CLINICAL REVIEW of NDA 202872/S-002

Application Type	Efficacy Supplement
Application Number(s)	202872 S-002
Priority or Standard	S
Submit Date(s)	October 10, 2017
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Division / Office	DTOP/OAP
Reviewer Name(s)	Lucious Lim, M.D., M.P.H.
Review Completion Date	March 29, 2018
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

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 202872 S-002 be approved with the labeling revisions found in this review.

1.2 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.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommended postmarket risk evaluations and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended postmarket clinical study requirements and commitments.

2 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. 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.

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.

2.1 Product Information

Established Name:	loteprednol etabonate ophthalmic gel 0.5%
Proposed Trade Name:	Lotemax
Chemical Class:	new formulation
Pharmacological Class:	corticosteroid
Indication	treatment of post-operative inflammation and pain following ocular surgery
Dosing Regimen:	One or two drops into the conjunctival sac of the affected eye four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period.

2.2 Tables of Currently Available Treatments for Proposed Indications

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

2.3 Availability of Proposed Active Ingredient in the United States

Loteprednol etabonate has been marketed in the US since 1998 as Lotemax and Alrex ophthalmic suspension drug products, since 2005 in a fixed combination with tobramycin as Zylet, since 2011 as Lotemax ophthalmic ointment and since 2012 as Lotemax ophthalmic gel.

Drug	NDA	Indication
Lotemax (loteprednol etabonate ophthalmic suspension, 0.5%)	20-583	Treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, SPK, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation. It is also indicated for the treatment of post-operative inflammation following ocular surgery.
Alrex (loteprednol etabonate ophthalmic suspension, 0.2%)	20-803	Temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.
Zylet (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension)	50-804	Treatment of 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.
Lotemax (loteprednol etabonate ophthalmic ointment, 0.5%)	200-738	Treatment of post-operative inflammation and pain following ocular surgery

2.4 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

3.1 Submission Quality and Integrity

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.

3.2 Compliance with Good Clinical Practices

The clinical study included in this application conforms with Good Clinical Practices.

3.3 Financial Disclosures

See Section 9.3 of this review. Bausch and Lomb certified that it has no financial arrangements with any of the clinical investigators who participated in Study 670 titled "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". This is the only clinical study submitted in support of this supplement.

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 (b) (4)	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 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

Non-clinical ocular toxicity studies with 0.5% loteprednol etabonate ophthalmic suspension have been conducted in rabbits for up to 26-week and in dogs for up to 52- week in NDA 20-583. For the development of 0.5% loteprednol etabonate ophthalmic gel, the sponsor conducted a 29-day repeat topical ocular dose study in rabbits to establish the safety profile and a companion 27-day repeat topical ocular dose study in rabbits with toxicokinetic evaluation of systemic exposure to LE. The study reports showed no significant toxicity findings.

The current label for the marketed loteprednol etabonate stated that LE was not genotoxic in a battery of genotoxicity tests. LE has been shown to be embryotoxic and teratogenic. No carcinogenic studies have been conducted for LE.

See Pharm/Tox review for additional findings.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

Not performed for this application.

4.4.3 Pharmacokinetics

Clinical pharmacokinetic studies were conducted during the development of Lotemax (Loteprednol Etabonate Ophthalmic Suspension, 0.5%) and Zylet (Loteprednol Etabonate 0.5% and Tobramycin 0.3% Ophthalmic Suspension), and the data has been submitted previously in the NDAs for these products.

Results from a bioavailability study with Lotemax suspension in normal volunteers established that plasma levels of LE and PJ-91, its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of 1 drop in each eye of LE suspension 0.5%, 8 times daily for 2 days and then 4 times daily (QID) for 41 days. Because the ointment formulation of LE is not expected to produce higher systemic exposure than the suspension formulation of LE, there were no clinical PK studies conducted with the gel formulation.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

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

5.2 Review Strategy

The source of clinical data utilized in this review include the study listed in section 5.1.

5.3 Discussion of Individual Studies/Clinical Trials

Study 670

Title: 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 for Study 670

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.

