SUMMARY REVIEW of NDA 202872/S-002

Application Type	Efficacy Supplement
Application Number(s)	202872 S-002
Original Submit Date(s)	October 10, 2017
Established Name	Loteprednol etabonate ophthalmic gel 0.5%
(Proposed) Trade Name	Lotemax
Therapeutic Class	Corticosteroid
Applicant	Bausch and Lomb
Formulation(s)	Ophthalmic gel
Dosing Regimen	One (1) to two (2) drops in the affected eye four times daily for 14 days followed by a 14 day taper.
Indication(s)	Treatment of post-operative inflammation and pain following ocular surgery
Intended Population(s)	Patients ages 18 years and older with post-operative inflammation and pain

1 Introduction and Regulatory 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 ocular inflammatory disorders when the inherent hazard of steroid use is accepted to obtain an advisable diminution of edema and inflammation and treatment of postoperative inflammation following ocular surgery.

The original application was for a new formulation, 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.

This application is in response to PREA PMR 1927-1: A Randomized, Multicenter, Double Masked, Parallel-Group Study Assessing Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Cataract Surgery for Childhood Cataract (Study 670). Study 670 was also completed in response to a Pediatric Written Request (WR), but the applicant missed the due date of June 2017. The applicant understood that they had not met the strict terms of the WR and did not request an extension to the WR due date.

2 Important Safety Issues With Consideration to Related Drugs

Lotemax is a topical corticosteroid. Ocular AEs generally associated with 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.

3 Ethics and Good Clinical Practices

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information requests for the sponsor. There is no evidence that the study reviewed in this supplemental NDA was not conducted in accordance with acceptable clinical ethical standards.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Qualitative and Quantitative Composition of Loteprednol Etabonate Ophthalmic Gel

Component	Reference to Quality Standard	Function	Concentration	
			mg/g	% w/w
Loteprednol Etabonate	In-house	Active	5.00	0.500
(b) (4)				
(b) (4)				

The formulation of loteprednol etabonate ophthalmic gel that was used in the clinical studies is the same as the formulation currently marketed.

4.2 Non-clinical Pharmacology/Toxicology

The labeling has been updated to conform with current regulations, 21 CFR 201.57(c)(9), Use in specific populations: Pregnancy, Labor, and Lactation.

4.3 Clinical Pharmacology

4.3.1 Mechanism of Action

Loteprednol etabonate ophthalmic gel is topical, anti-inflammatory corticosteroid for ophthalmic use.

4.3.2 Pharmacodynamics

Not performed for this supplemental application.

4.3.3 Pharmacokinetics

Not performed for this supplemental application.

5 Clinical Data

Protocol #	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/ Patients Enrolled
670 Safety/ efficacy study	Prospective, multi-center randomized, active-controlled, double-masked	Patients 0 to 11 years of age undergoing surgery for childhood cataract	Loteprednol etabonate ophthalmic gel 0.5% Prednisolone acetate ophthalmic solution 1%	1-2 drops QID x 14 days, followed by 1-2 drops BID x 7 days, followed by 1-2 drops QD x 7 days.	Approx. 28 days	107

Study 670: A Randomized, Multicenter, Double-Masked, Parallel-Group Study Assessing the Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Surgery for Childhood Cataract

Study Design

This study was a prospective, multi-center, double-masked, parallel group, randomized, active-controlled trial designed to evaluate the efficacy and safety of loteprednol etabonate (LE) ophthalmic gel, 0.5% compared to prednisolone acetate (PA) ophthalmic suspension 1% (PA) for the treatment of postoperative inflammation following ocular surgery for childhood cataract. Post-operatively, subjects were randomized in a 1:1 ratio to receive LE Gel or PA Suspension.

Visit 1 was the Screening Visit. Visit 2 was the day of surgery. At Visit 3 (Post-operative Day 1), eligibility for randomization was assessed. Eligible subjects completed post-operative study Visits 4 through 8.

Subjects instilled one or two drops of masked study drug into the study eye four times a day, at approximately four hour intervals for 14 days. The initial dose occurred at Visit 3 (Post-operative Day 1). Treatment was tapered to twice a day during post-operative days 15 to 21 and tapered further to once a day during post-operative days 22 to 28. The last dose was administered on the day before Visit 6 (Post-operative Day 28).

