CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208219Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review and Deputy Division Director Summary Review

Date	February 22, 2019
From	William M. Boyd, M.D., and Wiley A. Chambers M.D.
Subject	Cross-Discipline Team Leader Review and Deputy Division Director Summary Review
NDA	208219
Applicant	Bausch & Lomb Incorporated
Date of Submission	April 25, 2018
PDUFA Goal Date	February 25, 2019
Proprietary Name	Lotemax SM
Established or Proper Name	loteprednol etabonate ophthalmic gel, 0.38%
Dosage Form(s)	Topical ophthalmic gel
Regulatory Action	Approval
Indication(s)	treatment of postoperative inflammation and pain following ocular surgery

1. Benefit-Risk Assessment

Lotemax SM (loteprednol etabonate ophthalmic gel), 0.38% will be approved for the treatment of postoperative inflammation and pain following ocular surgery based on adequate and well controlled clinical trials.

Lotemax SM (loteprednol etabonate ophthalmic gel), 0.38% is a reformulation of Lotemax (loteprednol etabonate ophthalmic gel) 0.5% at a lower strength. The applicant claims that the new drug product has a smaller average particle size which serves to increase ocular penetration and residence time in anterior segment tissues, however a head to head comparision between loteprednol products with different average particle sizes was not performed. It is not known whether the difference in average particle size results in any differences. Per the 10/19/2018, submission to the NDA, "SM" in Lotemax SM stands for a "submicron" formulation. Submicron formulation is not a recognized dosage form, and the established name remains loteprednol etabonate ophthalmic gel. The currently proposed product, loteprednol etabonate ophthalmic gel 0.38%, has not been directly compared clinically to the approved loteprednol etabonate ophthalmic gel 0.5%. Thus the relative efficacy of the two products is unknown.

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
The data contained in this submission establishes the efficacy of Lotemax SM (loteprednol etabonate ophthalmic gel) 0.38% by demonstrating that in patients who underwent cataract surgery, a statistically higher percentage of patients had complete resolution of anterior chamber cells (cell score = 0) in the study eye at Postoperative Day 8 for LE gel 0.38% versus vehicle; a statistically higher percentage of patients had Grade 0 pain in the study eye at Postoperative Day 8 for LE gel 0.38% versus vehicle. There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the LE gel 0.38% three times daily group compared to vehicle. The potential benefits of Lotemax SM (loteprednol etabonate ophthalmic gel) 0.38% through reduction of post-operative inflammation and pain following ocular surgery in adults outweigh the identified risks as demonstrated in the clinical studies submitted with this NDA application.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Inflammation, including postoperative inflammation, can lead to permanent damage to the anterior and posterior segments of the eye.	Postoperative inflammation can be controlled and managed by the use of nonsteroidal or steroid products in the postoperative setting.
Current Treatment Options	Currently available treatments for postoperative inflammation following ocular surgery include the use of steroidal or nonsteroidal anti-inflammatory drug products.	This product, if approved, would provide an alternative formulation of an already approved steroid, administered as one drop 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
Benefit	Reduction, specifically clearance, of inflammation in the form of clearing of anterior chamber cells is a benefit; anterior chamber cells can be monitored by direct visualization of the anterior changer of the eye.	Lotemax SM had statistically significant higher incidences of subjects with complete clearing of anterior chamber cells and of subjects who were pain free at post-surgery Day 8 compared to vehicle.
Risk and Risk Management	Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision ,an increased risk of posterior subcapsular cataract formation and suppression of the host immune response. This product will only be indicated for short term use.	The clinical trials contained in this application demonstrated that the potential adverse events associated with the prolonged use of corticosteroids could be monitored and were unlikely to occur with short term use (2 weeks).

2. Background

Loteprednol etabonate (LE) is a corticosteroid that was originally developed as a topical ophthalmic suspension 0.5% (Lotemax). Lotemax is approved for the treatment of steroid responsive inflammatory conditions when the inherent hazard of steroid use is accepted to obtain an advisable diminution of edema and inflammation and for the treatment of postoperative inflammation following ocular surgery. Alrex (loteprednol etabonate ophthalmic suspension) 0.2% is approved for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis. A fixed combination product consisting of LE 0.5%/tobramycin 0.3% ophthalmic suspension (Zylet) is approved for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. LE ointment 0.5% (Lotemax) is approved for the treatment of post-operative inflammation and pain following ocular surgery.

