2018) SD 7 (response to nonclinical information request, submitted 7/27/2018) SD 11 (revised labeling, submitted 10/19/2018)
Applicant's letter date:	April 25, 2018
CDER stamp date:	April 25, 2018
Product:	Lotemax SM (loteprednol etabonate ophthalmic gel) 0.38%
Indication:	Treatment of inflammation and pain following ocular surgery
Applicant:	Bausch & Lomb Incorporated Bridgewater, New Jersey 08807
Review Division:	Division of Transplant and Ophthalmology Products (DTOP), Office of Antimicrobial Products (OAP), CDER, HFD-590
Reviewer:	Andrew J. McDougal, PhD, DABT, DTOP
Supervisor:	Lori E. Kotch, PhD, DABT, DTOP
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1 Executive Summary

1.1 Introduction

- The Applicant, Bausch & Lomb Incorporated (B&L) is a wholly-owned subsidiary of Valeant Pharmaceuticals North America, LLC. B&L submitted NDA 208219 on April 25, 2018 under the 505(b)(1) pathway for loteprednol etabonate ophthalmic gel, 0.38%.
    - CDER's Division of Medication Error and Prevention Analysis has granted the proprietary name of Lotemax SM as "conditionally acceptable" (Chaudhry, 1/02/2019, NDA 208219).
    - The 0.38% gel uses "submicron particles" of loteprednol etabonate, to achieve higher exposure of ocular tissues compared to larger particles.
- Following topical ocular instillation in rabbits, distribution was: tear fluid > bulbar conjunctiva > cornea > iris/ciliary body > aqueous humor
    - Lotemax Gel (0.5% loteprednol) results in higher loteprednol exposure in the tear film and bulbar conjunctiva than the 0.38% gel.
    - Distribution to the cornea, iris/ciliary body, and aqueous humor was comparable.
    - With repeat dosing (4x over one day), the 0.38% gel resulted in higher systemic exposure to loteprednol than Lotemax gel (0.5%).
- The Applicant owns all nonclinical data needed to support the safety of this NDA. The NDA includes cross-reference to the Applicant's IND 102654 and NDA 202872.
- Internal EDR link: \\CDSESUB1\evsprod\NDA208219\208219.enx
- Internal SharePoint link for labeling: http://sharepoint.fda.gov/orgs/CDER-OND/dtopndas/NDA%20208219%20%20loteprednol%20etabonate/Forms/AllItems.aspx

1.2 Brief Discussion of Nonclinical Findings

- The established pharmacologic class (EPC) for loteprednol is "corticosteroid"[1]. It is approved in several topical ocular dosage forms, for the treatment of inflammation (or pain and inflammation). "Loteprednol etabonate is structurally similar to other corticosteroids. … It is highly lipid soluble which enhances its penetration into cells."
- Loteprednol etabonate (loteprednol) is a corticosteroid approved for topical ocular dosing; it is teratogenic at clinically-relevant doses and should not be used during pregnancy. No effect on fertility was detected. No milk concentration data are available.

[1] EPC Text Phrase list accessed via: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/lawsactsandrules/ucm428333.pdf

- Loteprednol etabonate was first approved in 1998, simultaneously for three NDAs (NDA 20583, NDA 20841, and NDA 20803). The same DART package has been submitted or cross-referenced for each subsequent B&L loteprednol NDA. The original PT review by David A. Shriver, Ph.D. (for NDA 20583) is referenced by subsequent P/T reviews. No new DART studies have been conducted.
- For NDA 208219, the Applicant conducted two rabbit PK studies, testing a slightly different formulation of loteprednol etabonate ophthalmic gel 0.38% than the Lotemax SM formulation
    - Plasma exposure following topical ocular dosing was demonstrated
    - Ocular distribution was characterized
- The GLP 28-day topical ocular toxicity study in rabbits (report # 8288734) administered the clinical formulation (0.38% gel) at one dose level: four times daily to one eye (OD), at 2 ¾ hour intervals.
    - This dose level was the ocular NOAEL. It provides a 1.66x dose margin for ocular safety compared to the labeled dose (i.e. the difference in dosing four times per day versus three times per day).
    - This dose level of Lotemax SM caused adrenal atrophy in the treated rabbits: up to 50% decrease in organ weight, with slight decreased cell size in the adrenal cortex. No recovery was observed (in rabbits allowed one week recovery after the cessation of treatment prior to sacrifice).
- A rat oral PK study was submitted to characterize systemic exposure to the PJ-90 and PJ-91 metabolites, (b) (4) .

505(b)(2) Consideration

- The 505(b)(2) pathway is not applicable.
- NDA 208219 is submitted under the 505(b)(1) pathway. The Applicant owns all nonclinical data needed to support the safety of this NDA. The NDA includes cross-reference to the Applicant's IND 102654 and NDA 202872. DTOP previously (at the January 30, 2018) concurred with this filing strategy.

1.3 Recommendations

1.3.1 Approvability

P/T recommends approval of the NDA.

1.3.3 Labeling

- For loteprednol etabonate, B&L recently submitted labeling to NDA 202872/S-02 to comply with the Pregnancy and Lactation Labeling Rule (PLLR). Approved labeling was published on July 20, 2018[2].
- For NDA 208219 (Lotemax SM), B&L is incorporating the fertility, developmental and reproductive toxicology (DART) studies from their NDA 202872 by cross-reference.
- The nonclinical dose margins presented in labeling are calculated using the labeled strength, dosage and administration:
    - For NDA 202872/S-02 (Lotemax):
        - The strength is 5 mg of loteprednol etabonate per gram of gel (0.5%).
        - The labeled dosage is: "one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period."
        - The PLLR review (McDougal, 3/20/2018) used 40 µl as the drop size. Therefore, the 0.5% gel = 200 µg/drop.
        - Assuming one eye is dosed with 2 drops/dose, four times daily, the total number of drops/day is 8, and the total daily dose is 1.6 mg/person/day.
    - Lotemax SM is 0.38% loteprednol etabonate, indicated for thrice daily dosing (TID) of one eye with one drop. P/T's calculations use the drop size of 40 mg (0.152 mg of loteprednol/dose). Assuming one eye is dosed with 1 drop/dose three times per day, the total number of drops/day is 3, and the total daily dose is 0.456 mg/person/day.

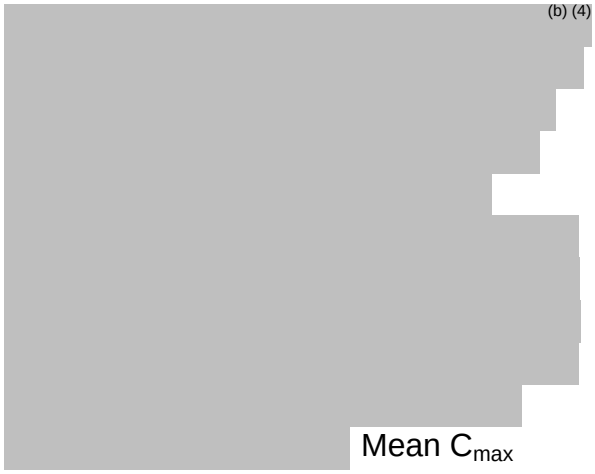
Applicant's proposed labeling (submitted 10/19/2018)[3]	P/T recommendations
8.1 Pregnancy <u>Risk Summary</u> There are no adequate and well controlled studies with loteprednol etabonate in pregnant women.	[no change]
(b) (4)	Loteprednol etabonate produced teratogenicity at clinically relevant doses

[2] NDA 202872/S-002 labeling accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202872s002lbl.pdf
[3] Accessible via: \\cdsesub1\evsprod\nda208219\0012\m1\us\draft-labeling-text.doc

(b) (4)	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 last trimester of pregnancy through lactation, survival of offspring was reduced at doses (b) (4) 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.	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.
	(b) (4)
Data *Animal Data*	*Data* *Animal Data*
(b) (4)	Embryofetal studies were conducted in pregnant rabbits administered loteprednol

(b) (4)	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

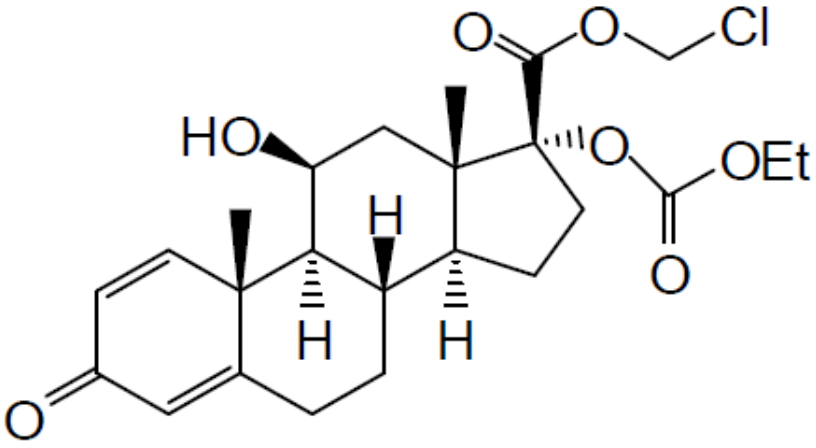
	mg/kg (10.6 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg.
(b) (4)	A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal 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 (b) (4)	**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.