Grading Scales Used

Anterior Chamber Cells (for those subjects that could be examined with a slit lamp): Assess accumulation of white blood cells in aqueous. Pigment cells and red blood cells were to be ignored. Assess anterior chamber using a high power field slit beam of 1 mm x 1 mm.
0 = No cells seen
1 = 1 - 5 cells
2 = 6 - 15 cells
3 = 16 - 30 cells
4 = >30 cells

Anterior Chamber Flare (for those subjects that could be examined with a slit lamp): Assess scattering of a slit lamp light beam when directed into the anterior chamber (Tyndall effect)

0 = None	No Tyndall effect
1 = Mild	Tyndall effect barely discernible
2 = Moderate	Tyndall effect in anterior chamber is moderately intense. Iris pattern is seen clearly
3 = Severe	Tyndall effect in anterior chamber is severely intense. Iris pattern cannot be seen clearly
4 = Very severe	Tyndall effect is very severely intense. The aqueous has a white and milky appearance

Anterior Chamber Inflammation (for those subjects that could only be examined with a pen light and a 20D magnifying lens):

0 = None	Clear anterior chamber with no visible clouding (Tyndall effect and cells combined). Red reflex normal
1 = Mild	Mild anterior chamber clouding. Clear iris pattern on visualization. Red reflex normal
2 = Moderate	Moderate anterior chamber clouding.
3 = Severe	Severe anterior chamber clouding. Iris pattern not clearly visualized. Red reflex diminished
4 = Very severe	Severe anterior chamber clouding with a white and/or milky appearance of the anterior chamber. Red reflex absent or severely diminished

Schedule of Visits and Parameters

Table 9-1: Schedule of Visits and Parameters

All study tasks were to be performed by qualified study site personnel as indicated on the delegation of authority log under the supervision of the Principal Investigator. Furthermore, all ocular signs must be evaluated by an ophthalmologist.

PROCEDURE/ASSESSMENTS[1]	Visit 1 Screening	Visit 2 Surgery/Randomization /Begin Treatment	Visit 3 Follow-up	Visit 4 Follow-up	Visit 5 Follow-up	Visit 6 Follow-up/ End Treatment	Visit 7 Follow-up	Visit 8 Study Exit
	Day -15 (±14 days)	Day 0[2]	Day 1[3]	Day 7 (±2 days)	Day 14 (±3 days)	Day 28 (±7 days)	Day 42 (±7 days)	Day 90 (±14 days)
Informed consent, assent (when applicable), and authorization as appropriate for local privacy regulations	X							
Demographic data	X							
Current and relevant medical and ocular history	X							
Ocular symptoms	X		X	X	X	X	X	X
VA assessment	X	X	X	X	X	X	X	X
Slit lamp (biomicroscopy or magnifying lens with penlight)[4]	X	X	X	X	X	X	X	X
IOP (Goldman or equivalent)[4]	X	X	X	X	X	X	X	X
Fundoscopy[5]		X	X		X			X
Eligibility determination	X	X						
Randomization		X						
AEs[6]/Concomitant medications	X	X	X	X	X	X	X	X
Weigh study drug and inspect diaries		X	X	X	X	X		
Dispense study drug and diaries		X[7]	X	X	X			
Collect study drug and diaries						X		
Exit subject								X

[1] All ophthalmic assessments were to be performed bilaterally.
[2] Visit 2 must occur within 29 days of Visit 1. Screening and surgery cannot take place on the same day.
[3] Visit 3 (Postoperative day 1) should occur on the next calendar day post-surgery.
[4] Every effort should be made to obtain slit lamp assessments and the assessment with the 20D magnifying lens and penlight should only be performed if a slit lamp or handheld slit lamp examination cannot be performed. Once one of the methods had been chosen it should be employed throughout the study for each subject. IOP should also be measured with the same method throughout the study for each subject.
[5] Fundoscopy was to be performed bilaterally either at Visit 2 (surgery/randomization) or Visit 3 (day 1), at Visit 5 (day 14), and at Visit 8 (day 90).
[6] Collection of AEs extends from the time the subject's parent/guardian signs informed consent until the last study visit.
[7] The subject's parent/legal guardian will be trained with regard to the correct instillation of eye drops without using study drug prior to their administration of the initial dose.

Primary Efficacy Variable: Mean grade of anterior chamber inflammation at Visit 5 (Post-operative Day 14)

Patient Demographics (ITT Population)

Treatment Group		LE Gel n (%)	PA n (%)
Total enrollment in study		N=53	N=52
Race	White	26 (49.1%)	23 (44.2%)
	Black/African American	8 (15.1%)	10 (19.2%)
	American Indian/ Alaskan Native	0	0
	Asian	1 (1.9%)	1 (1.9%)
	Native Hawaiian/ Pacific Islander	0	0
	Other	18 (34.0%)	18 (34.6%)
	p-value, Pearson Chi-squared test	0.9410	
Age	Mean ± SD	3.7 (3.22)	4.3 (3.39)
	Median	3.0	4.0
	Min, Max	0, 11	0, 10
	p-value, two-sample t-test	0.3796	
	Age categories: ≤ 3 years > 3 years	 28 (52.8%) 25 (47.2%)	 24 (46.2%) 28 (53.8%)
	p-value, Pearson Chi-squared test	0.4939	
	Male	31 (59.5%)	26 (50.0%)