LE ophthalmic gel 0.5% (LE Gel) for the treatment of post-operative inflammation and pain following ocular surgery was approved on September 28, 2012. The objective of a gel formulation was to provide an alternative ophthalmic delivery dosage form for patients requiring treatment for inflammation and pain following ocular surgery.

Currently Available Treatments for Proposed Indication

Name of Drug	**Indication**
Vexol	Treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis
Durezol	Treatment of inflammation and pain following ocular surgery
Lotemax Ointment	Treatment of post-operative inflammation and pain following ocular surgery
Lotemax Suspension	Treatment of post-operative inflammation and pain following ocular surgery
Lotemax Gel	Treatment of post-operative inflammation and pain following ocular surgery

Lotemax is a topical corticosteroid. Ocular AEs generally associated with prolonged use of ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Other reactions include acute anterior uveitis, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, and ptosis.

The product development of loteprednol etabonate ophthalmic gel, 0.38% was conducted under IND 102654. On June 10, 2013, an End-of-Phase 2 meeting was held to discuss the proposed development program for loteprednol etabonate ophthalmic gel, 0.38%. On January 30, 2018, a Pre-NDA was held to discuss the application submission plan. At this meeting the Agency discussed the

requirements for a PREA study and would consider NDA 202872 S-002[1] under review at that time in lieu of a pediatric post marketing requirement. Subsequently, NDA 202872 S-002 was approved on July 10, 2018. The applicant requested a full waiver from conducting a PREA study for loteprednol etabonate ophthalmic gel, 0.38%; however since the current application is a reformulation of loteprednol and not a new active ingredient, new dosage form, new dosing regimen or new route of administration, PREA does not apply.

3. Product Quality

From the Quality Assessment reviews in DARRTS dated 1/25/2019 and 2/22/2019:

The drug product is 5 g-fill gel in 10 mL (b) (4) white LDPE round bottle, fitted with (b) (4) white (b) (4) controlled drop tip and capped with a (b) (4) pink, polypropylene, (b) (4) closure.

Drug Substance

Bausch & Lomb (B&L) performs various tests on in-coming (b) (4) material from (b) (4). The tests are summarized in Table 3.2.S.4.1–1. (b) (4) The specifications provided in Table 3.2.S.4.1–2 have been established (b) (4).

[1] On July 20, 2018, NDA 202872 S-002 Lotemax (loteprednol etabonate ophthalmic gel) 0.5% was approved to treat post-operative inflammation following ocular surgery for childhood cataract in pediatric patients under the age of 12 years. There were no new safety concerns raised in this supplemental application concerning the use of LE ophthalmic gel 0.5% to treat post-operative inflammation following ocular surgery for childhood cataract in pediatric patients under the age of 12 years.

Tables 3.2.S.4.1–1. (b) (4) and 3.2.S.4.1–2 (b) (4)

Specification of (b) (4) Loteprednol Etabonate

Test	Analytical Procedure/Method	Acceptance Criteria
Description	Visual	White to off-white crystalline powder
Identification	IR/ Current USP (b) (4)	IR absorption spectrum exhibits maxima and minima at the same wavelengths as that of the reference standard
Residue on Ignition	Current USP <281>	(b) (4)
Loss on Drying[a]	Current USP <731>	
Particle Size	Light Scattering/ C-1572	
Related Compounds[a] (b) (4)	HPLC/ C-1289	
Residual Solvents (b) (4)	GC/ C-1675 or Current USP <467>	
Specific Rotation	Current USP <781>	
Assay[a]	HPLC/ C-1289	
Bioburden[a]	Current USP <61>	

[a]Required for retest interval

(b) (4)

Source: Module 3.2.S.4.1 Specification

Drug Product

The drug product, loteprednol etabonate (LE) 0.38% gel, is a sterile white to off-white gel for topical ophthalmic administration. The qualitative and quantitative composition is described in Table 3.2.P.1–1.