Inclusion Criteria

This study included subjects who met the following inclusion criteria at Visit 1 (Screening):

1. Subjects who were male or female, 0 to 11 years of age, on the date the Informed Consent Form (ICF) was signed.
2. Subjects who had the ability to understand and provide assent (when applicable) and whose parent/legally authorized representative had the ability to understand and provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved ICF, and provide authorization for local privacy regulations.
3. Subjects whose parent/legally authorized representative was able and willing to comply with all treatment and follow-up procedures.
4. Subject was a candidate for routine, uncomplicated surgery for childhood cataract (aspiration, with or without posterior capsulotomy with or without anterior vitrectomy, and with or without posterior chamber intraocular lens [IOL] implantation, not combined with any other surgery and without the planned use of iris hook and/or pupil stretching).

This study included subjects who met the following criteria at Visit 2 (Surgery/Randomization):

1. Subjects who had undergone routine, uncomplicated surgery for childhood cataract (aspiration, with or without posterior capsulotomy, with or without posterior chamber IOL implantation, not combined with any other surgery).

Exclusion Criteria

This study excluded subjects who met one or more of the following exclusion criteria:

1. Subjects who have a severe/serious ocular condition, or any other unstable medical condition that, in the Investigator's opinion, may preclude study treatment or follow-up, e.g.:
   − presence of any active or suspected viral, bacterial, or fungal disease in the study eye
   − subjects with post-traumatic cataract in the study eye
   − active uveitis in the study eye
   − ocular neoplasm in the study eye
2. Subjects with glaucoma, ocular hypertension, or those receiving intraocular pressure (IOP) lowering therapy in either eye or systemically.
3. Subjects with a history of steroid-induced IOP elevation in either eye.
4. Subjects who have suspected permanent low vision or blindness (e.g., legal definition of blindness: visual acuity [VA] of ≤ 20/200 or visual field of ≤ 20 degrees) in the fellow non-study eye. (The study eye must not be the subject's only sighted eye.)
5. Subjects who have had ocular surgery (including laser therapy) in the study eye within 90 days prior to randomization on Visit 2 (Surgery/Randomization).
6. Subjects who are expected to require treatment with systemic or ocular (study eye) corticosteroids other than study drug during the 90 days following cataract surgery or have used any systemic or ocular corticosteroids (study eye) within 14 days prior to cataract surgery. (Ocular therapy with corticosteroids in the fellow eye is permitted.)
7. Subjects who are expected to require concurrent systemic or ocular therapy (study eye) with nonsteroidal anti-inflammatory drugs (NSAIDs), or concurrent ocular therapy (either eye) with mast cell stabilizers, antihistamines, or decongestants during the 90 days following cataract surgery or have received any of the above medications within 2 days prior to surgery (intraoperative NSAIDs for mydriasis in the study eye are NOT permitted; ocular therapy with NSAIDs in the fellow eye is permitted).
8. Subjects who are expected to require concurrent ocular (either eye, e.g., Restasis) or systemic immunosuppressant therapy during the 90 days following cataract surgery or have used ocular (either eye) immunosuppressants within 30 days prior to surgery or systemic immunosuppressants within 10 months prior to surgery.
9. Subject or subject's breastfeeding mother or wet nurse who is expected to use corticosteroids (except corticosteroid inhalers and dermatological corticosteroids, as long as they are not used on the eyelids or surrounding area) or immunosuppressants during the 90 days following cataract surgery.
10. Subjects who have a history or presence of chronic generalized systemic disease that the Investigator believes may either increase the risk to the subject or confound the results of the study (e.g., Diabetes mellitus, human immunodeficiency virus [HIV],

acquired immunodeficiency syndrome [AIDS]).
11. Female subjects who have started menarche prior to Visit 1 (Screening).
12. Subjects who have known hypersensitivity or other contraindication to the study drug(s) or any components in the drug formulation.
13. Subjects who have participated in an investigational drug or device study within 30 days prior to Visit 1 (Screening).
14. Subjects who were previously randomized in this study.

Primary Efficacy Variable

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

Secondary Efficacy Variables

- Mean grade of anterior chamber inflammation at Visits 4 and 6 (Post-operative Days 7 and 28)
- Proportion of subjects with Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 anterior chamber inflammation at each visit (Post-operative Days 7, 14, and 28)
- Presence/absence and total area, if present, of synechiae at each visit (Postoperative Days 7, 14, and 28)
- Presence/absence and total number, if present, of precipitates on the implant and cornea at each visit (Postoperative Days 7, 14, and 28)