Sex	Female	22 (41.5%)	26 (50.1%)
	p-value, Pearson Chi-squared test	0.3826	
Ethnicity	Hispanic or Latino	24 (45.3%)	20 (38.5%)
	Not Hispanic or Latino	29(54.7%)	32(61.5%)
	Unknown	0	0
	p-value, Pearson Chi-squared test	0.4788	

Source: Table 14.1.3.1

Subject Disposition and Reason for Discontinuation

Disposition and Discontinuation	LE Gel n (%)	PA n (%)
Total Randomized	54	53
Treated		
As randomized	53 (98.1%)	52 (98.1%)
Not as randomized	1 (1.9%)	1 (1.9%)
Randomized but not treated	0	0
Safety Population	54 (100.0%)	53 (100.0%)
Completed	39 (72.2%)	44 (83.0%)
Discontinued	15 (27.8%)	9 (17.0%)
ITT Population	53 (98.1%)	52 (98.1%)
Completed	40 (75.5%)	43 (82.7%)
Discontinued	13 (24.5%)	9 (17.3%)
Per Protocol (PP) Population	40 (74.1%)	43 (81.1%)
Completed	39 (97.5%)	40 (93.0%)
Discontinued	1 (2.5%)	3 (7.0%)
Total Study Completion		
Completed	40 (74.1%)	43 (81.1%)
Discontinued	14 (25.9%)	10 (18.9%)
Primary reason for Discontinuation		
Withdrew consent	0	1 (10.0%)
Lost to follow-up	1 (7.1%)	1 (10.0%)
Administrative issue	0	0
Adverse event	1 (7.1%)	1 (10.0%)
Rescue therapy	11 (78.6%)	5 (50.0%)
Failure to follow required study procedures	0	1 (10.0%)
Investigator decision	0	0
Onset of menarche	0	0
Other reason	1 (7.1%)	1 (10.0%)

ITT Population with LOCF and PP Population with Observed Data
Primary Efficacy at Visit 5 (Post-operative Day 14)

Primary Efficacy Analysis	**LE Gel N = 53**	**PA Suspension N = 52**
ITT with LOCF	n = 53	n= 52
Mean Grade of Study Eye ACI at Visit 5 (Post-operative Day 14)		
ANOVA LS Mean (LS Mean 2-sided 95% CI)	0.644 (0.372,0.916)	0.638 (0.358,0.919)
LS Mean Difference, LE – PA (2-sided 95% CI)	0.006 (-0.281, 0.292)	
PP with Observed Data	n = 38	n = 43
Mean Grade of Study Eye ACI at Visit 5 (Post-operative Day 14)		
ANOVA LS Mean (LS Mean 2-sided 95% CI)	0.570 (0.352,0.788)	0.613 (0.391,0.834)
LS Mean Difference, LE - PA (2-sided 95% CI)	-0.043 (-0.289, 0.203)	

Note: Non-inferiority was determined if the upper bound of the 95%CI on the difference is less than 0.35.

Review of Safety
Nonfatal SAEs
Two subjects, both in the LE Gel treatment arm experienced a serious adverse event.

Site/Patient #	**Timing of SAE**	**SAE**	**Narrative of SAE**
Site #280266 Subject # (b) (6)	Occurred after discontinuation of treatment	Aphakic glaucoma OU	3-month old male with a history of congenital cataract OU underwent cataract extraction OD (study eye) (b) (6) and OS (b) (6). Study eye was treated with LE Gel from 1/7/14 to 2/4/14. Subject diagnosed with aphakic glaucoma OU on 3/20/14. The study eye underwent trabeculotomy and the fellow eye underwent gioniotomy on (b) (6). The event is resolved with sequelae as of 4/2/14.
Site #110892 Subject # (b) (6)	Occurred after discontinuation of treatment	Bronchiolitis	4-month old female underwent cataract extraction surgery and was treated in the study eye with LE Gel for 2 weeks followed by tapering. Study medication was discontinued on 12/13/16. Subject was diagnosed with bronchiolitis and hospitalized on (b) (6). The subject was discharged on (b) (6) and the evens resolved.

Source: Section 12.3.2

These adverse events are either consistent with the age or general findings in the population of subjects undergoing cataract extraction.