Table 3.2.P.1–1 Qualitative and quantitative composition of LE 0.38% gel

Component[1]	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 (b) (4)	NF/ Ph.Eur.	Alkalizing agent		
Poloxamer 407	NF	(b) (4)		
Edetate disodium dihydrate	USP/NF			
Boric acid	NF/ Ph.Eur.			
Water for injection	USP/ Ph.Eur.			
		Total		-

[1] The quantities of inactive ingredient in the formulation do not exceed the FDA's IID limit for the route of administration.

(b) (4)

(b) (4)

USP = United States Pharmacopeia; Ph.Eur.= European Pharmacopoeia; NF = National Formulary
Source: Module 3.2.P.1 Description and Composition of the Drug Product

Table 3.2.P.5.1–1 Release and shelf life specifications for LE 0.38% gel

Test	Procedure	Release Criteria	Shelf Life Criteria
Description	Visual	White to off-white gel	
Container Description	Visual	Not applicable	A white plastic bottle with dropper tip and pink cap, (b) (4)
Particulate Matter	Visual	Essentially free of foreign particulate matter	Not applicable
Identification A	HPLC C-1908	The retention time for loteprednol etabonate peak in the sample corresponds to that of the standard.	Not applicable.
Identification B	HPLC C-1908	The loteprednol etabonate peak in the sample and reference standard both exhibit a UV maximum at (b) (4) nm	Not applicable.
Loteprednol Etabonate Assay	HPLC C-1908	(b) (4) % of label claim (label claim = 0.38%)	
Related Substances	HPLC C-1909		
(b) (4)		NMT (b) (4) %	
		NMT %	
		NMT %	
		NMT %	
		NMT %	
		NMT %	
		NMT %	
		NMT %	
Total Related Substances		NMT %	
Benzalkonium Chloride	HPLC C-1907	(b) (4) % of label claim (label claim = 0.003%)	
pH	USP <791>	(b) (4)	
Viscosity	USP <912>	(b) (4) cps	
Osmolality	USP <785>	(b) (4) mOsm/kg	
Content Uniformity	USP <3> for semisolid products in tubes/ HPLC C-1908	(b) (4)	
Content Uniformity	USP <3> for semisolid products in tubes/ HPLC C-1908		
Sterility	USP <71>	Meets USP Requirements	
Antimicrobial Effectiveness	USP <51>	Not applicable	Meets USP Requirements
Fill Weight	Weight Check	5 g fill: NLT (b) (4) g[a] 0.5 g fill: NLT g[a]	Not applicable
Weight Loss/Gain	Manual C-1303	Not applicable	NMT (b) (4) %
Particle Size Distribution	Light diffraction C-1920	(b) (4)	

[a] An in-process fill weight of NLT (b) (4) g will ensure that NLT 5 g and NLT (b) (4) g will ensure and NLT 0.5 g, respectively will be delivered from the container at the time of release.
GT = greater than; NLT = not less than; NMT = not more than; USP = United States Pharmacopeia
Source: Module 3.2.P.5.1 Specifications

Container Closure

The primary packaging components summarized in Table 3.2.P.7.1–1 are used by Bausch & Lomb (B&L) for the commercial product. The primary components are (b) (4) . Incoming packaging components are inspected for cleanliness, visual, and dimensional attributes.

Table 3.2.P.7.1–1 Summary of primary packaging components

Components		5 g fill	0.5 g fill
Bottle	Vendor	(b) (4)	
	Size	10 mL	4 mL
	Description	White (b) (4) round, (b) (4)	
	Resin Manufacturer/Type	(b) (4)	
	Colorant Manufacturer/Type		
	Cross-Reference		
Tip	Vendor		
	Size	15 mm	
	Description	White, (b) (4) controlled drop tip, (b) (4)	
	Resin Manufacturer/Type	(b) (4)	
	Colorant Manufacturer/Type		
	Cross-Reference		
Cap	Vendor		
	Size	15 mm	
	Description	Polypropylene, pink, (b) (4)	
	Resin Manufacturer/Type	(b) (4)	
	Colorant Manufacturer/Type		
	Cross-Reference		