12.3 Pharmacokinetics (b) (4)  Mean C_{max} values for loteprednol etabonate in plasma were 0.133 ng/mL and 0.160 ng/mL after a single administration and on Day 15, respectively. The mean AUC_{0-t} values for loteprednol etabonate in plasma were 0.148 hr•ng/mL and 0.353 hr•ng/mL after a single administration and on Day 15 after 2 weeks of three times daily dosing, respectively.	[No changes proposed, copied here for context]
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.	[no change]
(b) (4)	Treatment of female and male rats with 25 mg/kg/day of loteprednol etabonate (533 times the RHOD based on body surface area, assuming 100% absorption)

(b) (4)	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).

2 Drug Information

2.1 Drug

CAS Registry Number	82034-46-6
Generic name	Loteprednol Etabonate (LE)
Trade name:	Lotemax
Notable code names	LE LO 287M HGP-1 P-5604 OPC-5604 BOL-303011-X
Chemical name	chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate
Molecular formula	$C_{24}H_{31}ClO_7$
Molecular weight	466.96
Structure	 **Figure 1: Structure of loteprednol etabonate**
Pharmacological class	Corticosteroid

2.2 Relevant INDs, NDAs, and DMFs

- The Applicant's form 356h cross references Investigational New Drug (IND) file 102654, NDA 202872, and Drug Master File (DMF) (b) (4).
- The NDA's module 1.4.4 Cross Reference to Previously Submitted Information[4] incorporates by reference the nonclinical and clinical information previously submitted to IND 102654 and NDA 202872.
    - Tables 2 and 3 of module 1.4.4 (not copied here) list each nonclinical study referenced to support the safety of Lotemax SM.
    - IND 102654 is the predecessor IND for this NDA 208219. Bausch & Lomb submitted the original IND on 9/30/2009.
    - DMF (b) (4) is held by (b) (4). The subject is loteprednol etabonate. A letter of authorization is included[5] (under NDA module 1.4.1).
- Pharmos was the original Applicant for loteprednol. Three NDAs (20583, 20841, 20803) received original approval on the same date. Subsequently, B&L has submitted and received approval for three additional NDAs (new formulations).
- B&L submitted labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR) to NDA 202872. Approved labeling was published on July 20, 2018.
- Another Applicant, Kala Pharmaceuticals Inc., submitted NDA 210565 for Inveltys™ under the 505(b)(2) pathway [relying on NDA 20583], and received approval on 8/22/2018.

Table 1: Approved loteprednol etabonate NDAs

Lotemax®	NDA 020583	B&L	Loteprednol etabonate ophthalmic suspension, 0.5%	Original approval 3/09/1998[6]
	NDA 020841	Pharmos (discontinued)	Loteprednol etabonate ophthalmic suspension, 0.5%	Original approval also 3/09/1998[7]
	NDA 200738	B&L	loteprednol etabonate	Original approval 4/15/2011[8]

[4] Accessible via: \\cdsesub1\evsprod\nda208219\0001\m1\us\cross-reference.pdf
[5] Accessible via: \\cdsesub1\evsprod\nda208219\0001\m1\us\loa-dmf-(b) (4)-le.pdf
[6] For NDA 20583, the original Applicant was Pharmos Corp. The current Applicant is Bausch and Lomb. Labeling accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20583lbl.pdf
[7] For NDA 20841, labeling accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20841lbl.pdf
[8] For NDA 200738, abeling accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/200738s000lbl.pdf

			ophthalmic ointment, 0.5%	
	NDA 202872	B&L	loteprednol etabonate ophthalmic gel, 0.5%	Original approval 9/28/2012[9]. Labeling updated 7/20/2018[10].
Alrex	NDA 20803	B&L	Loteprednol etabonate ophthalmic suspension, 0.2%	Original approval 3/09/1998[11]
Zylet	NDA 50804	B&L	loteprednol etabonate and tobramycin ophthalmic suspension, 0.5%/0.3%	Original approval 12/14/2004[12]. Most recent labeling update 2/06/2013.[13]
Inveltys™	NDA 210565	Kala	Loteprednol etabonate ophthalmic suspension, 1%	Original approval 8/22/2018[14]

2.3 Drug Formulation

- The Applicant intends the submicron particle size of loteprednol etabonate in Lotemax SM to increase distribution into the eye. The particle size distribution is a controlled specification (NDA module 3.2.P.5.1):
  - D_{v10}: ≤ (b) (4) microns
  - D_{v50}: ≤ microns
  - D_{v90}: ≤ microns

[9] For NDA 202872, labeling accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202872lbl.pdf
[10] For NDA 202872/S-002, labeling accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202872s002lbl.pdf
[11] For NDA 20803, labeling accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20803lbl.pdf
[12] For NDA 50804, the original (2004) labeling was accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/050804lbl.pdf
[13] For NDA 50804, the 2013 labeling was accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050804s018lbl.pdf
[14] For NDA 210565, labeling accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210565s000lbl.pdf

- The drug product composition is presented in NDA module 2.3.P.1 (Description and Composition of Drug Product)[15]:

Table 2: Lotemax SM drug product formulation

Component	Reference to Quality Standard	Function	Label strength: 0.38%	
			Amount (mg/g fill)	%(w/w)
Loteprednol etabonate, (b) (4)	In-house	Active ingredient	(b) (4)	0.38%
Glycerin	USP/ Ph.Eur.	(b) (4)		(b) (4)
Propylene glycol	USP/ Ph.Eur.			
Sodium chloride	USP/ Ph.Eur.			
Benzalkonium chloride	NF/ Ph.Eur.	Anti-microbial agent		0.003%
Polycarbophil	USP	(b) (4)		(b) (4)
Hypromellose (b) (4)	USP			
Sodium hydroxide	NF/ Ph.Eur.	Alkalizing agent		
Poloxamer 407	NF	(b) (4)		
Edetate disodium	USP/NF			
Boric acid	NF/ Ph.Eur.			
Water for injection	USP/ Ph.Eur.			
		Total		-

USP = United States Pharmacopeia; Ph.Eur.= European Pharmacopoeia; NF = National Formulary

- The NDA's Module 3.2.P.7 (Container Closure System)[16] reports that two bottle sizes are proposed: a 10 ml bottle (with 5 g fill) and a 4 ml bottle (with 0.5 g fill). Both bottles have the same 15 mm (b) (4) controlled drop tip, (b) (4) .

[15] Accessible via: \\cdsesub1\evsprod\nda208219\0001\m2\23-qos\23p1-desc-comp-dp.pdf
[16] Accessible via: \\cdsesub1\evsprod\nda208219\0001\m2\23-qos\23p7-container-closure-system.pdf

- Module 3.2.P.2.4 (Container Closure System)[17] reports the mean weights of the dispensed drop (for the 3 bottles tested) were 41.9 ± 2.3, 41.8 ± 1.2, and 40.0 ±2.2 mg/drop. The amount of loteprednol delivered per drop was 0.162 ± 0.009, 0.159 ± 0.005, and 0.152 ± 0.009 mg respectively. As a reference values for calculating nonclinical dose margins, this review uses **40 mg** drop weight, and **0.152 mg** loteprednol/drop.

2.4 Comments on Novel Excipients

- No novel excipients for topical ocular dosing.
- NDA module 3.2.P.2.1 (Components of the Drug Product) notes that the excipients are only slightly different than the approved Lotemax gel, with the addition of Hypromellose (b) (4) and Poloxamer 407 in place of (b) (4). These are both qualified by previous listings in FDA's Inactive Ingredient Search (IIS)[18] (b) (4)

Table 3: Formulation comparison: Lotemax® (LE 0.5% gel) and Lotemax SM (LE 0.38% gel)

Component	Function	LE 0.38% sub-micron Gel	Lotemax® (LE 0.5% gel)
Loteprednol etabonate,	Active ingredient	(b) (4)	
Hypromellose (b) (4)	(b) (4)		
Tyloxapol			
Glycerin			
Propylene glycol			
Sodium chloride			
Benzalkonium chloride	Anti-microbial agent		
Polycarbophil	(b) (4)		
Sodium hydroxide (b) (4)	Alkalizing agent		
Poloxamer 407	(b) (4)		
Edetate disodium			
Boric acid			
Water for injection			

[17] Accessible via: \\cdsesub1\evsprod\nda208219\0001\m3\32-body-data\32p-drug-prod\le-0-38-gel-gel\32p2-pharm-dev\32p24-cont-closure-system.pdf
[18] FDA's internal version of the Inactive Ingredient Search accessed via: http://intranetapps.dev.fda.gov/scripts/cder/iig/getiigWEB.cfm

Total	**1g**	-

2.5 Comments on Impurities/Degradants of Concern

- The NDA's module 2.3.P.5 (Control of Drug Product) presents impurity specifications. CMC (personal communications, Zhang/McDougal and Kotch, October 2019) asked about three in particular:
  - (b) (4)
  - o
  - o
- From a regulatory perspective, there are no safety concerns for these three impurities. The total daily dose of loteprednol from Lotemax SM is 0.152 mg/person/day [i.e. based on tid dosing of one eye with one 40 mg drop]. Therefore, these three exposures correspond to:
  - (b) (4)
  - o
  - o
- These three exposures were previously qualified under the Applicant's Lotemax Gel 0.5% (NDA 202872) for topical and systemic exposure.
- Relatedly, the Applicant has data demonstrating that (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

- Based on the Applicant's proposed labeling (submitted 4/25/2018, with minor revisions on 10/19/2018):
  - Proposed indication is: "treatment of post-operative inflammation and pain following ocular surgery"
  - Proposed dosage and administration is: "Apply one drop of TRADENAME 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."
- The product is 0.38% loteprednol etabonate, 3.8 mg/g. Based on a drop size of 40 mg and a dose of 0.152 mg/drop[19], the daily dose per eye is 0.456 mg/eye/day (= 456 µg/eye/day). Based on the assumption that ocular surgery will be performed unilaterally (i.e. only one eye dosed with loteprednol), the daily dose is 456 µg/person/day.