Adverse Events Associated with Discontinuation

Site #	Patient #	Treatment	Adverse Event
280266	(b) (6)	LE Gel	Suture related complication
280266	(b) (6)	PA Suspension	Iridocyclitis; Posterior capsular opacification

Source: Listing 16.2.6.2

Emergent AEs in ≥1% of Study Eyes - Safety Population

	LE Gel N=54 n (%)	PA Suspension N=53 n (%)
Total number of TEAEs	16 (29.6)	14 (26.4)
Eye Disorders	13 (24.1)	7 (13.2)
Amblyopia	1 (1.9)	0
Conjunctivitis	0	1 (1.9)
Conjunctivitis viral	1 (1.9)	0
Eye discharge	1 (1.9)	1 (1.9)
Eye irritation	1 (1.9)	0
Eye pain	5 (9.3)	2 (3.8)
Eyelid oedema	4 (7.4)	2 (3.8)
Glaucoma	1 (1.9)	0
Iridocyclitis	0	1 (1.9)
Lacrimation increased	1 (1.9)	0
Ocular Hyperaemia	3 (5.6)	0
Photophobia	1 (1.9)	0
Posterior capsule opacification	1 (1.9)	0
Strabismus	1 (1.9)	0
Vitreous disorder	1 (1.9)	0
General Disorders and Administration Site Conditions	2 (3.7)	4 (7.5)
Discomfort	2 (3.7)	3 (5.7)
Instillation site pain	0	1 (1.9)
Injury, Poisoning and Procedural Complications	1 (1.9)	4 (4.7)
Injury	0	2 (3.8)
Post procedural complication	0	1 (1.9)
Posterior capsule opacification	0	1 (1.9)
Suture related complication	1 (1.9)	0

Source: Table 12-3

Non-ocular Treatment-Emergent AEs in ≥1% of Study Eyes - Safety Population

	LE Gel N=54 n (%)	PA Suspension N=53 n (%)
Total number of TEAEs	13 (24.1)	15 (28.3)
Gastrointestinal Disorders	0	1 (1.9)
Diarrhoea	0	1 (1.9)
General Disorders and Administration Site Conditions	2 (3.7)	7 (13.2)
Discomfort	1 (1.9)	2 (3.8)
Feeling hot	0	1 (1.9)
Pyrexia	1 (1.9)	2 (3.8)
Swelling	0	1 (1.9)
Vaccination site pain	0	1 (1.9)
Immune System Disorders	0	2 (3.8)
Seasonal allergy	0	2 (3.8)
Infections and Infestations	5 (9.3)	7 (13.2)
Bronchiolitis	1 (1.9)	0
Ear infection	2 (3.7)	1 (1.9)
Gastroenteritis	2 (3.7)	1 (1.9)
Nasopharyngitis	2 (3.7)	4 (7.5)
Pharyngitis streptococcal	1 (1.9)	0
Tinea infection	0	1 (1.9)
Upper respiratory tract infection	0	1 (1.9)
Injury, Poisoning and Procedural Complications	2 (3.7)	2 (3.8)
Anthropod bite	1 (1.9)	0
Contusion	0	1 (1.9)
Excoriation	1 (1.9)	0
Fall	1 (1.9)	0
Injury	0	1 (1.9)
Nervous System Disorders	1 (1.9)	1 (1.9)
Headache	1 (1.9)	1 (1.9)
Respiratory, Thoracic and Mediastinal Disorders	2 (3.7)	2 (3.8)
Cough	2 (3.7)	1 (1.9)
Rhinorrhoea	0	1 (1.9)
Skin and Subcutaneous Tissue Disorders	1 (1.9)	3 (5.7)
Dermatitis	0	1 (1.9)
Erythema	0	1 (1.9)
Rash	1 (1.9)	1 (1.9)

Source: Table 12-5

6 Advisory Committee Meeting

No issues were identified that were expected to benefit from an advisory committee discussion.

7 Labeling Recommendations

The labeling has been revised to incorporate the results of the Pediatric Study and to update the labeling format to be consistent with PLLR labeling regulations. See attached labeling at the end of this review.

8 Risk Benefit Assessment

The clinical data submitted in support of this supplement demonstrates that LE ophthalmic gel 0.5% administered QID for 14 day is non-inferior to PA ophthalmic suspension 1% administered QID for 14 days to treat post-operative inflammation following ocular surgery for childhood cataract. Study 670 met the pre-specified primary efficacy endpoint, the mean grade anterior chamber inflammation (ACI) at Visit 5 (Post-operative Day 14).

There are 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.

9 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

There are no recommended postmarketing risk evaluations and mitigation strategies.

10 Regulatory Action

This supplemental application will be approved with the labeling listed below.

6 PAGES OF DRAFT LABELING IMMEDIATELY FOLLOWING THIS PAGE HAVE BEEN WITHHELD IN FULL UNDER B(4)

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/

WILEY A CHAMBERS
07/18/2018