Study 670 – Table of Investigators

Investigator	**Investigator Number**	**Number of Subjects Randomized (loteprednol/prednisolone)**
Raymond G. Areaux, MD (replaced by E.D. Bothun, MD) University of Minnesota Minnesota Lion's Children's Eye Clinic Minneapolis, MN 55454	110892	6
Erick D. Bothun, MD (replaced by R. G. Areaux, MD) University of Minnesota Minnesota Lion's Children's Eye Clinic Minneapolis, MN 55454	1202582	0
Dawn Duss, MD	140451	0

Investigator	Investigator Number	Number of Subjects Randomized (loteprednol/prednisolone)
(replaced by A. Pogrebriak, MD) Nemours Children's Clinic Jacksonville, FL 32207		
Alexander Pogrebriak,, MD (replaced by D. Duss, MD) Nemours Children's Clinic Jacksonville, FL 32207	260871	6
Matthew D. Gearinger, MD University of Rochester Medical Center Flaum Eye Institute Rochester, NY 14642	170260	4
Carlos Gonzales, MD Houston Eye Associates Houston, TX 77025	170095	3
Suqin Guo, MD The Institute of Ophthalmology and Visual Science UMDNJ New Jersey Medical School Newark, NJ 07103	170255	10
Phoebe D. Lenhart, MD Emory Eye Center Atlanta, GA 30322	220248	4
Stephen Lipsky, MD Thomas Eye Group, PC Sandy Springs, GA 30328	220724	0
Norman Medow, MD Montefiore Hospital Medical Center Bronx, NY 10467	230725	0
Faruk H. Orge, MD University Hospitals of Cleveland d/b/a University Hospitals Case Medical Center Mayfield Heights, OH 44124	250265	1
David A. Plager, MD Indiana Pediatric Ophthalmology and Adult Strabismus, Riley Outpatient Center	260249	9

Investigator	Investigator Number	Number of Subjects Randomized (loteprednol/prednisolone)
Indianapolis, IN 46202		
Bibiana Jin-Wan Reiser, MD The Vision Center Children's Hospital Los Angeles Los Angeles, CA 32207	280266	58
Nicholas A. Sala, MD Pediatric Ophthalmology of Erie Erie, PA 16501-1725	838313	3
Federico G. Velez, MD Stein Eye Institute – UCLA Los Angeles, CA 90095	320875	3
Serena Wang, MD UTSW Medical Center at Dallas Department of Ophthalmology Dallas, YX 75390-9057	330781	0
	Total Randomized	107

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is treatment of post-operative inflammation and pain following ocular surgery.

6.1.1 Methods

Description of the clinical trial design is contained in Section 5.3.

6.1.2 Demographics

Study 670 - Patient Demographics (ITT Population)

		Study 670	
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	
Sex	Male	31 (59.5%)	26 (50.0%)
	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

6.1.3 Subject Disposition

Study 670 - Subject Disposition and Reason for Discontinuation

Disposition and Discontinuation	LE Gel n (%)	PA n (%)	All Subjects n (%)
Total Randomized	54	53	107
Treated			
As randomized	53 (98.1%)	52 (98.1%)	105 (98.1%)
Not as randomized	1 (1.9%)	1 (1.9%)	2 (1.9%)
Randomized but not treated	0	0	0
Safety Population	54 (100.0%)	53 (100.0%)	107 (100.0%)
Completed	39 (72.2%)	44 (83.0%)	83 (77.6%)
Discontinued	15 (27.8%)	9 (17.0%)	24 (22.4%)
ITT Population	53 (98.1%)	52 (98.1%)	105 (98.1%)
Completed	40 (75.5%)	43 (82.7%)	83 (79.0%)
Discontinued	13 (24.5%)	9 (17.3%)	22 (21.0%)
Per Protocol (PP) Population	40 (74.1%)	43 (81.1%)	83 (77.6%)
Completed	39 (97.5%)	40 (93.0%)	79 (05.2%)
Discontinued	1 (2.5%)	3 (7.0%)	4 (4.8%)
Total Study Completion			
Completed	40 (74.1%)	43 (81.1%)	83 (77.6%)
Discontinued	14 (25.9%)	10 (18.9%)	24 (22.4%)
Primary reason for Discontinuation			
Withdrew consent	0	1 (10.0%)	1 (4.2%)
Lost to follow-up	1 (7.1%)	1 (10.0%)	2 (8.3%)
Administrative issue	0	0	0
Adverse event	1 (7.1%)	1 (10.0%)	2 (8.3%)
Rescue therapy	11 (78.6%)	5 (50.0%)	16 (66.7%)
Failure to follow required study procedures	0	1 (10.0%)	1 (4.2%)
Investigator decision	0	0	0
Onset of menarche	0	0	0
Other reason	1 (7.1%)	1 (10.0%)	2 (8.3%)
Source: Table 10-1			