[a] (b) (4)

Source: Module 3.2.P.7 Container Closure System

Inspections

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
Bausch & Lomb, Inc.	**1000113778**	**SES** DP Manufacturing, Release and Stability Testing, Microbiological testing, Packaging and Labeling	• District File Review	• **Approve**
(b) (4)		(b) (4)	NFE	NFE
		SES Alternate Secondary Packaging and Labeling site	NFE	NFE
		SES Alternate Secondary Packaging and Labeling site	NFE	NFE
Bausch & Lomb, Inc.	1313525 merged into 1317628	CTL Alternate testing site for Release and Stability Testing, Microbiological testing	Approve based on Profile	Approve based on Profile
(b) (4)		CTL Alternate Raw material testing site	NFE	NFE

The drug product manufacturing facility, Bausch & Lomb (FEI:1000113778) is classified as NAI based on the recent inspection ending Jan 30, 2019. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on Feb 22, 2019. Therefore, NDA 208219 is recommended for APPROVAL from the product Quality perspective.

4. Nonclinical Pharmacology/Toxicology

Summarized from the Pharmacology/Toxicology review in DARRTS dated 1/25/2019:
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. Loteprednol etabonate as a corticosteroid is teratogenic in non-human animals at clinically-relevant doses. No effect on fertility was detected. No milk concentration data are available.

Loteprednol etabonate was first approved in 1998. 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, and 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) .

Pharmacology/Toxicology recommends approval of the application.

5. Clinical Pharmacology

From the Clinical Pharmacology review in DARRTS dated 1/22/2019:

The focus of the Clinical Pharmacology review of this NDA was to assess the systemic PK exposure of LE at the proposed dosing regimen for Lotemax SM. **Study 881** characterized the PK exposure of LE in 18 healthy adult subjects following topical bilateral ocular administration of 1 drop TID of Lotemax SM for 15 days.

Methods and Results: PK was assessed both after single and multiple doses of Lotemax SM. Serial blood samples were collected for PK analysis of LE on following dosing on Day 1 (single dose) and Days 15 and 16 (multiple dose) The PK parameters for LE were calculated by noncompartmental methods and can be seen in the table below.

Table 1. Summary of Lotemax SM Pharmacokinetic Parameters in Healthy Adult Subjects

	Study Day 1			Study Day 15		
	T_{max} (hr)	C_{max} (ng/mL)	AUC_t (hr.ng/mL)	T_{max} (hr)	C_{max} (ng/mL)	AUC_t (hr.ng/mL)
Nquant	18	18	8	18	18	18
Mean	0.23[a]	0.13	0.15	0.26[a]	0.16	0.35
SD	0.20-2.0[b]	0.06	0.15	0.20-1.9[b]	0.06	0.32

Source: Adapted from Study 881 PK Report

Abbreviations: AUC_t = area under the curve from the time of dosing to the time of the last measurable concentration; C_{max} = maximum observed drug plasma concentration; Nquant = number of subjects with quantifiable observation; SD = standard deviation; T_{max} = time at which C_{max} occurred.

a. Median values are presented for T_{max}.

b. Minimum-Maximum are presented for T_{max}.

Bioanalytical: Plasma concentrations of LE were analyzed using a validated LC/MS/MS method. The analytical ranges of the assay were validated from 0.05 to 100 ng/mL for LE and the lower limit of quantitation (LLOQ) for LE was 0.05 ng/mL. Review summary of the information from the submitted bioanalytical validation and performance reports is provided in the table below.

