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APPLICATION NUMBER:

202872Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products[1]
Subject	Division Director Summary Review
NDA Number	NDA 202872
Related IND	IND 102654
Applicant Name	Bausch & Lomb Pharmaceuticals, Inc.
Application Type	505(b)(1)
Date of Original Submission	November 29, 2011 (standard review)
PDUFA Goal Date	September 29, 2012
Proprietary Name / **Established (USAN) Name**	Lotemax Loteprednol etabonate ophthalmic gel
Dosage Form **Dosage Strength** **Preservative** **Route of Administration**	Sterile ophthalmic gel 0.5% Benzalkonium chloride 0.003% Topical
Proposed Indication(s)	treatment of post-operative inflammation and pain following ocular surgery
How Supplied	5 g in a 10 mL LDPE bottle with a controlled drop tip
Action for Application	*Approval*

[1] The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lucious Lim, William Boyd 9/27/2012
CDTL Review	Bill Boyd 9/26/2012
Deputy Director Review	Wiley Chambers 9/27/2012
Statistical Review	Rima Izem, Yan Wang 8/23/2012
Clinical Pharmacology Review	Gerlie Gieser, Philip Colangelo 5/17/2012
Pharmacology/Toxicology Review	Robeena Aziz, Lori Kotch 8/24/2012
CMC – ONDQA, Division II, Branch V Review	Lin Qi, Rapti Madurawe 8/17/2012
Product Quality Microbiology Review	Denise Miller, Stephen Langille 8/9/2012
OSI/DGCPC	Kassa Ayalew, Susan Leibenhaut, Susan Thompson, 8/8/2012
OSE/DMEPA Proprietary Name Letter	Zachary Oleszczuk, Carol Holquist 9/24/2012 Carol Holquist 9/25/2012
OSE/DMEPA Labeling and Label Review - PI and carton/container	Jung Lee, Irene Chan, Carol Holquist 3/8/2012
OPDP/DPDP (formerly DDMAC)	Christine Corser 8/16/2012
Project Manager	June Germain, Judit Milstein

CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion, (formerly DDMAC=Division of Drug Marketing, Advertising and Communication)
PMHT=Pediatric and Maternal Health Staff
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
ONDQA=Office of New Drug Quality Assessment
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)

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1. Summary and Recommendations

Lotemax (loteprednol etabonate ophthalmic gel) 0.5% has been shown to be safe and effective for the treatment of post-operative inflammation and pain following ocular surgery in two randomized, masked vehicle-controlled Phase 3 clinical trials. The product is a gel, and there are currently two other 0.5% Lotemax formulations approved for the same indication, the Lotemax suspension and Lotemax ointment.

The dosing of the gel involves inverting the closed bottle and shaking it once to fill the tip before instilling drops. The dosing regimen involves applying one to two drops into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

The clinical, statistical, pharmacology/toxicology, clinical pharmacology, CMC and microbiology sterility reviewers recommend approval. Clinical site and manufacturing facility inspections are complete and acceptable. The proprietary name Lotemax was approved September 25, 2012. Labeling and labels were reviewed, any difference in recommendations were reconciled and finalized. There are no outstanding issues precluding approval.

The application will be issued an *Approval* letter for NDA 202872.

1.1 Product Quality Microbiology Sterility Deficiencies:

None

1.2 Post-Marketing Studies:

None

1.3 Other Issues

None

2. Background

Lotemax (loteprednol etabonate ophthalmic gel) 0.5% is the third presentation of a 0.5% ophthalmic loteprednol product from Bauch & Lomb (B&L) being approved by FDA.

- Loteprednol etabonate ophthalmic suspension 0.5% was approved on March 9, 1998 (NDA 20583) for the indications of treatment of steroid responsive inflammatory conditions, acute anterior uveitis, and treatment of post-operative inflammation following ocular surgery (NDA 20841), under the trade name Lotemax. The approved labeling for this product is not in PLR format.
- Loteprednol etabonate ophthalmic ointment 0.5% was approved on April 15, 2011 (NDA 202738) for the indication of treatment of post-operative inflammation and pain following ocular surgery, under the trade name Lotemax. The labeling for this product is in PLR format.