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for study 670 was:

- Mean grade of anterior chamber inflammation (ACI) at Visit 5 (Post-operative Day 14)

Primary Efficacy Analysis

The primary efficacy analysis was to be based on the ITT population with missing data imputed using the last observation carried forward (LOCF) method and the primary endpoint mean grade of anterior chamber inflammation at Visit 5 (Post-operative Day 14). The mean grade of anterior chamber inflammation at Visit 5 (Post-operative Day 14) was to be analyzed using an analysis of variance ANOVA) model with treatment as a classification variable.

The least mean squares mean for each treatment group, the difference in the least squares mean between the two treatment groups (LE Gel – PA Suspension), and the two-sided 95% confidence interval for the difference were to be presented. The null hypothesis was to be rejected and non-inferiority established if the upper limit of the confidence interval was ≤0.35.

Analysis Population

Intent to Treat (ITT): The ITT population included all randomized subjects and had at least one post-treatment assessment.

Per Protocol (PP): The PP population included all ITT subjects who remain in the study through Visit 5 (Postoperative Day 14) and who did not deviate from the protocol in any way likely to seriously affect the primary outcome of the study.

Study 670 – 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 is determined if the upper bound of the 95%CI on the difference is less than 0.35.

Source: Table 11-1

Reviewer's Comments: *The ITT with LOCF and PP with observed data analyses are similar. The upper bound of the 95% CI on the mean difference, LE – PA, for the mean grade anterior chamber inflammation (ACI) at Visit 5 (Post-operative Day 14) are 0.292 and 0.203, respectively. LE ophthalmic gel 0.5% demonstrates non-inferiority to PA ophthalmic suspension 1%.*

6.1.5 Analysis of Secondary Endpoints(s)

The planned secondary endpoints for this study included the following:

- Mean grade of anterior chamber inflammation at Visits 4 and 6 (Post-operative Days 7 and 28)
- Proportion of subjects with Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 anterior chamber inflammation at each visit (Post-operative Days 7, 14, and 28)
- Presence/absence and total area, if present, of synechiae at each visit (Postoperative Days 7, 14, and 28)
- Presence/absence and total number, if present, of precipitates on the implant and cornea at each visit (Postoperative Days 7, 14, and 28)

Secondary Efficacy - Mean Grade of Study Eye ACI at Visit 4 (Post-operative Day 7) and Visit 6 (Post-operative Day 28)

Secondary Analyses	**LE Gel N = 53**	**PA Suspension N = 52**
ITT Population with Observed Data		
Mean Grade of Study Eye ACI at Visit 4 (Post-operative Day 7)	n = 52	n = 44
ANOVA LS Mean (LS Mean 2-sided 95% CI)	0.913 (0.668,1.158)	0.783 (0.528,1.038)
LS Mean Difference, LE - PA (2-sided 95% CI)	0.130 (-0.133, 0.392)	
Mean Grade of Study Eye ACI at Visit 6 (Post-operative Day 28)	n = 39	n = 44
ANOVA LS Mean (LS Mean 2-sided 95% CI)	0.172 (0.022,0.322)	0.330 (0.178,0.482)
LS Mean Difference, LE - PA (2-sided 95% CI)	-0.158 (-0.326, 0.011)	
PP Population with Observed Data	**N = 40**	**N = 43**
Mean Grade of Study Eye ACI at Visit 4 (Post-operative Day 7)	n = 40	n = 43
ANOVA LS Mean (LS Mean 2-sided 95% CI)	0.862 (0.685,1.039)	0.775 (0.593,0.957)
LS Mean Difference, LE - PA (2-sided 95% CI)	0.087 (-0.113, 0.287)	
Mean Grade of Study Eye ACI at Visit 6 (Post-operative Day 28)	n = 38	n = 41
ANOVA LS Mean (LS Mean 2-sided 95% CI)	0.170 (0.016,0.324)	0.345 (0.186,0.504)
LS Mean Difference, LE - PA (2-sided 95% CI)	-0.175 (-0.352, 0.002)	

Note: ANOVA model with fixed effect terms for treatment and site was performed as appropriate. Non-inferiority is determined if the upper bound of the 95%CI on the difference is less than 0.35.
Source: Table 11-2