Table 1. Summary of the Bioanalytical Method

Validation Report	Validation report provided	☒Yes ☐No
	Validation report acceptable	☒Yes ☐No
Performance Report	Samples analyzed within the established stability period	☒Yes ☐No
	Quality control samples range acceptable	☒Yes ☐No
	Sample chromatograms provided	☒Yes ☐No
	Accuracy and precision of the calibration curve acceptable	☒Yes ☐No
	Accuracy and precision of the quality control samples	☒Yes ☐No
	Overall performance acceptable	☒Yes ☐No

Based on the findings of PK **Study 881**, the reviewer agrees with the Applicant's conclusion regarding systemic exposure to LE following single and multiple topical ocular dosing of one drop of Lotemax SM TID bilaterally for 15 days (only one dose was administered on Day 15 of the Study) in healthy adult subjects. The mean C_{max} values were < 0.2 ng/mL on day 1 following the first dose and on day 15 following multiple doses of Lotemax SM. The mean AUC_t were < 0.5 hr.ng/mL on day 1 following the first dose and on day 15 following multiple doses of Lotemax SM.

The Clinical Pharmacology review team recommends approval of NDA 208219.

6. Clinical Microbiology

Not applicable. Product is not an anti-infective.

7. Clinical/Statistical- Efficacy

From the Medical Officer review in DARRTS dated 1/22/2019:

Table of Studies/Clinical Trials

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Number of Subjects	Diagnosis of Patients	Duration of Treatment
Study 842	Efficacy and Safety of LE GEL 0.38% versus vehicle in the treatment of inflammation and pain following cataract surgery	Prospective, multi-center, randomized, double masked, placebo controlled LE GEL 0.38% Topical ocular BID and TID	514 eyes randomized 171 LE BID 171 LE TID 172 vehicle	Male and female subjects following routine uncomplicated cataract surgery	14 Days
Study 843	Efficacy and Safety of LE GEL 0.38% versus vehicle in the treatment of inflammation and pain following cataract surgery	Prospective, multi-center, randomized, double masked, placebo controlled LE GEL 0.38% Topical ocular BID	326 eyes randomized 163 LE BID 163 vehicle	Male and female subjects with specified amount of anterior chamber cells following routine uncomplicated cataract surgery	14 Days
Study 875	Efficacy and Safety of LE GEL 0.38% versus vehicle in the treatment of inflammation and pain following cataract surgery	Prospective, multi-center, randomized, double masked, placebo controlled LE GEL 0.38% Topical ocular BID and TID	600 eyes randomized 201 LE BID 200 LE TID 199 vehicle	Male and female subjects with specified amount of anterior chamber cells following routine uncomplicated cataract surgery	14 Days

The three phase 3 studies were conducted with LE gel 0.38%, (Study 842, Study 843, and Study 875). Study 842 and Study 875 included BID and TID dosing groups, and Study 843 only included a BID dosing group. Otherwise, the three studies used nearly identical protocols.

The primary efficacy endpoints for the Phase 3 studies were the proportion of subjects with complete resolution of anterior chamber cells (cell score = 0) in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle, and the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle. The primary analyses used the ITT population with missing values and post-rescue values imputed as treatment failures.

Primary Efficacy Analysis: ITT Population

Study 842 and 875: Proportion of Subjects with Complete Resolution of Anterior Chamber Cells and Complete Resolution of Ocular Pain in the Study Eye at Visit 5 (Postoperative Day 8); ITT Population - Missing Values and Post-Rescue Values Imputed as Treatment Failure

	Study 842			Study 875		
	Vehicle BID & TID (N=172)	LE gel 0.38% BID (N=171)	LE gel 0.38% TID (N=171)	Vehicle BID & TID (N=199)	LE gel 0.38% BID (N=201)	LE gel 0.38% TID (N=200)
Complete Resolution of AC Cells in the Study Eye (Cell Score = 0)						
Yes, n (%)	16 (9%)	46 (27%)	49 (29%)	40 (20%)	52 (26%)	61 (31%)
Difference [1]		18%	19%		6%	10%
(95% CI)		(10%, 25%)	(11%, 27%)		(-2%, 14%)	(2%, 19%)
P-value [2]		<.0001	<.0001		0.1703	0.0169
Complete Resolution of Ocular Pain in the Study Eye (Pain Score = 0)						
Yes, n(%)	82 (48%)	126 (74%)	125 (73%)	99 (50%)	151 (75%)	151 (76%)
Difference [1]		26%	25%		25%	26%
(95% CI)		(16%, 36%)	(15%, 35%)		(16%, 35%)	(17%, 35%)
P-value [2]		<.0001	<.0001		<.0001	<.0001