- Loteprednol etabonate ophthalmic solution 0.2% was approved on March 9, 1998 (NDA 20803) for the indication of temporary relief of the signs and symptoms of seasonal allergic conjunctivitis, under the trade name Alrex.
- Loteprednol etabonate and tobramycin ophthalmic suspension 0.5% / 0.3% was approved on December 14, 2004 (NDA 50504) for the indication 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. The trade name for this combination product is Zylet.

B&L developed the current drug formulation with the goal that the gel would provide additional benefits (b) (4) Of note, no clinical trials to assess these proposed benefits were done; therefore no statements on the putative benefit are incorporated in labeling.

The pre-IND meeting was held on August 4, 2008 to discuss the development plan of the gel formulation, IND 102654 was submitted September 30, 2009, and the end-of-Phase 2 meeting was held August 26, 2009. The pre-NDA meeting was held April 29, 2011 during which clinical, nonclinical and chemistry issues were discussed.

On November 29, 2011 B&L submitted NDA 202872 for (b) (4) (loteprednol etabonate ophthalmic gel), 0.5% for (b) (4): the treatment of inflammation and pain following ocular surgery (b) (4)

On January 13, 2012 the Division (DTOP) requested a teleconference with B&L to discuss filing issues. During the meeting held January 17, 2012 B&L was advised that while there were studies to support filing the post-operative inflammation and pain indication, (b) (4) B&L (b) (4) submitted revised labeling. The application was filed for the post-operative inflammation and pain indication.

3. CMC/Product Quality Microbiology

For complete details see reviews by Drs. Lin Qi and Denise Miller.

3.1 Product Information

- Active Ingredient: Loteprednol Etabonate
- Route of Administration: Ophthalmic
- Dosage Form: Ophthalmic Gel
- Strength: 0.5%
- Preservative: benzalkonium chloride 0.003%.
- How Supplied: 5 g in a 10 mL LDPE bottle with a controlled drop tip
- Storage: Store upright at 15°C to 25°C (59°F to 77°F)

- Container and Closure Systems: 5 g fill weight in a 10 mL LDPE bottle and a 0.5 g fill weight in a 4 mL LDPE bottle, both with (b) (4) tips and pink polypropylene caps
- Sample products: 0.5 g in 4 mL bottle, 5 g in 10 mL bottle

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Component	Reference to Quality Standard	Function	Concentration (mg/g)	% w/w
Loteprednol Etabonate (b) (4) sterile	In-house	Active	5.0	0.500
Edetate Disodium Dihydrate	USP	(b) (4)		
Glycerin, (b) (4)	USP			
Propylene Glycol	USP			
Boric Acid	USP			
Polycarbophil	USP			
Sodium Chloride	USP			
Tyloxapol	USP			
Sodium Hydroxide (b) (4)	In-house	pH adjuster	To adjust pH to 6.4-6.7	Adjust pH to 6.4-6.7
Benzalkonium Chloride Solution, (b) (4)	NF	Antimicrobial Preservative	(b) (4)	
Water for Injection	USP	(b) (4)		

Label claim for BAK is 30 ppm or 0.003%

Loteprednol etabonate ophthalmic gel, 0.5% is an aqueous (b) (4) formulation containing (b) (4) (polycarbophil) (b) (4) The product has thyrotrophic properties, thus it converts to a liquid (suspension) upon application of shear stress such as when expelling a drop for topical application to the eye, and converts back to the gel form rapidly when the shear is removed. Therefore bottle inversion dispenses the drug as a fluid.