Reviewer's Comments: *There are no significant differences between groups at Visit 4 or 6. Analysis of cell and flare (not shown) is not significantly different.*

Secondary Efficacy - Proportion of Subjects with Synechiae at Each Visit (Post-operative Days 7, 14, and 28)

Secondary Analyses	**LE Gel**	**PA Suspension**
ITT Population with Observed Data	**N = 53**	**N = 52**
Presence/Absence Synechiae of Study Eye at Visit 4 (Post-operative Day 7)	n (%)	n (%)
Presence	1 (1.9)	1 (2.0)
Absence	52 (98.1)	48 (98.0)
Missing	0	3
Risk Difference for Presence, LE – PA (2-sided 95% CI)	-0.002 (-0.055, 0.052)	
p-value, Fischer's Exact Test	>0.9999	

Source: Table 14.2.3.1

Reviewer's Comments:
The presence of synechiae was infrequent. There were no significant differences in the proportion of subjects with synechiae in the study eye at Visits 4 (Post-operative Day 7), 5 (Post-operative Day 14), or 6 (Post-operative Day 28) in the ITT with observed data population.

6.1.6 Other Endpoints
None.

6.1.7 Subpopulations
The primary efficacy endpoint (Mean grade of anterior chamber inflammation (ACI) at Visit 5 (Post-operative Day 14) were compared between the LE Gel and PA Suspension treatment groups for the following subpopulations: age (0 to 3 years and > 3 years), IOL implantation (yes or no) and iris color (blue, brown, green, hazel or other).

Reviewer's Comments:
The study was not powered to demonstrate to detect non-inferiority for subgroups. No significant differences based on age, iris color or IOL was found.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations
Only one dosing regimen was studied.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects
Long-term effectiveness was not evaluated. The treatment is for an acute surgical event.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study 670

7.1.2 Categorization of Adverse Events

Treatment-emergent adverse events (TEAEs) were defined as any adverse event (AE) collected from the time the subject's parent/legal guardian gave informed consent until the last study visit, Visit 8 (Post-operative Day 90). An assessment of all AEs was to be made by the Investigator as to the severity, action taken with study treatment, and causal relationship to study drug.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable. Only one clinical study was conducted.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 54 patients were exposed to LE Gel and received at least one dose of during the clinical trial.

Study 670 - Treatment Exposure (Safety Population)

	LE Gel N=54	**PA Suspension N=53**	**All Subjects N=107**
n	53	53	106
Days of Exposure			
Mean (SD)	23.5 (9.60)	25.6 (7.80)	24.6 (8.77)
Median	29.0	29.0	29.0
Min, Max	1, 29	1, 29	1, 29

Source: Table 14-1

7.2.2 Explorations for Dose Response
LE Gel was administered in one dose. No dose response information was obtained.

7.2.3 Special Animal and/or In Vitro Testing
No special toxicology studies were conducted with LE Gel.

7.2.4 Routine Clinical Testing
The routine clinical testing required to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, IOP, etc.) were adequately addressed in the design and conduct of the clinical trial.

7.2.5 Metabolic, Clearance, and Interaction Workup
Studies to evaluate metabolism, clearance, and interaction were not performed due to the negligible systemic absorption of LE Gel given by the topical route of administration.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class
Adverse events for this class of drugs (topical corticosteroids) are well known. Refer to Section 2.2 for currently approved products. 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.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the clinical trial.

7.3.2 Nonfatal Serious Adverse Events

Study 670 – 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

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

7.3.3 Dropouts and/or Discontinuations

Study 670 - Discontinuations (All Randomized Subjects)

Discontinuation	LE Gel n (%)	PA n (%)	All Subjects n (%)
Total Randomized	54	53	107
Total Study Completion			
Completed	40 (74.1%)	43 (81.1%)	83 (77.6%)
Discontinued	14 (25.9%)	10 (18.9%)	24 (22.4%)
Primary reason for Discontinuation			
Withdrew consent	0	1 (10.0%)	1 (4.2%)
Lost to follow-up	1 (7.1%)	1 (10.0%)	2 (8.3%)
Administrative issue	0	0	0
Adverse event	1 (7.1%)	1 (10.0%)	2 (8.3%)
Rescue therapy	11 (78.6%)	5 (50.0%)	16 (66.7%)
Failure to follow required study procedures	0	1 (10.0%)	1 (4.2%)
Investigator decision	0	0	0
Onset of menarche	0	0	0
Other reason	1 (7.1%)	1 (10.0%)	2 (8.3%)

Source: Table 10-1

Study 670 - 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

Reviewer's Comments:

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

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuation are presented in section 7.3.3. There were no other significant adverse events identified.