2.7 Regulatory Background

- The drug product was developed under IND 102654. Following pre-IND interactions, the original IND was submitted on October 1, 2009. A pre-NDA

[19] Based on the data presented in NDA module 3.2.P.2.4 Container Closure System. See section 2.3 of this review (above) for additional information.

teleconference meeting was held between the Applicant and DTOP on January 30, 2018 (minutes by Germain, 2/20/2018, IND 102654).

- The NDA was submitted on April 25, 2018. The PDUFA goal date is February 25, 2019.
- .
- CDER's Division of Medication Error and Prevention Analysis has granted the proprietary name of Lotemax SM as "conditionally acceptable" (Chaudhry, 1/02/2019, NDA 208219).

3 Studies Submitted

3.1 Studies Reviewed

The Applicant submitted six nonclinical study reports to the NDA:

Report #	Report title
141410VSMB_BRN (BRNLOTE_141410_RPL-VP)	Method Validation for the Quantitation of Loteprednol Etabonate, PJ-90, and PJ-91 in Treated Rat Plasma by Turbo Ion Spray LC/MS/MS
2013-GMP-042	Investigation of the Systemic Pharmacokinetics of Loteprednol Etabonate Following Repeated (QID) Topical Ocular Administration to New Zealand White Rabbits
BL13001	Investigation of the Effect of Particle Size and Concentration on the Ocular Pharmacokinetics of Loteprednol Etabonate Following a Single Topical Ocular Administration to Dutch Belted Rabbits
8313586	Determination of the Pharmacokinetics of Loteprednol Etabonate and Two Metabolites, PJ-91 and PJ-90, after a Once Daily Oral Gavage of Loteprednol Etabonate to Rats for 28 Days
8288734	28-Day Ocular Instillation Toxicity and Toxicokinetic Study with Loteprednol Etabonate in New Zealand White Rabbits with a 7-Day Recovery Phase
BLM016drkls	*In silico* toxicology consultancy report. Toxicological analysis of nine potential impurities of Loteprednol etabonate using Derek Nexus and Leadscope

Note: Report # 882734 had been finalized prior to submission of the NDA. Apparently due to an oversight, the draft study report was submitted to the original NDA on 4/25/2018. The final study report was submitted to the NDA on 7/27/2018.

3.2 Studies Not Reviewed

None; all PT studies submitted to the NDA have been reviewed.

3.3 Previous Reviews Referenced

- The P/T reviews conducted under B&L's IND 102654 are referenced, by Dr. Chen (3/21/2011) and by Dr. Ruhland (6/06/2013, 9/20/2013, 2/13/2018)
- The recent P/T reviews for NDA 210565 (McDougal, 7/19/2018 and 8/01/2018) and the P/T reviews cited therein are referenced.
- The P/T PLLR review for NDA 202872/S-02 (McDougal, 3/20/2018) and the P/T reviews cited therein are referenced.
- The P/T reviews for the approved loteprednol NDAs are referenced:
    - For NDA 20583, a published redacted P/T review[20] is available via Drugs@FDA. This reviewer also obtained the full (paper) review from CDER Archives (NDA 20583 volume A2).
    - For NDA 20841, the P/T review[21] references the P/T review for NDA 20-583. No new nonclinical studies were conducted. Both NDAs were approved on the same day. This reviewer's understanding is that the essential difference between the two NDAs is the Applicant (Bausch and Lomb for NDA 20583; Pharmos Corp. for NDA 20841). NDA 20841 is now discontinued.
    - The P/T reviews for NDA 20803[22] and for NDA 202872[23] explain that the DART studies submitted under NDA 20583 were used to support each NDA. No new DART studies were conducted.
    - For NDAs 20583, 20803, 20841 and 200738, the original labeling is the most recent labeling presented on the Drugs@FDA website.

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[20] The P/T review for NDA 20583 was performed by David A. Shriver, Ph.D. However, the original P/T review does not have his name associated, or a completion date. Published redacted review accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20583_LOTEMAX_pharmr_P1.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20583_LOTEMAX_pharmr_P2.pdf

[21] Weir, 4/25/1997, NDA 20841. Published redacted review accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020841_LOTEMAX%200.5%25_pharmr.pdf

[22] Shriver, NDA 20803. Published redacted review accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20-803_ALREX_PHARMR.PDF

[23] Aziz, NDA 202872. Published redacted review accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202872Orig1s000PharmR.pdf

4 Pharmacology

4.1 Primary Pharmacology

No new primary pharmacology, secondary pharmacology, or safety pharmacology studies were submitted to NDA 208219. The Applicant cross-references their studies previously submitted to NDA 202872 for primary and secondary pharmacology. P/T previously determined that these studies were adequate, and they were not re-reviewed for NDA 208219.

Note: the Applicant reports (NDA module 1.4.4 Cross-reference to Previously Submitted Information) that no safety pharmacology studies have been conducted for loteprednol etabonate. Loteprednol is a corticosteroid; P/T defers to the Clinical review team, regarding the availability of clinical data for higher doses of loteprednol etabonate to address safety pharmacology.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK

- The Applicant cross-referenced PK and ADME data previously submitted to NDA to NDA 202872.
- Additionally, the Applicant submitted one validation report, two PK studies, and one ocular distribution study to NDA 208219.
- The Applicant reports (NDA Module 2.6.4 Pharmacokinetics Written Summary) that the quantitation range for loteprednol etabonate in rabbit plasma has improved over time. Early work used HPLC/UV; subsequent work uses HPLC/MS-MS.
    - For toxicology study # 8288734 (reviewed below), the quantitation range is 0.05 to 100 ng/ml.

Report title	**Method Validation for the Quantitation of Loteprednol Etabonate, PJ-90, and PJ-91 in Treated Rat Plasma by Turbo Ion Spray LC/MS/MS**	
Report #	• BRNLOTE_141410_RPL_VP (Applicant's report #) • 141410VSMB_BRN (Study laboratory's report #)	
Key findings	• This validation was performed to support toxicology study # 8313586 • The concentration range for quantitation of loteprednol, PJ-90, and PJ-91 in rat plasma were determined	
Report details:	Study laboratory	(b) (4)

<table>
<tr><td rowspan="3"></td><td>NDA location</td><td>Module 4.2.2.1 Pharmacokinetics – Analytical Methods and Validation Reports [\\cdsesub1\evsprod\nda208219\0001\m4\42-stud-rep\422-pk\4221-analyt-met-val\brnlote-141410-rpl-vp\brnlote-141410-rpl-vp.pdf]</td></tr>
<tr><td>Report status and date</td><td>Final; March 9, 2018</td></tr>
<tr><td>GLP compliance and Quality Assurance (QA)</td><td>• No claim of GLP made in the report
• The report has a signed QA statement</td></tr>
<tr><td>Method notes</td><td colspan="2">• Detection method: liquid chromatography/mass spectrometry (LC/MS/MS)</td></tr>
<tr><td>Results summary</td><td colspan="2"><table><tr><th>Analyte</th><th>Range of quantitation</th></tr><tr><td>Loteprednol etabonate</td><td>0.0500 to 100 ng/ml</td></tr><tr><td>PJ-90</td><td>0.0500 to 100 ng/ml</td></tr><tr><td>PJ-91</td><td>1.00 to 100 ng/ml</td></tr></table></td></tr>
</table>

<table>
<tr><td>Report title</td><td colspan="2">Investigation of the Systemic Pharmacokinetics of Loteprednol Etabonate Following Repeated (QID) Topical Ocular Administration to New Zealand White Rabbits</td></tr>
<tr><td>Report #</td><td colspan="2">2013-GMP-042</td></tr>
<tr><td>Key findings</td><td colspan="2">• Comparing commercial Lotemax gel (loteprednol etabonate 0.5%) to a formulation with 0.38% loteprednol prepared with sub-micron particles in rabbits, the 0.38% formulation resulted in higher systemic exposure (higher C_{max} and AUC).
• This study did not test the clinical formulation of Lotemax SM (Table 2 above).
• The formulation of the two test articles tested in this study was identical (excepting the loteprednol), and is slightly different from the drug product for Lotemax SM (Table 2 above).
o Lotemax SM's formulation has (b) (4) Poloxamer 407 (b) (4), and (b) (4) Hypromellose (b) (4). The tested formulations have (b) (4)% tyloxapol instead. The other excipients are the same.
o The particle size for the 0.38% gel tested is comparable to Lotemax SM.</td></tr>
<tr><td rowspan="2">Report details:</td><td>Study laboratories</td><td>• Test facility: (b) (4)</td></tr>
</table>