[1] Difference in percent of subjects with complete resolution (LE gel 0.38% - Vehicle).
[2] P-value comparing each LE 0.38% arm to Vehicle is from a Pearson Chi-squared test.
Source: Table 14.2.1.1 in CSR 842; Table 14.2.1.1 in CSR 875

In both trials 842 and 875, a significantly greater proportion of subjects in the LE gel TID treatment group compared with the vehicle group had complete resolution of anterior chamber cells, and complete resolution of ocular pain at Visit 5 (Postoperative Day 8).

Study 843: Proportion of Subjects with Complete Resolution of Anterior Chamber Cells and Complete Resolution of Ocular Pain in the Study Eye at Visit 5 (Postoperative Day 8) (ITT Population – Missing Values and Post-Rescue Values Imputed as Treatment Failure)

	LE gel 0.38% BID (N=163)	Vehicle BID (N=163)
Complete Resolution of AC Cells in the Study Eye (Cell Score = 0), n (%)	38 (23%)	29 (18%)
Difference[a] (95% CI)	5% (-3, 14)	
P-value[b]	0.2174	
Complete Resolution of Ocular Pain in the Study Eye (Pain Score = 0), n (%)	120 (74%)	97 (60%)
Difference[a] (95% CI)	14% (4, 24)	
P-value[b]	0.0069	

Source: Section 14.2, Table 14.2.1.1

Note: Assessments of complete resolution of AC cells and of ocular pain were mutually independent.
[a] Difference in percent of subjects with complete resolution (LE gel 0.38% - vehicle).
[b] P-value comparing the LE gel 0.38% group to the vehicle group is from a Pearson Chi-squared test.

In Study 843, the BID group was not statistically better than the vehicle for resolution of inflammation (Pearson Chi-squared test: p = 0.2174). Resolution of pain was gated and therefore not evaluated after the failure to demonstrate significance in inflammation resolution.

Summary of Efficacy:
In two randomized, multicenter, double-masked, parallel group, vehicle-controlled trials in patients who undergone cataract extraction with intraocular lens implantation (842 and 875), 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.

8. Safety

From the Medical Officer review in DARRTS dated 1/22/2019:

The three phase 3 studies conducted with LE gel 0.38%, (Study 842, Study 843, and Study 875) were pooled for the integrated safety analyses pertaining to adverse events, visual acuity, biomicroscopy findings, fundoscopy, IOP, ocular symptoms, and drop sensation.

Extent of Exposure
The overall extent of exposure is based on the results of the pooled phase 3 studies. A total of 904 subjects were exposed to LE gel, 0.38% (535 of whom received BID treatment, and 369 of whom received TID treatment), and a total of 533 subjects received vehicle (BID or TID).

Deaths
No deaths were reported during any trial of Lotemax SM.

Non-Fatal Serious Treatment-Emergent Adverse Events

Table 2.7.4.5–3: Serious Treatment-Emergent Adverse Events -- ITT Population

Subject	Study	Preferred Term	Treatment Group	Eye	Study Day	
					Onset	Stop
(b) (6)	842	endophthalmitis	Vehicle	OD	day 7	ongoing
	842	small intestinal obstruction	LE gel BID	non- ocular	day 11	day 16
	843	endophthalmitis	Vehicle	OD	day 8	day 19
	875	hypokalaemia	Vehicle	non- ocular	day 16	day 18

Source: Module 2.7.4.5.3.2 Other Serious Adverse Events

Four subjects experienced a total of four serious adverse events. Two events were ocular and occurred in the subjects in the vehicle group, and two events were non-ocular, and occurred in the LE gel 0.38% BID group and vehicle group. No serious adverse events occurred in subjects in the LE gel 0.38% TID group.