7.3.5 Submission Specific Primary Safety Concerns
None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events
Treatment-emergent adverse events (TEAEs) were defined as any adverse event (AE) collected from the time the subject's parent/legal guardian gave informed consent until the last study visit, Visit 8 (Post-operative Day 90). An assessment of all AEs was to be made by the Investigator as to the severity, action taken with study treatment, and causal relationship to study drug.

Study 670 - 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	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

Study 670 – 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

Reviewer's Comments: *Over all, the most common adverse drug reactions were eye pain (9%), eyelid edema (7%), and ocular hyperemia (6%).*

7.4.2 Laboratory Findings

Not performed.

7.4.3 Vital Signs

Not performed.

7.4.4 Electrocardiograms (ECGs)

Not performed.

7.4.5 Special Safety Studies/Clinical Trials

Corticosteroids have a known risk of increasing IOP and therefore IOP was monitored at every visit.

Reviewer's Comments:

The IOP findings are consistent with the age and general findings in the population of subjects undergoing cataract extraction.

7.4.6 Immunogenicity

N/A – Immunogenicity testing was not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No dose response information was obtained.

7.5.2 Time Dependency for Adverse Events

N/A – LE Gel does not have a delayed onset of action. Exploration of time to onset was not conducted.

7.5.3 Drug-Demographic Interactions

No drug-demographic interactions analyses were performed.

7.5.4 Drug-Disease Interactions

No drug-disease interaction analyses were performed.

7.5.5 Drug-Drug Interactions

No drug interactions were reported in any clinical study involving LE Gel.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been conducted

7.6.2 Human Reproduction and Pregnancy Data

No information was obtained on the use of LE Gel in these populations.

7.6.3 Pediatrics and Assessment of Effects on Growth

The clinical trials did not enroll any pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Based on postmarketing safety data collected through 31 Dec 2010 for LE as the active pharmaceutical ingredient (including Lotemax suspension, Alrex, and Zylet), no case of overdose or substance-related disorder has been reported. There have been no reports of drug abuse, steroid abuse, or intentional drug misuse at the patient level.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Loteprednol etabonate is the active pharmaceutical ingredient in LE ointment and is the same sterile form of the API that has been marketed in the following drug products:

- Lotemax - Loteprednol Etabonate Ophthalmic Suspension, 0.5%, marketed since March 1998
- Alrex - Loteprednol Etabonate Ophthalmic Suspension, 0.2%, marketed since March 1998
- Zylet - Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%, 0.3% launched December 2004
- Lotemax - Loteprednol Etabonate Ophthalmic Ointment, 0.5%, approved April 2011

In addition to the U.S., Lotemax, Alrex, and Zylet have been approved in countries throughout Latin America, Europe, and Asia/Pacific regions.

Quantities Shipped of Marketed Products

Product	Dates	Total Units (b) (4)
Lotemax	Mar 1998 – 31 Dec 2010	
Alrex	Mar 1998 – 31 Dec 2010	
Zylet	Dec 2004 – 31 Dec 2010	
Total		

There have been no Marketing Authorization withdrawals to date for Lotemax, Alrex, or Zylet.

9 Appendices

9.1 Literature Review/References

An independent literature review did not reveal any additional information relevant to this application.

9.2 Advisory Committee Meeting

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

9.3 Clinical Investigator Financial Disclosure

Application Number: NDA 202872 S-002
Submission Date(s): October 10, 2017
Applicant: Bausch and Lomb Inc.
Product: loteprednol etabonate ophthalmic gel 0.5%

Reviewer: Lucious Lim, M.D., M.P.H.
Date of Review: April 10, 2018
Covered Clinical Study (Name and/or Number): Study #670

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 16		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): **N/A** Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Bausch and Lomb has adequately disclosed financial interests/arrangements with the clinical investigators in Study #670. Bausch and Lomb certified that it has no financial arrangements with any of the clinical investigators who participated in Study #670 entitled "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".

9.4 Labeling Recommendations

See labeling recommendations which follow in the attached label.

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

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/s/

LUCIOUS LIM
05/08/2018

WILLIAM M BOYD
05/08/2018