<table>
<tr><td></td><td></td><td>• Bioanalytical facility: Bausch & Lomb, Drug Metabolism and Pharmacokinetics, 1400 North Goodman Street, Rochester, NY 14609</td></tr>
<tr><td></td><td>NDA location</td><td>NDA module 4.2.2.2 Pharmacokinetics – Absorption [\\cdsesub1\evsprod\nda208219\0001\m4\42-stud-rep\422-pk\4222-absorp\2013-gmp-042\2013-gmp-042.pdf]</td></tr>
<tr><td></td><td>Report date</td><td>August 23, 2013</td></tr>
<tr><td></td><td>GLP compliance</td><td>No (page 1 explicitly states that it is not GLP-compliant]</td></tr>
<tr><td>Methods</td><td>Test articles</td><td>• For the 0.38% gel: 3.90 mg/ml loteprednol etabonate. Particle size (D_{V50}) = (b) (4) µM
o The actual dose was 0.39% (0.39 mg/ml)
o Review note: the term D_{V50} refers to median particle size.</td></tr>
<tr><td></td><td>Formulation:</td><td>Other than the dose (and particle size) of loteprednol, the test articles' formulation was the same:

Table 4: Test articles formulation (report # 2013-GMP-042)
<table><tr><td>Glycerin</td><td rowspan="8">(b) (4)</td></tr><tr><td>Propylene Glycol</td></tr><tr><td>Sodium chloride</td></tr><tr><td>Benzalkonium chloride</td></tr><tr><td>Polycarbophil</td></tr><tr><td>Sodium hydroxide</td></tr><tr><td>Edetate disodium</td></tr><tr><td>Tyloxapol</td></tr></table></td></tr>
<tr><td></td><td>Rabbit model</td><td>A total of 6 female New Zealand White rabbits with healthy eyes were used.
• 5-7 months of age
• Body weight range 2.51 to 4.22 kg</td></tr>
<tr><td></td><td>Dosing:</td><td>• Two groups of 3 rabbits, dosed with either Lotemax Gel, or the 0.38% submicron formulation.
• On the day of dosing, rabbits received four 50 µl doses into the right eye, at 3 hour intervals.
• The lower OD eyelid was pulled away from the globe; instillation was made into the conjunctival sac.</td></tr>
</table>

		• "Due to its viscosity, the test article was dispensed slowly to ensure that the entire volume had been delivered." • Lids were held together for 5 seconds after instillation, to help distribute the dose across the eye.
	Blood collection	Blood samples were collected: • 15 minutes prior to the 4th dose ($C_{-0.25hr}$) • After the 4th dose, at: 15, 30, 60 minutes, 2, 4 and 24 hours. • Analysis of loteprednol in plasma using LC/MS/MS method for rabbit plasma "developed and validated at (b) (4)" • Limit of quantitation is 0.0500 ng/ml to 100 ng/ml
Results:	**Table 5: Plasma TK following dosing of rabbits (OD x 4 at 3 hour intervals) with a 0.39% formulation (report # 2013-GMP-042)**	

	$C_{-0.25h}$ (ng/ml)	C_{max} (ng/ml)	Tmax (h)	AUC_{0-24h} (ng*h/ml)
Lotemax Gel (0.5%) 250 µg/dose	0.150 ± 0.184	1.00 ± 0.537	0.25	5.80 ± 4.53
Submicron formulation (0.39%) 190 µg/dose	0.186 ± 0.114	0.302 ± 0.0832	0.25	0.332 ± 0.0701

$C_{-0.25hr}$ sample was collected 15 minutes prior to the last dose

Report title	**Investigation of the Effect of Particle Size and Concentration on the Ocular Pharmacokinetics of Loteprednol Etabonate Following a Single Topical Ocular Administration to Dutch Belted Rabbits**
Report #	BL13001
Key findings	• For Lotemax SM, the Applicant considers particle size of loteprednol etabonate to be a critical attribute. • This study compared four formulations with different particle sizes • Formulation 1 has the smallest particle size (D_{V50} = (b) (4) µm), which approximates Lotemax SM (D_{V50} ≤ (b) (4) µm). Distribution was: tear film > bulbar conjunctiva > cornea > iris/ciliary body > aqueous humor • Lotemax Gel (0.5%, dose of 175 µg/eye) resulted in higher loteprednol concentrations in the tear film and bulbar conjunctiva

<table>
<tr><td></td><td colspan="2">compared to Formulation 1 (0.38%, dose of 133 µg/eye). Distribution to the other tissues measured (cornea, aqueous humor, iris/ciliary body) was comparable between the two formulations.
• No measurements for plasma PK, safety, or tolerability</td></tr>
<tr><td rowspan="4">Report details:</td><td>Study laboratories:</td><td>• Test facility: (b) (4)
• Bioanalytical laboratory: Bausch & Lomb, Drug Metabolism and Pharmacokinetics, 1400 North Goodman Street, Rocheste, NY 14609</td></tr>
<tr><td>NDA location</td><td>NDA module 4.2.2.3 Pharmacokinetics – Distribution [\\cdsesub1\evsprod\nda208219\0001\m4\42-stud-rep\422-pk\4223-distrib\bl13001\bl13001.pdf]</td></tr>
<tr><td>Report date</td><td>July 24, 2013</td></tr>
<tr><td>GLP compliance</td><td>No (page 1 explicitly states that it is not GLP-compliant]</td></tr>
<tr><td rowspan="4">Methods</td><td>Test articles</td><td>Table 6: Loteprednol particle sizes for the formulations tested in the rabbit ocular distribution study (report # BL13001)
<table>
<tr><th></th><th>Loteprednol etabonate (mg/ml)</th><th>Particle size (D_{V50}) µm</th></tr>
<tr><td>Formulation 1</td><td>3.90</td><td rowspan="4">(b) (4)</td></tr>
<tr><td>Formulation 2</td><td>3.96</td></tr>
<tr><td>Formulation 3</td><td>7.44</td></tr>
<tr><td>Lotemax Gel (Formulation 4)</td><td>5</td></tr>
</table></td></tr>
<tr><td>Formulation</td><td>Excepting the loteprednol dose and particle size, the formulation is the same as tested in report # 2013-GMP-042 (Table 4 above)</td></tr>
<tr><td>Rabbit model</td><td>• A total of 108 male Dutch Belted rabbits (b) (4) with healthy eyes were used (27/formulation)
○ 7-8 months of age
○ Weight range 1.56 to 2.69 kg</td></tr>
<tr><td>Dosing</td><td>• Each rabbit received single 35 µl dose bilaterally (i.e. both eyes dosed once)
• Doses were instilled into the lower conjunctival sac.</td></tr>
</table>

		• Immediately after dosing, eyelids were held closed "for several seconds" to allow distribution of the test article over the eye surface.
	Tissue collection and analysis	• 3 rabbits/formulation were sacrificed at 5, 15, 30 minutes, and 1, 2, 4, 8, 12, and 24 hours after dosing. o Tear fluid was collected with Schirmer tear strips o Bulbar conjunctiva and aqueous humor were collected in situ during the euthanasia procedure. o Eyes were enucleated and flash-frozen. Cornea and iris/ciliary body tissues were collected from frozen eyes. • Tissue samples were shipped to B&L for bioanalysis. • Loteprednol concentrations were analyzed by LC/MS/MS o The detection methods were developed at B&L for rabbit ocular tissues, and is not "fully validated" • Limits of quantitation: o Tear fluid: 12.5 ng/g to 125 mg/g o Bulbar conjunctiva: 1.45 ng/g to 1.45 mg/g o Cornea: 1.22 ng/g to 12.2 µg/g o Aqueous humor: 0.100 to 1000 ng/ml o Iris/ciliary body: 0.962 to 9620 ng/g

Results:

- For all formulations, distribution was: tear fluid > bulbar conjunctiva > cornea > iris/ciliary body > aqueous humor
- Formulations 1 and 2 had the same dose (133 µg/eye). Formulation 1, with small particle size, resulted in higher exposures (C_{max} and AUC) than formulation 2.
- Comparing formulation 1 (0.38%, particle size ~ Lotemax SM) against Lotemax Gel (formulation 4, 175 µg/eye), Lotemax Gel results in higher (statistically significant) concentrations in the tear film and bulbar conjunctiva. Concentrations in other tissues were comparable (slightly higher for Lotemax Gel).
- From the report (page 10):

Table 7: Ocular distribution results for 4 formulations tested in the rabbit (report # BL13001)