Common Ocular Adverse Events

Table 2.7.4.5–2: Common Ocular Adverse Events (≥1% in Any Treatment Group) in the Study Eye -- Safety Population

Systerm Organ Class Preferred Term	Vehicle N=533 n (%) [Events]	LE 0.38% BID N=535 n (%) [Events]	LE 0.38% TID N=369 n (%) [Events]	All LE Gel N=904 n (%) [Events]
Pooled for Studies 842, 843 and 875				
Eye disorders				
Photophobia	12 (2.3) [14]	6 (1.1) [6]	3 (0.8) [3]	9 (1.0) [9]
Eye pain	14 (2.6) [15]	7 (1.3) [9]	1 (0.3) [1]	8 (0.9) [10]
Conjunctival hyperaemia	6 (1.1) [9]	2 (0.4) [2]	[0]	2 (0.2) [2]
Corneal oedema	9 (1.7) [9]	[0]	[0]	[0]

Abbreviations: LE, loteprednol etabonate ophthalmic gel, 0.38%; N, number of subjects per treatment group; n, number of subjects in a specific category; TEAE, treatment emergent adverse event
Notes: At each level of summation (overall, system organ class, preferred term), subjects reporting more than 1 adverse event are counted only once. Percentages are based on the number of subjects in the Safety Population. The number in brackets represents the total number of events reported. Adverse events are coded using MedDRA Version 16.1.
Source: ISS Table 14.3.2.1

The most common adverse events in the study eye (occurring at an incidence of ≥ 1.0% in any treatment group) were photophobia, eye pain, conjunctival hyperaemia, and corneal edema (refer to Table 2.7.4.5–2). Higher proportions of subjects in the vehicle group compared with the LE gel BID and LE gel TID groups experienced these events.

Non-Ocular Adverse Events

All non-ocular treatment-emergent adverse events were reported in less than 1% of subjects in each treatment group. The most common non-ocular event was headache (vehicle: 0.9%, 5/533; LE gel BID: 0.2%, 1/535; LE gel TID: 0.8%, 3/369). All other non-ocular events, with the exception of bronchitis were reported in single subjects per treatment groups. Bronchitis was reported in two patients.

Summary of Safety:

In three randomized, multicenter, double-masked, parallel group, vehicle-controlled trials in patients who undergone cataract extraction with intraocular lens implantation, Lotemax SM was safe and well-tolerated when dosed three times a day in adults for the treatment of postoperative inflammation and pain following ocular surgery.

The most common adverse events in the study eye were photophobia, eye pain, conjunctival hyperaemia, and corneal edema. These events were reported in a higher percentage of patients treated with vehicle and are more likely related to the surgery performed. The most common non-ocular event was headache.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

On January 30, 2018, a Pre-NDA was held to discuss the application submission plan. At this meeting the Agency discussed the requirements for a PREA study and would consider NDA 202872 S-002 currently under review in lieu of a pediatric post marketing requirement. Subsequently, NDA 202872 S-002[2] was approved on July 10, 2018. The applicant requested a full waiver from conducting a PREA study for loteprednol etabonate ophthalmic gel, 0.38%; however since the current application is a reformulation of loteprednol and not a new active ingredient, new dosage form, new dosing regimen or new route of administration, PREA does not apply. No pediatric studies have been conducted with LOTEMAX SM.

11. Other Relevant Regulatory Issues

Biostatistics

Per the Biostatistics review dated 1/24/2019: The primary efficacy results as well as supportive analyses of secondary efficacy endpoints, provide evidence supporting the efficacy of the TID administration of Lotemax SM for the treatment of ocular inflammation and pain following cataract surgery.