The dosage form is designed to be a thixotropic gel as summarized in the CMC review. The reviewers discussed whether the product should be appropriately called a gel or a suspension, and whether the determination should be made based on the characteristics of the product while in inter-state commerce (gel) or the product when applied to the eye of the patient (suspension). While the suggestion was made to consider labeling the product as a suspension, there was no objection to calling the product a gel, as requested by the applicant. Agreement on the dosage form was reached during the wrap-up meeting on September 14, 2012.

3.2 Quality Microbiology Sterility

The manufacturing process involves an (b) (4)

(b) (4)

Endotoxin, testing, sterility testing, antimicrobial effectiveness testing are acceptable.

Comment:
The application is recommended for approval from the Product Quality and Microbiology Sterility perspective. Adequate information is provided to assure the identity, strength, purity and quality of the product. An "Acceptable" recommendation has been made by the Office of Compliance regarding manufacturing facilities. Labeling has been completed and the trade name Lotemax was approved by DMEPA.

4. Nonclinical Pharmacology/Toxicology

Dr. Robeena Aziz, the Pharmacology/Toxicology Reviewer, noted that this NDA references previously- approved B&L applications for Lotemax suspension (NDA 20583), Lotemax ointment (NDA 200738), Zylet (b) (4) NDA 50804), and Alrex (NDA 20803), which contain the active ingredient, loteprednol etabonate but in a suspension or ointment form. The inactive ingredients in the gel formulation are within the limits of previously approved ophthalmic drug products (CDER Inactive Ingredient Search for Approved Drug Products). The gel product contains (b) (4) preservative, benzalkonium chloride (BAK), than other formulations (label claim 0.003% based on CMC review).

The following is a summary based on the Pharmacology/Toxicology review:

To support the development of the loteprednol etabonate (LE) gel formulation, three pharmacokinetic ocular distribution studies and two repeat dose ocular toxicology studies were conducted in rabbits to evaluate the ocular administration of this polycarbophil-based gel, containing 50 ppm BAK. These studies were reviewed by Dr. Conrad Chen under IND 102654.

The polycarbophil based formulation yielded somewhat higher ocular exposure in tears and conjunctiva, but the exposure in cornea and aqueous humor was similar to the marketed products. The plasma loteprednol etabonate concentrations were < 1ng/mL in most animals. The results from the three ocular PK studies show that ocular exposure with the gel is similar or somewhat greater (1.2 to 3.0 fold) than that observed with the Lotemax suspension.

In a 29-day repeat dose ocular toxicity study in rabbits with 7-day recovery period, there were no significant ocular findings reported. Decrease in actively growing hair follicles, evident in both the eyelids of treated animals, was observed; the eyelashes and meibomian glands were not affected. This finding is consistent with the known steroid modulation of hair follicle cycling. Systemically, adrenal weights decreased and histologically cortical atrophy was observed. The systemic NOAEL was less than 0.4% and systemic effects of topical corticosteroids were typical of those observed in other studies.

In a 27-day repeat dose ocular toxicokinetic study in rabbits, after the 4th dose on Day 1, there was an increase in systemic exposure with increase in dose from 0.4% to 0.7%. No accumulation of loteprednol etabonate was observed between Day 1 and Day 27.

In summary, the results of the toxicology studies showed no significant ocular findings during the course of the study and the ocular NOAEL to be 0.7% and the systemic NOAEL was less than 0.4%.

Comment: The application is recommended for approved from a pharmacology/toxicology standpoint, and labeling is consistent with NDA 200738 and accceptable.

5. Clinical Pharmacology/Biopharmaceutics

For complete details, see review by Drs. Gieser and Colangelo. Some highlights are provided below:

There were no Clinical Pharmacokinetics studies conducted specifically for LE ophthalmic gel 0.5%. The composition of the gel formulation is different from the approved Lotemax ophthalmic suspension because of the incorporation of a (b) (4) (polycarbophil, (b) (4) (propylene glycol, (b) (4) and (b) (4) concentration of preservative, (b) (4) (b) (4) (b) (4) The sponsor believes that these modifications are expected to improve the physico-chemical properties, dosage uniformity, and ocular tolerability of the gel formulation compared to the suspension, without the blurring effect on vision of the ointment.