Dose Group	Tissue/Matrix	C_{max} (µg/g)	T_{max} (h)	$AUC_{(0\text{-}24h)}$ (µg*h/g)
Group 1: Submicron Formulation 0.38% (3.8 mg/mL) (133 µg/eye)	Tear fluid	614 ± 691	0.0833	260 ± 49.2
	Bulbar Conjunctiva	12.0 ± 12.7	0.0833	33.5 ± 4.30
	Cornea	3.29 ± 1.13	0.0833	6.93 ± 0.798
	Aqueous Humor	0.0281 ± 0.00665	1	0.0421 ± 0.00247[a]
	Iris/Ciliary Body	0.165 ± 0.0793	0.25	0.338 ± 0.0314
Group 2: (b) (4) Formulation 0.38% (3.8 mg/mL) (133 µg/eye)	Tear fluid	201 ± 269	0.0833	157 ± 26.4
	Bulbar Conjunctiva	78.7 ± 102	0.25	55.0 ± 10.6
	Cornea	2.22 ± 1.01	0.25	3.61 ± 0.436
	Aqueous Humor	0.0135 ± 0.00313	0.5	0.0183 ± 0.00107
	Iris/Ciliary Body	0.126 ± 0.0758	0.25	0.299 ± 0.0335
Group 3: Unmodified Formulation 0.75% (7.5 mg/mL) (262.5 µg/eye)	Tear fluid	673 ± 1020	0.25	384 ± 101[a]
	Bulbar Conjunctiva	22.4 ± 31.0	0.25	96.6 ± 18.0
	Cornea	2.59 ± 1.20	0.0833	8.38 ± 1.43
	Aqueous Humor	0.0190 ± 0.0273	0.25	0.0282 ± 0.00382
	Iris/Ciliary Body	0.255 ± 0.311	0.25	0.491±0.0586
Group 4: Lotemax Gel 0.5% (5 mg/mL) (175 µg/eye)	Tear fluid	871 ± 942	0.25	483 ± 96.6[a]
	Bulbar Conjunctiva	16.4 ± 19.7	0.25	95.0 ± 16.7
	Cornea	2.61 ± 1.13	0.0833	6.66 ± 0.672
	Aqueous Humor	0.0112 ± 0.00586	0.5	0.0228 ± 0.00349
	Iris/Ciliary Body	0.102 ± 0.118	0.0833	0.385 ± 0.0841

Abbreviations: C_{max}: Maximum mean (± SD) concentration observed after dosing; T_{max}: time C_{max} was observed; $AUC_{(0\text{-}24h)}$: Mean (± SE) area under the concentration versus time curve from the time of dosing through 24h.

[a] AUC and/or standard error (SE) estimates calculated in Excel (reported) vary slightly from values obtained in WinNonlin due to rounding differences.

Note: For aqueous humor, the relevant units for C_{max} and AUC are µg/mL and µg*h/mL, respectively.

- Note: no safety/tolerability endpoints were measured.

Report title	**Determination of the Pharmacokinetics of Loteprednol Etabonate and Two Metabolites, PJ-91 and PJ-90, after a Once Daily Oral Gavage of Loteprednol Etabonate to Rats for 28 Days**
Report #	8313586
Key findings	Systemic qualification of PJ-90 and PJ-91 up to the NOAEL (0.5 mg/kg/day)[24]

[24] In NDA module 2.6.6 (Toxicology Written Summary), the Applicant reports that the oral NOAEL for report # PTC/9 was the low-dose, 0.5 mg/kg/day for 28-days. This reviewer did not verify this conclusion.

		• PJ-90 is qualified up to 0.91 ng/ml • PJ-91 is qualified up to 2.55 ng/ml
		• This is an oral PK study (not topical ocular). SD rats were dosed orally (gavage) with 0.5, 5, or 50 mg/kg/day loteprednol (in (b) (4) % methylcellulose) for 28 days. • Plasma PK for loteprednol etabonate, PJ-90, and PJ-91 were measured, and PK parameters calculated. • The purpose of this study was to provide bridging data to the 28-day rat oral toxicology study (report # PTC/9; submitted to NDA 22872 and incorporated into NDA 208219 by cross-reference) • These two studies together (reports # PTC/9 and # 8313586) qualify systemic exposure to the metabolites PJ-90 and PJ-91 up to the concentrations detected.
Report details:	Study laboratories:	• In-life study location: (b) (4) • Dose-analysis was conducted by B&L • Bioanalysis was conducted by (b) (4)
	NDA location	The Applicant submitted this report under NDA module 4.2.3.2 Repeat-dose toxicity – rabbit. However, this study is a PK study (not a toxicology study). [\\cdsesub1\evsprod\nda208219\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\8313586\8313586.pdf]
	Report date	April 4, 2018
	GLP compliance and QA	• Yes: the study report has signed GLP and QA statements. • The dose-analysis has a statement claiming GLP compliance, but no QA statement was included. • The bioanalysis report has signed GLP and QA statements.
Methods	Test article	Loteprednol etabonate, lot # 140420842D
	Formulation	(b) (4) % carboxymethylcellulose
	Animal model	• Total of 54 Sprague Dawley rats (27 male, 27 female) • Age: 7 to 8 weeks at start of dosing • Body weight: 184 to 258 grams at start of dosing
	Dosing:	Groups of 9/sex/dose received a once daily oral gavage dose of 0.5, 5, or 50 mg/kg/day of loteprednol etabonate for 28 consecutive days • Dose levels: 0.5, 5, 50 mg/kg/day

		• Dose volume: 10 ml/kg
	Safety Endpoints:	• Twice daily checks for mortality and morbidity. • Once daily cage-side observations • Body weight was measured weekly
	PK sampling	• Blood was collected from 3 rats/sex/dose per time point on D1 and D28, at: pre-dose, 5, 15, 30, 45, 60 minutes, and 2, 4, 6, and 12 hours post-dose

Results

- Safety endpoints: no apparent treatment effect on body weight or clinical signs. All animals gained weight.
- TK: dose-proportional plasma exposure to loteprednol was observed. Consistent with previous studies, exposure to loteprednol results in detectable PJ-90 and PJ-91, demonstrating that rats metabolize loteprednol to PJ-90 and PJ-91.
- Table 8 was copied from NDA module 2.6.4 (Toxicology Written Summary). The subsequent three tables provide additional summary information, and were copied from the study report.

Table 8: Serum PK summary for the oral rat 28-day study (report # 8313586)

	LE Dose (mg/kg)	Day 1				Day 28					
		C_{max} (ng/mL)		AUC_{0-t} (ng•h/mL)		C_{max} (ng/mL)		AUC_{0-t} (ng•h/mL)		AUC_{0-24} (ng•h/mL)	
		M	F	M	F	M	F	M	F	M	F
LE	0.5	1.70	3.75	6.87	15.8	2.93	3.66	5.72	10.3	5.99	10.5
	5	6.85	19.2	32.6	144	6.68	25.3	20.2	108	20.2	108
	50	27.4	54.7	112	346	26.9	88.5	169	360	169	360
PJ-91	0.5	0.04	0.08	0.31	0.63	0.09	0.07	0.91	0.28	0.91	0.49
	5	0.54	0.92	4.51	6.24	0.50	0.82	6.66	8.16	6.66	8.16
	50	1.70	3.04	16	18.5	2.29	2.63	45.3	49.4	45.3	49.4
PJ-90	0.5	2.33	2.63	11.3	8.79	2.55	3.39	10.8	10.0	15.9	12.7
	5	40.5	17.8	219	121	52.2	26.2	233	141	233	153
	50	89.7	38.7	591	329	101	69.9	790	563	790	563

Table 9: Loteprednol plasma PK results for the oral rat 28-day study (report # 8313586)

Pharmacokinetic parameters for Loteprednol Etabonate in rat plasma: Days 1 and 28

Interval	Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	DN C_{max} [(ng/mL)/(mg/kg/day)]	T_{max} (hr)	AUC_{0-t} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	DN AUC_{0-12} [(ng·hr/mL)/(mg/kg/day)]	AUC_{0-24} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)	AR C_{max}	AR AUC_{0-12}
Day 1	1	0.5	M	1.70	3.39	2.00	6.87	6.87	13.7	NA	NC	NC	NA	NA
			F	3.75	7.51	0.750	15.8	15.8	31.7	NA	17.0	3.06	NA	NA
			MF	2.34	4.68	2.00	11.4	11.4	22.7	NA	12.7	3.82	NA	NA
	2	5	M	6.85	1.37	2.00	32.6	32.6	6.52	NA	34.1	2.47	NA	NA
			F	19.2	3.85	1.00	144	144	28.9	NA	146	1.56	NA	NA
			MF	12.4	2.47	2.00	88.5	88.5	17.7	NA	89.7	1.75	NA	NA
	3	50	M	27.4	0.549	2.00	112	112	2.24	NA	119	2.78	NA	NA
			F	54.7	1.09	2.00	346	346	6.92	NA	442	4.95	NA	NA
			MF	41.1	0.821	2.00	229	229	4.58	NA	277	4.36	NA	NA
Day 28	1	0.5	M	2.93	5.85	2.00	5.72	5.72	11.4	5.99	NA	5.81	1.72	0.833
			F	3.66	7.33	0.750	10.3	10.3	20.6	10.5	NA	1.91	0.976	0.651
			MF	2.67	5.34	2.00	8.02	8.02	16.0	8.23	NA	2.62	1.14	0.706
	2	5	M	6.68	1.34	2.00	20.2	19.4	3.88	20.2	NA	3.89	0.975	0.595
			F	25.3	5.06	2.00	108	105	20.9	108	NA	2.27	1.32	0.725
			MF	16.0	3.20	2.00	64.1	62.0	12.4	64.1	NA	2.77	1.29	0.701
	3	50	M	26.9	0.538	2.00	169	154	3.07	169	NA	4.23	0.979	1.37
			F	88.5	1.77	2.00	360	295	5.90	360	NA	8.53[a]	1.62	0.853
			MF	57.7	1.15	2.00	265	224	4.49	265	NA	6.73[a]	1.40	0.980

AR Accumulation ratio.
F Female.
M Male.
MF Male/female combined data.
NA Not applicable.
NC Not calculated.
a Predose sample was used as 24 hour postdose sample for estimation of $t_{1/2}$. As $t_{1/2}$ value was longer than half the sampling period (12 hours), this value should be interpreted cautiously.