Table 1: Applicant's Primary Efficacy Analysis (ITT)

	Treatments			% Diff (95% CI)	
	Vehicle N=172	BID N=171	TID N=171	BID- Vehicle	TID- Vehicle
Outcome	Study 842				
ACC; n (%)	16 (9.3)	46 (26.9)	49 (28.7)	17.6 (9.7, 25.5)	19.4 (11.3, 27.4)
Pain: n (%)	82 (47.7)	126 (73.7)	125 (73.1)	26.0 (16.0, 36.0)	25.4 (15.4, 35.4)
	Study 875				
Outcome	Vehicle N=199	BID N=201	TID N=200	BID- Vehicle	TID- Vehicle
ACC; n (%)	40 (20.1)	52 (25.9)	61 (30.5)	5.8 (-3.6, 15.2)	10.4 (1.9, 18.9)
Pain: n (%)	99 (49.7)	151 (75.1)	151 (75.5)	25.4 (14.9, 35.9)	25.8 (16.6, 34.9)

Source: Table 6 of the Applicant's study reports. n=number of subjects with complete resolution; ACC: Anterior chamber cells; Pain: Ocular pain

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

Eight investigators had disclosable financial interests/arrangements (Form FDA 3455). The (b) (6) eyes enrolled by these investigators constituted only (b) (6)% of the toal eyes enrolled (too few to influence the overall clinical results). See table below.

[2] In a trial to evaluate the safety and efficacy of Lotemax gel, 0.5% in pediatric subjects 0 – 11 years of age, Lotemax gel, 0.5% demonstrated non-inferiority to Prednisolone Acetate Ophthalmic suspension, 1% for the treatment of intraocular inflammation following childhood cataract surgery.

Investigator / Sub-investigator	Site	Eyes Enrolled in Study 842	Eyes Enrolled in Study 875
[redacted]	(b) (6)		Not in study
			Not in study
			Not in study

OSI

A routine Office of Scientific Investigations (OSI) audit was requested. Per the OSI review dated 12/7/2018: Clinical inspections were requested for the following identical protocols in support of this application: Protocols 842 and 875, "A Phase 3, Multi-Center, Double-Masked, Vehicle-Controlled, Randomized, Parallel-Group Study to Assess Loteprednol Etabonate Ophthalmic Gel, 0.38% (BID and TID) versus Vehicle Gel for the Treatment of Ocular Inflammation and Pain Following Cataract Surgery." The clinical sites of Drs. Dao and Van were selected for inspection as the highest enrollers in their respective studies.

Site # Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site #028 **Jung Dao, M.D.** Cornea and Cataract Consultants of Arizona 3815 East Bell Road, Suite 2500 Phoenix, AZ 85032	875 Subjects: 39	30 Oct -6 Nov2018	NAI
Site #146 **Da-Thuy Van, D.O**. Texas Clinical Research Center 1100 Gulf Freeway, Suite 114 League City, TX 77573	842 Subjects: 35	16-19 Oct 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

Based on the results of these inspections, the identical studies (Protocols 842 and 875) appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the

respective indication. The final classification of the inspections of both Drs. Dao and Van was No Action Indicated (NAI).

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, (b) (4), and granted conditional acceptance on 7/9/2018. The applicant withdrew the proposed proprietary name, (b) (4), from review on 10/19/2018.

DMEPA finalized a review of a second proposed proprietary name, Lotemax SM, and granted conditional acceptance on 1/2/2019. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

Clinical expressed concerns that the name, Lotemax SM, is potentially misleading. Per the 10/19/2018 submission, "SM" stands for a "submicron" formulation. Submicron formulation is not a recognized dosage form, and there is no evidence to suggest that the particle size of this product distinguishes it from other loteprednol gel formulations. The established name remains loteprednol etabonate ophthalmic gel.

DMEPA completed a labeling review of the 10/19/2018 carton/container labeling on 12/31/2018. The proposed container label and carton labeling were found acceptable from a medication error perspective.

OPDP

The Office of Prescription Drug Promotion (OPDP) completed separate reviews of the draft, substantially complete USPI and carton/container labeling on 1/25/2019 and 1/29/2019.

12. Postmarketing Recommendations

A risk management plan is not necessary given the known risks of this class of products. There are no recommended Post-Marketing Requirements or Commitments.

13. Labeling

Lotemax SM (loteprednol etabonate ophthalmic gel), 0.38% will be approved for the treatment of postoperative inflammation and pain following ocular surgery based on adequate and well controlled clinical trials with the labeling below (submitted 2/15/2019).

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
02/22/2019 03:58:29 PM

WILEY A CHAMBERS
02/22/2019 04:14:44 PM