Dr. Gieser did not agree with the applicant's proposal to state in the LE gel package insert *12.3 Pharmacokinetics* that the (b) (4) (b) (4)

The clinical reviewers agreed with removing this unsubstantiated information from labeling.

Loteprednol is an analogue of prednisolone. Corticosteroids inhibit the inflammatory response to a variety of inciting agents and can delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. While glucocorticoids are known to bind to and activate the glucocorticoid receptor, the molecular mechanisms involved in glucocorticoid/glucocorticoid receptor-dependent modulation of inflammation are not clearly established. However, corticosteroids are thought to inhibit prostaglandin production through several independent mechanisms.

Dr Aziz notes that in general, primary pharmacology studies showed that LE has similar activity to dexamethasone (DEX) and betamethasone-17-valerate (BMV) and similar anti-inflammatory effectiveness to 1% prednisolone acetate (PA). Receptor binding studies show that LE has 4.3 times greater binding affinity than DEX for glucocorticoid (Type II) receptors,

and that LE binds competitively to transcortin, a corticosteroid-binding plasma protein. The two major metabolites of LE are PJ-91 and PJ-90. Neither metabolite binds to the glucocorticoid receptor indicating that there is systemic absorption of the parent molecule and not its metabolites.

She further notes that as with other corticosteroids, LE decreased scar formation, inhibited inflammatory cell infiltration, inhibited fibroblast proliferation, and decreased tensile strength of the resulting scar. No clear effect on intraocular pressure was noted with LE. Topical ocular treatment of normotensive rabbits with LE (0.1%, 1 dose per hour for 7 hours on two consecutive days) did not result in a sustained rise in IOP during the 55-h interval following the first administration".

Comment:
The application is recommended for approval from a clinical pharmacology review, and labeling revisions have been incorporated.

6. Clinical Microbiology/Immunology

Not applicable.

7. Clinical/Statistical-Efficacy

For complete details of the studies, designs, endpoints and analyses, see clinical reviews by Drs. Lim, Boyd, and Chambers and statistical review by Drs. Izem and Wang.

In support of efficacy, the application contained results of two randomized, multicenter, double-masked, vehicle placebo-controlled Phase 3 trials (Study 576 and Study 577) in 813 patients (797 US, 16 Germany) randomized to one of the two arms: LE QID for 14 days after cataract surgery (n=409) versus vehicle control (n-404).

In each trial, the primary efficacy endpoints were evaluated at day 8 post-surgery:

- Complete resolution (without rescue medication) of anterior chamber cell inflammation at Visit 5 (Day 8 post-operatively). Anterior chamber cell inflammation was quantified by investigators in a 5-point grade scale (0 to 4).
- Complete resolution (without rescue medication) of pain Visit 5 (Day 8 post-operatively). Ocular pain was assessed by patient and recorded by investigator in a 6-point grade scale (0 to 5).

Complete resolution for each scale is defined as a grade of 0. In both endpoints, receiving rescue medication at any time before study visit was considered a treatment failure.

All patients were included in the ITT and safety population, over 90 to 95% were in the PP population.

7.1 Efficacy Results:

The efficacy results for the ITT population are summarized in the table below. The outcomes were comparable for the PP population as reflected in the reviews.

For resolution of anterior chamber cells, the effect size was 15% (95% CI = 6%, 23%) in study 576 and 17% (95% CI = 9%, 26%) in study 577. For proportion of ocular pain resolution, the effect size was 31% (95% CI =21%, 41%) in study 576 and 30% (95% CI =20%, 39%) in study 577. Other exploratory analyses in the review support the efficacy claim.