Table 10: PJ-90 PK results for the oral rat 28-day study (report # 8313586)

Pharmacokinetic Parameters for PJ-90 in Rat Plasma: Days 1 and 28

Interval	Dose Group	Loteprednol Etabonate Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	DN C_{max} [(ng/mL)/(mg/kg/day)]	T_{max} (hr)	AUC_{0-t} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	DN AUC_{0-12} [(ng·hr/mL)/(mg/kg/day)]	AUC_{0-24} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)	MP C_{max}	MP AUC_{0-12}	AR C_{max}	AR AUC_{0-12}
Day 1	1	0.5	M	2.33	4.66	2.00	11.3	17.1	34.1	NA	NC	NC	1.37	2.48	NA	NA
			F	2.63	5.25	1.00	8.79	12.2	24.5	NA	NC	NC	0.700	0.773	NA	NA
			MF	2.38	4.76	2.00	10.1	14.6	29.3	NA	NC	NC	1.02	1.29	NA	NA
	2	5	M	40.5	8.11	2.00	219	219	43.7	NA	220	1.51	5.92	6.71	NA	NA
			F	17.8	3.56	2.00	121	121	24.2	NA	125	2.16	0.927	0.838	NA	NA
			MF	29.2	5.84	2.00	170	170	34.0	NA	172	1.77	2.36	1.92	NA	NA
	3	50	M	89.7	1.79	4.00	591	591	11.8	NA	NC	NC	3.27	5.28	NA	NA
			F	38.7	0.773	4.00	329	329	6.59	NA	NC	NC	0.707	0.953	NA	NA
			MF	64.2	1.28	4.00	460	460	9.20	NA	NC	NC	1.56	2.01	NA	NA
Day 28	1	0.5	M	2.55	5.09	4.00	10.8	15.9	31.8	15.9	NA	NC	0.871	2.78	1.09	0.932
			F	3.39	6.78	2.00	10.0	12.7	25.3	12.7	NA	NC	0.925	1.23	1.29	1.03
			MF	2.67	5.35	2.00	10.4	14.3	28.6	14.3	NA	NC	1.00	1.78	1.12	0.975
	2	5	M	52.2	10.4	2.00	233	215	43.1	233	NA	3.56	7.81	11.1	1.29	0.985
			F	26.2	5.25	2.00	141	141	28.2	153	NA	2.79	1.04	1.35	1.47	1.16
			MF	39.2	7.84	2.00	193	178	35.6	193	NA	3.13	2.45	2.87	1.34	1.05
	3	50	M	101	2.01	4.00	790	665	13.3	790	NA	NC	3.75	4.33	1.12	1.13
			F	69.9	1.40	2.00	563	440	8.79	563	NA	7.36[a]	0.791	1.49	1.81	1.33
			MF	75.3	1.51	4.00	677	552	11.0	677	NA	NC	1.30	2.46	1.17	1.20

AR Accumulation ratio.
F Female.
M Male.
MF Male/female combined data.
MP Metabolite to parent ratio.
NA Not applicable.
NC Not calculated.
a Predose sample was used as 24 hour postdose sample for estimation of $t_{1/2}$. As $t_{1/2}$ value was longer than half the sampling period (12 hours), this value should be interpreted cautiously.

Table 11: PJ-91 PK results for the oral rat 28-day study (report # 8313586)

Pharmacokinetic Parameters for PJ-91 in Rat Plasma: Days 1 and 28

Interval	Dose Group	Loteprednol Etabonate Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	DN C_{max} [(ng/mL)/(mg/kg/day)]	T_{max} (hr)	AUC_{0-t} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	DN AUC_{0-12} [(ng·hr/mL)/(mg/kg/day)]	AUC_{0-24} (ng·hr/mL)	$t_{1/2}$ (hr)	MP C_{max}	MP AUC_{0-12}	AR C_{max}	AR AUC_{0-12}
Day 1	1	0.5	M	0.0400	0.0800	2.00	0.309	0.309	0.617	NA	NC	0.0236	0.0449	NA	NA
			F	0.0762	0.152	6.00	0.629	0.629	1.26	NA	NC	0.0203	0.0397	NA	NA
			MF	0.0544	0.109	6.00	0.469	0.469	0.938	NA	NC	0.0232	0.0413	NA	NA
	2	5	M	0.541	0.108	6.00	4.51	4.51	0.901	NA	NC	0.0789	0.138	NA	NA
			F	0.918	0.184	6.00	6.24	6.24	1.25	NA	NC	0.0477	0.0432	NA	NA
			MF	0.729	0.146	6.00	5.37	5.37	1.07	NA	NC	0.0590	0.0607	NA	NA
	3	50	M	1.70	0.0340	6.00	16.0	16.0	0.321	NA	NC	0.0619	0.143	NA	NA
			F	3.04	0.0609	12.0	18.5	18.5	0.369	NA	NC	0.0556	0.0534	NA	NA
			MF	2.31	0.0461	12.0	17.2	17.2	0.345	NA	NC	0.0561	0.0754	NA	NA
Day 28	1	0.5	M	0.0947	0.189	2.00	0.908	0.532	1.06	0.908	NC	0.0324	0.0930	2.37	1.72
			F	0.0697	0.139	6.00	0.281	0.490	0.981	0.490	NC	0.0190	0.0475	0.915	0.779
			MF	0.0767	0.153	2.00	0.695	0.507	1.01	0.695	7.93[a]	0.0287	0.0632	1.41	1.08
	2	5	M	0.495	0.0989	2.00	6.66	4.29	0.858	6.66	9.94[a]	0.0741	0.221	0.915	0.952
			F	0.815	0.163	6.00	8.16	6.07	1.21	8.16	NC	0.0322	0.0580	0.888	0.973
			MF	0.605	0.121	6.00	7.41	5.18	1.04	7.41	NC	0.0378	0.0835	0.829	0.964
	3	50	M	2.29	0.0457	12.0	45.3	22.1	0.442	45.3	NC	0.0851	0.144	1.35	1.38
			F	2.63	0.0526	2.00	49.4	23.2	0.465	49.4	NC	0.0297	0.0788	0.864	1.26
			MF	2.46	0.0491	12.0	47.4	22.7	0.454	47.4	NC	0.0426	0.101	1.07	1.31

AR Accumulation ratio.
F Female.
M Male.
MF Male/female combined data.
MP Metabolite to parent ratio.
NA Not applicable.
NC Not calculated.
Note: Due to the lack of a distinct elimination phase on Day 1, $AUC_{0-\infty}$ and $t_{1/2}$ values were unable to be calculated for any profile.
a Predose sample was used as 24 hour postdose sample for estimation of $t_{1/2}$. As $t_{1/2}$ value was longer than half the sampling period (12 hours), this value should be interpreted cautiously.

6 General Toxicology

- The Applicant submitted one new repeat-dose toxicology study to support NDA 208219, that has not previously been reviewed under NDA.
- The Applicant also cross-references the repeat-dose toxicity data previously submitted to NDA 202872.

6.2 Repeat-Dose Toxicity

Study title: 28-Day Ocular Instillation Toxicity and Toxicokinetic Study with Loteprednol Etabonate in New Zealand White Rabbits with a 7-Day Recovery Phase

Study no.:	8288734
Study report location:	NDA module 4.3.3.2 Repeat-dose toxicity – rabbit. • The draft report was submitted to the NDA on 4/25/2018 (\\cdsesub1\evsprod\nda208219\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\8288734\8288734.pdf) • The final report was submitted to the NDA on 7/27/2018 (\\cdsesub1\evsprod\nda208219\0007\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\8288734\8288734.pdf)
Conducting laboratory and location:	(b) (4)
Report status and date:	Final report, March 7, 2014
Date of study initiation:	July 23, 2013
GLP compliance:	Yes, signed
QA statement:	Yes, signed
Drug, lot #, and % purity:	Loteprednol etabonate ophthalmic gel, 0.38% • D_{V50} = (b) (4) µm • Lot # RPG-130701-02 • Purity 96%

Key Study Findings

- This study compared vehicle to one dose level of loteprednol (the 0.38% gel, administered to one eye 4x/day) in NZW rabbits.
- Treatment caused a very slight decrease in body weight gain, and dramatic adrenal cortex atrophy [up to 50% adrenal organ weight loss; slight "decreased cells" observed by histopathology].
  - These effects are consistent with known systemic pharmacology of loteprednol.
  - These effects demonstrate that pharmacologically-active concentrations of loteprednol etabonate occur in rabbits following topical ocular dosing with loteprednol 0.38% gel.
- The test article did not cause adverse ocular effects; the ocular NOAEL is the test dose, 0.38% loteprednol (0.19 mg/eye/dose = 0.76 mg/eye/day = 0.76 mg/rabbit/day)

  - The clinical labeled dose is one drop three times per day in one eye; the clinical drop size is 40 mg (equivalent to 0.152 mg of loteprednol/dose = 0.456 mg/eye/day = 0.456 mg/person/day).
  - For ocular exposure, the rabbit results provide a 1.66x dose margin.
- The design of the study appears adequate to assess potential ocular toxicity.
- The test article formulation (0.38% gel) has slightly smaller particle sizes than the clinical drug product.
- Plasma TK was measured, and TK parameters were calculated. The highest observed systemic concentration was 3.61 ng/ml.

- Review notes:
  - For this NDA PT review, only the final study report was reviewed.
  - The test article analysis, bioanalysis, ophthalmology, and pathology reports are signed, with GLP and QA statements. The work was performed at (b) (4) (i.e. no other GLP laboratories).

Methods

Doses:	• Control animals received vehicle in the right eye (OD); the left eye (OS) was untreated. • Loteprednol animals received the test article OD, and vehicle OS
Frequency of dosing:	QID (4 times daily); each dose was given 2 ¾ hours ± 15 minutes apart, for 28 consecutive days
Route of administration:	Topical ocular instillation • Lower eyelid was gently pulled away from eyeball • One drop as instilled into the conjunctiva sac using a positive-displacement pipette • After dosing, eyelids were held together “for at least 5 seconds” to distribute test article across the eye
Dose volume:	50 µl per dose (200 µl/eye/day)
Formulation/Vehicle:	o The formulation is the same as the final clinical drug product formulation (Table 2 of this review).
Species/Strain:	New Zealand White Rabbit
Number/Sex/Group:	• Main group: 5/sex/group (sacrificed on D29) • Recovery group: 3/sex/group (sacrificed on D36, after 7 days of recovery)
Age at start of dosing:	14 weeks old
Weight at start of dosing:	Males: 2.409 to 2.875 kg Females: 2.307 to 2.846 kg

Test article formulation

- The test article and vehicle were used as supplied by B&L. The formulation was not reported to the study laboratory (report page 14).

- NDA module 2.3.P.2 Pharmaceutical Development[25] reported that the vehicle and test article for this study differ only in the presence/absence of 0.38% loteprednol etabonate. The composition matches the clinical drug product formulation exactly.
- The range of particle sizes of the test article overlap with the clinical drug product's specifications, and includes smaller particle sizes:
  - For the test article (lot # RPG-130701-02, page 513):
    - VMD = (b) (4) µm
    - D_{V10} = (b) (4) µm
    - D_{V50} = µm
    - D_{V90} = µm
  - For comparison, the clinical drug formulation (Lotemax SM) has specifications of (NDA module 3.2.P.5.1):
    - D_{v10}: ≤ (b) (4) microns
    - D_{v50}: ≤ microns
    - D_{v90}: ≤ microns
  - Theoretically, this difference may have slightly increased ocular distribution and systemic absorption.

Observations and Results

Safety endpoints

- Animals were checked twice daily for mortality and morbidity.
- Cageside observations were noted once daily. Detailed observations were made weekly.
- Food consumption was assessed qualitatively.
- Blood was collected for clinical chemistry, hematology, and coagulation once pre-dose, and at sacrifice.
- No treatment-related effects were apparent for these endpoints.
- No urinalysis or safety pharmacology endpoints were assessed.

Body Weight

- Body weight was recorded weekly.
- Body weight gain was slightly reduced in treated animals compared to controls. This reviewer considers the effect treatment-related and consistent with expected pharmacology (systemic exposure to a corticosteroid), but not adverse.
  - For males: from D8-15, control males gained 97 grams (3.4% weight gain); treated males gained 67 grams (2.4% weight gain). This difference was statistically significant ($p \leq 0.05$ by two-sample t-test)
  - For females: control females gained 132 g from D1-8 (+5.1%) and 324 g from D1-29 (+12.6%). Treated females gained 56 g from D1-8 (+7.6%) and 197 g from D1-29 (+7.6%). These differences are also statistically significant ($p \leq 0.05$ by two-sample t-test)

[25] Accessible via: \\cdsesub1\evsprod\nda208219\0001\m2\23-qos\23p2-pharm-dev.pdf

Ocular endpoints

- Methods:
  - Ocular irritation was scored using the Draize scoring system: pre-dose, on D1, and then weekly. Scoring was done "at least 15 minutes after the first daily dose and prior to the second daily dose".
  - Ophthalmic examinations were performed by a board-certified veterinary ophthalmologist: pre-dose, on D1 and 28 of dosing, and on D7 of recovery. Endpoints included slit lamp biomicroscopy (to evaluate the adnexa and anterior portions of the eye), fundoscopy with fluorescein staining, and scoring of ocular irritation using a modified Hackett-McDonald scale.
  - Intraocular pressure (IOP) and esthesiometry (corneal sensitivity, measured using a Cochet-Bonnet esthesiometer applied to the "approximate center of each cornea"; results are blink response data) were measured pre-dose, D1, D28, and D7 of recovery. During dose, assessments were made < 30 minutes prior to the first daily dose, and within 30 minutes after the second daily dose.
- Results:
  - No treatment-related effects apparent.
  - The study ophthalmologist concluded, "Topical application of 0.38% loteprednol etabonate was well tolerated, with no test article-related abnormal ophthalmic observations, IOP changes, or clinically important alterations in corneal sensitivity."
    - This reviewer questioned the potential significance of the language "clinically important" alterations in cornea sensitivity. Review of the esthesiometry data found that the results appear variable from animal to animal. This reviewer concurs that no treatment-related effect is clearly apparent. Loteprednol may have slightly decreased corneal sensitivity for some treated animals (which would be consistent with intended pharmacology), but the effect is unclear.
    - From report page: 880

Table 12: Esthesiometry results for the rabbit 28-day topical ocular toxicity study (report # 8288734)

Results of Threshold Range Analysis of Esthesiometry Data

		Dosing Day 1		Dosing Day 28		Recovery Day 7	
Group	Item	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye	Right Eye
1	Mean	14.7	15.9	19.1	20.9	15.0	16.7
	SD	4.99	5.54	4.17	8.41	6.32	6.83
	N	16	16	16	16	6	6
2	Mean	13.4	14.7	21.3	20.3	16.7	17.5
	SD	3.52	3.40	6.71	4.99	2.58	6.12
	N	16	16	16	16	6	6

Threshold Range = 7.0 to 26.8 based on a mean of 16.9 with a standard deviation of 3.30.

Gross Pathology

Standard gross pathology was conducted. No treatment-related findings were apparent.

Organ Weights

- A standard battery of organ weights was assessed: adrenals, brain, epididymes, heart, kidneys, liver, ovaries, prostate, seminal vesicles, spleen, testes, thymus, and uterus.
- Treatment caused a 50% decrease in adrenal weight.
- From report page 716:

Table 13: Topical ocular administration of 0.38% loteprednol etabonate gel caused 50% adrenal weight loss in rabbits (report # 8288734)

	Loteprednol etabonate			
Sex	Males		Females	
Dose Level (%)	0	0.38	0	0.38
Adrenal				
Terminal Sacrifice				
Absolute Weight (g)	0.279	88%	0.385	50%*
Body Weight Ratio (%)	0.0096	89%	0.0134	55%*
Brain Weight Ratio (%)	2.7959	93%	4.0383	50%*
Recovery Sacrifice				
Absolute Weight (g)	0.302	69%	0.283	77%
Body Weight Ratio (%)	0.0104	72%	0.0099	73%
Brain Weight Ratio (%)	3.1451	71%	3.0295	72%

* = Statistically significant difference (absolute or relative) compared with respective control mean value.
Note: Values for absolute weight and ratio of organ weights (relative to body or brain) for dosed groups expressed as percentage control mean value.

Histopathology

Adequate Battery: Yes. Histopathology included the eye with bulbar conjunctivae, eyelids (upper and lower with palpebral conjunctivae), optic nerve, nictitating membrane, Harderian gland, nasal turbinates, adrenals, the weighted organs, and selected other tissues (e.g. lung, lymph nodes, salivary gland, skin)

Peer Review: None. The study anatomic pathologist was (b) (4) .