Study 576 – ITT Population

Primary Efficacy Analysis	LE Gel N = 203	Vehicle N = 203	P-value
Complete Resolution of AC cells at Visit 5 (Post-operative Day 8)			
Yes	62 (30.5%)	33 (16.3%)	< 0.001
No	141 (69.5%)	170 (83.7%)	
Subjects without Rescue Medication	122	100	
Subjects with Rescue Medication	17	70	
Subjects with Missing Data	2	0	
Grade 0 (no) Pain at Visit 5 (Post-operative Day 8)			
Yes	148 (72.9%)	85 (41.9%)	< 0.001
No	55 (27.1%)	118 (58.1%)	
Subjects without Rescue Medication	36	48	
Subjects with Rescue Medication	17	70	
Subjects with Missing Data	2	0	

Study 577 – ITT Population

Primary Efficacy Analysis	LE Gel N = 206	Vehicle N = 201	P-value
Complete Resolution of AC cells at Visit 5 (Post-operative Day 8)			
Yes	64 (31.1%)	28 (13.9%)	< 0.001
No	142 (68.9%)	173 (86.1%)	
Subjects without Rescue Medication	134	124	
Subjects with Rescue Medication	6	47	
Subjects with Missing Data	2	2	
Grade 0 (no) Pain at Visit 5 (Post-operative Day 8)			
Yes	156 (75.7%)	92 (45.8%)	< 0.001
No	50 (24.3%)	109 (54.2%)	
Subjects without Rescue Medication	42	60	
Subjects with Rescue Medication	6	47	
Subjects with Missing Data	2	2	

It was noted that subjects 70 years and younger had a larger treatment effect than patients over 71 years of age. The treatment effect for anterior chamber cell resolution was 21% in Study 576 and 24% in Study 577 for those 70 years of age and below, and 8% in Study 576 and 11% in study 576 for subjects 71 years and older. The treatment effect for pain resolution was 35%

in Study 576 and Study 577 for patients 70 years and below, and 28% in Study 576 and 25% in Study 577 for those 71 years and older. However, the trials were not powered to show a significant difference among the subgroups and there was overlap of the confidence intervals for these and other subgroup analyses (page 22 of review).

Comment:
The clinical reviewers and statistical reviewers recommend approval of the application. The gel product was superior to vehicle. Although the applicant considered that the gel formulation has advantages over the ointment and suspension, there were no clinical studies done to compare or show a clinical benefit of the gel product over the other approved Lotemax products, nor are any comparative statements included in labeling.

8. Safety

See clinical reviews by Drs. Lim, Boyd and Chambers for details.

In these trials, 406 patients received an average of 12 days (range 1 - 16 days) of LE. There were no deaths, discontinuations occurred in approximately 1-2% of patients, 0.5% due the adverse events.

Common adverse events were seen in 18.7% of LE gel and 21.7% vehicle patients. These included anterior cells inflammation, eye pain, photophobia, foreign body sensation, conjunctival hemorrhage, pruritis, corneal edema, blurred vision, lacrimation, posterior capsule opacification, and IOP increase. The individual events were seen in 2% to 4% of patients.

Systemic adverse events were seen in less than 4% of patients, and included exacerbation of bronchitis, syncope due to electrolyte imbalance, acute diverticulitis, cholecystitis, MI, or hypokalemia due to dehydration. Attribution to LE gel was not discussed, although some of these events were seen in patients given vehicle-control.

8.1 Adverse events of special interest

Loteprednol, as other ophthalmic corticosteroids, is contraindicated in most viral disease of the cornea and conjunctiva. Prolonged corticosteroid administration is associated with elevated intraocular pressure, posterior subcapsular cataract formation, delayed healing, and bacterial, viral, and fungal infections. Contact lenses should not be work during corticosteroid treatment. Appropriate warnings regarding these reactions are included in the product labeling.

Comment:
The reviewers recommend that the safety profile is acceptable. The adverse events reported in the loteprednol studies are consistent with events reported with this drug class, and are summarized in labeling.

9. Advisory Committee Meeting

The application was not presented before an Advisory Committee. There are other corticosteroids and non-steroidal anti-inflammatory drugs approved for treating post-operative inflammation and pain. The application did not raise any new scientific issues that warranted discussion at an open public meeting.

10. Pediatrics

The clinical trials did not enroll any pediatric patients. Safety and effectiveness in pediatric patients have not been established. The gel product was presented to PeRC on July 18, 2012. A pediatric study protocol to evaluate loteprednol compared to prednisolone was submitted and an SPA agreement letter issued July 27, 2012. The pediatric plan is included in the NDA Section 1.9.2. According to the pediatric record in DARRTS, pediatric studies are deferred until 12/31/2016 as the application is ready for approval in adults.

Previously, Lotemax suspension was studied in pediatric patients in response to a pediatric written request (WR). Pediatric exclusivity was granted; however, the trial failed to show efficacy. Lotemax ointment was granted a waiver for pediatric studies because the product causes blurring, thus hindering the child's ability to focus, and potentially interfering with amblyopia treatment.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection

Manufacturing facilities are acceptable based on the March 20, 2012 recommendation from the Office of Compliance (copy of EER report included in the CMC and CDTL reviews).

11.2 Office of Scientific Investigation (OSI) Audits

Inspections of two investigators were completed, one from Study 577 was considered NAI and another from Study 576 was considered VAI. Based on the inspectional findings at these sites, the OSI reviewer recommended that the efficacy and safety data obtained can be considered reliable in support of the application.

11.3 Debarment Certification

Bauch & Lomb certified that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

11.4 Financial Disclosure

Bausch & Lomb has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for loteprednol etabonate ophthalmic gel. One investigator who participated in the phase 3 Clinical Study 576 disclosed financial ties to the sponsor; he enrolled 3 patients.

11.5 Other Regulatory Issues

None

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA, and DPDP.

- **Package insert (PI):** The PI is written in PLR format, and is essentially the same (where applicable) as for the already approved Lotemax ointment. The current labeling has been reviewed by all groups, and includes the recommendations made by these groups, or where there were different viewpoints, the explanation for the final labeling is found in the CDTL review.

- **Carton and Container Labels**: The labels were reviewed by the Division, CMC and DMEPA, revisions were incorporated, or where there were different viewpoints, the explanation for the final labels is found in the CDTL review.

- **Proprietary Name**: The applicant proposed multiple proprietary names for this product to DMEPA, including (b) (4) all of which were found unacceptable by DMEPA. Finally the name Lotemax was considered acceptable. A summary of the names and reasons for rejecting or accepting the name(s) are summarized in the DMEPA proprietary name review dated September 24, 2012 and a letter stating that the name Lotemax is acceptable was issued by Dr. Holquist of DMEPA on September 25, 2012.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The application will be issued an *Approval* letter. All review disciplines recommend approval of the application, inspections were acceptable and labeling has been finalized.

13.2 Risk Benefit Assessment

Lotemax (loteprednol etabonate ophthalmic gel) 0.5% is a new formulation of loteprednol etabonate. It was tested in two randomized, masked Phase 3 trials and shown to be superior to vehicle-control for resolution of anterior chamber cell inflammation and resolution of pain following ocular surgery. The product is administered topically QID one day after and up to 14 days after surgery. The safety profile showed the rate of events was somewhat lower than the control and commonly reported events were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The benefits of resolving post-operative inflammation and pain outweigh the risk of anterior chamber inflammation, pain, photophobia which were seen no more frequently than in the control arm. Warnings associated with use of corticosteroids, including loteprednol are included in labeling.

13.3 Recommendation for Postmarketing Requirements (PMR) and Commitments (PMC)

None

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/s/

RENATA ALBRECHT
09/28/2012