Histological Findings

- All treated main-group rabbits (10/10) and all treated recovery-group rabbits (6/6) exhibited adrenal cortex “decreased cell size”. The severity was slight for all treated

main-group rabbits and 5/6 treated-recovery group rabbits. One treated recovery-group rabbit exhibited minimal severity.
  - The study authors considered this finding treatment-related, and this reviewer concurs.
  - No further details characterizing this histopathological observation were provided.
- Additionally, one treated recovery male exhibited adrenal cortex angiectasis.
- The adrenal medulla was not affected by treatment.
- One treated male (1/5, rabbit # F31117) had prostate minimal squamous cell metaplasia. [A search found no mention of the terms dysplasia, adeno*, or nodule]. In the absence of findings from other loteprednol studies, this single finding is considered incidental.

Toxicokinetics

- Comparing the C_{max} and AUC for Day 1 versus D27, accumulation is apparent for both males and females.

Table 14: Plasma TK results for the rabbit 28-day topical ocular toxicity study (report # 8288734)

Day	Group	Sex		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng·hr/mL)	$AUC_{8.25-20.25}$ (ng·hr/mL)	AR C_{max}	AR $AUC_{8.25-20.25}$
1	2	M	Mean	1.84	8.59	8.72	2.25	NA	NA
			SD	1.25	0.129	6.09	0.579	NA	NA
			N	8	8	8	6	NA	NA
		F	Mean	2.65	8.84	9.11	2.17	NA	NA
			SD	1.75	0.352	5.61	0.892	NA	NA
			N	8	8	8	2	NA	NA
27	2	M	Mean	2.69	8.57	13.7	3.62	1.76	1.89
			SD	1.73	0.114	8.08	1.10	1.50	0.627
			N	8	8	8	7	8	5
		F	Mean	3.61	8.51	18.2	4.36	2.23	2.99
			SD	2.61	0.0207	12.3	1.82	2.91	2.22
			N	8	8	8	6	8	2

M = Males; F = Females; C_{max} = Maximum observed concentration; T_{max} = Time of maximum observed concentration; AUC = Area under the concentration-time curve; AR = Accumulation ratio

Test article analysis

- Homogeneity and stability were measured, test article concentrations were with 5% of nominal.
- A certificate of analysis (COA) for the test article was included in the study report (page 525). Notably:
  - Total impurities = (b) (4) %
  - (b) (4)

- [redacted] (b) (4)
- Other individual impurities: ≤ [redacted] (b) (4) %

7 Genetic Toxicology

- No new genotoxicity studies were submitted to NDA 208219.
- The Applicant cross-references their data previously submitted to NDA 202872 for genotoxicity. P/T previously determined that these studies were adequate, and they were not re-reviewed for NDA 208219.
- Additionally, the Applicant submitted a quantitative structure-activity relationship (QSAR) analysis for 9 potential impurities.

Report title	**Toxicological analysis of nine potential impurities of Loteprendol Etabonate using Derek Nexus and Leadscope**	
Report #	BLM016drkls	
Key finding	• QSAR for 9 potential impurities predicted negative genotoxicity results.	
Rationale	• Per ICH M7(R1)[26], for identified impurities without experimental genotoxicity data, hazard identification based on "an assessment of Structure-Activity Relationships (SAR)" is recommended. • "Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based, and the second methodology should be statistical-based." • OND P/T generally accepts the two methods used for this study (Derek Nexus and Leadscope) as being adequate and complementary, for fulfilling ICH M7(R1) recommendations.	
Report details:	Study laboratory	[redacted] (b) (4)
	NDA location	NDA module 4.2.3.7 Other toxicology studies [\\cdsesub1\evsprod\nda208219\0001\m4\42-stud-rep\423-tox\4237-other-tox-stud\42377-other\blm016drkls\blm016drkls.pdf]
	Report date	September 11, 2017
• All 9 impurities were predicted to be negative.		

[26] ICH M7(R1). Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk Guidance for Industry. Accessible via: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf

- The structures tested by the two software programs are:

(b) (4)

(b) (4)

Figure 4: Structures of the (b) (4) and (b) (4) impurities

(b) (4)

Figure 5: Structures of the (b) (4) and (b) (4) impurities

(b) (4)

Figure 6: Structures of the (b) (4) and (b) (4) impurities

(b) (4)

Figure 7: Structure of the (b) (4) impurity

8 Carcinogenicity

No nonclinical carcinogenicity studies have been conducted with loteprednol etabonate.

9 Reproductive and Developmental Toxicology

- No new fertility, developmental or reproductive toxicology (DART) studies were submitted to NDA 202872. The Applicant cross-references their data previously submitted to NDA 202872. P/T previously determined that these studies were adequate, and they were not re-reviewed for NDA 208219.
- The Applicant's annotated draft labeling did not compare the Applicant's draft language for NDA 208219 to the published language for NDA 202872.
- The NDA's module 2.6.6 (Toxicology Written Summary)[27] does provide narrative summaries for each fertility, developmental, and reproductive toxicology study. Because no new DART data were submitted, these summaries were not reviewed for NDA 208219.

11 Integrated Summary and Safety Evaluation

- NDA 208219 for loteprednol etabonate ophthalmic gel 0.38% is submitted under the 505(b)(1) pathway.
- The rabbit 28-day topical ocular toxicity study (report # 8288734) tested the clinical formulation at one dose level, 0.38% (the clinical strength). The test dose (administered 4x/day unilaterally) was the NOAEL. For ocular safety, the dose margin is 1.66x.
    - This study provided additional support to qualify the two of the three impurities of potential interest ((b) (4)).
    - Treatment significantly decreased adrenal weight (and caused a non-recoverable decrease in adrenal cortex cell size), demonstrating the

[27] Accessible via \\cdsesub1\evsprod\nda208219\0001\m2\26-nonclin-sum\toxicology-written-summary.pdf

pharmacological activity of systemic exposure in rabbits following topical ocular dosing.

- The Applicant cross-referenced nonclinical and clinical data submitted to NDA 202872.
  - Ocular and systemic exposure to loteprednol, PJ-90, PJ-91, and other impurities are already well-qualified by the data submitted to NDA 202872.
- For both approved Lotemax gel, Inveltys, and Lotemax SM, the clinical indication is “treatment of postoperative inflammation and pain following ocular surgery”.

11.1 Dose margins for labeling

- The approaches used in recent P/T reviews (for NDA 202872/S-02 and for NDA 210565) for topical ocular loteprednol are referenced.
- The Clinical review discipline has explained (Boyd/McDougal, personal communication) that loteprednol would generally only be prescribed for one eye. If the patient needed surgery on both eyes at the same time, loteprednol would generally not be prescribed. Therefore, the calculations below assume treatment of only one eye.
- Consistent with previous loteprednol labeling, nonclinical data are inadequate to identify/calculate exposure margins based on comparative blood/plasma levels. Dose margins are presented by body surface area (BSA), with units of $mg/m^2/day$, based on the 2005 Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers[28] and assuming 100% absorption of the administered topical ocular dose.

- Lotemax SM is 0.38% loteprednol etabonate, indicated for thrice daily dosing (TID) of one eye with one drop. P/T’s calculations use the drop size of **40 mg** (**0.152 mg of loteprednol/dose**).
  - Assuming one eye is dosed with 1 drop/dose three times per day, the total number of drops/day is 3, and the total daily dose is 0.456 mg/person/day.
  - Assuming a reference human body weight of 60 kg, the 0.456 mg/person/day dose is the equivalent of 0.0076 mg/kg/day.
  - Using a correction factor (CF) of 37 to convert from mg/kg to mg/m^2 for patients, this dose is the equivalent of **0.2812 mg/m^2/day for Lotemax SM**.

[28] Accessed via: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078932.pdf

Table 15: Dose-margins for labeling

Species	Oral daily dose (mg/kg)	Oral daily dose (mg/m^2)[a]	P/T dose margin for		
			Lotemax Gel (0.5%; NDA 202872): clinical dose of 0.9866 mg/m^2/day	Invelyts (1%; NDA 210565): clinical dose of 0.8633 mg/m^2/day	for Lotemax SM (0.38%, NDA 208219): clinical dose of 0.2812 mg/m^2/day
Rabbit	0.1	1.2	1.2	1.4 x	4.26x
	0.4	4.8	4.8	5.6 x	17.0x
	0.5	6	6	7.0 x	21.3x
	3.0	36	36	41 x	128.0x
	6	72	72	83 x	256.0x
	12.5	150	150	174 x	533.4x
	25	300	300	347 x	1066.8x
	50	600	600	695 x	2133.7 x
	100	1200	1200	1390 x	4267.4 x
Rat	0.5	3	3	3.4 x	10.6 x
	5.0	30	30	34 x	106.6 x
	25	150	150	174 x	533.4 x
	50	300	300	347 x	1066.8 x
	100	600	600	695 x	2133.7 x

[a] Based on correction factors of 6 for the rat, and 12 for the rabbit, to convert the dose from mg/kg to mg/m^2.

- For context, NDA 202872/S-02 (Lotemax):
  - The labeled dosage is: “one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.”
  - The PLLR review (McDougal, 3/20/2018) used 40 µl as the drop size. Therefore, the 0.5% gel = 200 µg/drop.

- Assuming one eye is dosed with 2 drops/dose, four times daily, the total number of drops/day is 8, and the total daily dose is 1.6 mg/person/day.

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.

/s/

ANDREW J MCDOUGAL
01/25/2019 03:07:33 PM

LORI E KOTCH
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