Medical Officer's Review of NDA 50-804
SDN-89

NDA 50-804 **SDN-89**	**Submission Date:** September 15, 2010 **Received Date:** September 20, 2010 **Review Date:** February 1, 2011
Applicant:	Bausch & Lomb 7 Giralda Farms, Suite 1001 Madison, NJ 07940 (973) 360-6459 Contact: Fang Li
Drug:	Zylet (Loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension)
Pharmacologic Category:	Corticosteroid/anti-infective fixed combination
Dosage Form and Route of Administration:	Topical ocular ophthalmic suspension

Submitted:

Submitted is (b) (4) a request for determination of pediatric exclusivity for loteprednol products, Lotemax (loteprednol etabonate ophthalmic suspension 0.5%), NDA 20-583, Alrex (loteprednol etabonate ophthalmic suspension 0.2%), NDA 20-803, and Zylet (loteprednol etabonate 0.5% suspension), NDA 50-804.

Clinical Study #550 entitled "A Clinical Safety and Efficacy Evaluation of Zylet (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) compared to Lotemax (loteprednol etabonate ophthalmic suspension 0.5%), Tobramycin ophthalmic solution USP, 0.3%, and the Vehicle of Zylet for the Treatment of Blepharoconjunctivitis in Pediatric Subjects" was conducted in response to a Pediatric Written Request dated May 14, 2007 and amended December 16, 2009.

The Final Clinical Study Report for Study #550 (b) (4) are included in this submission.

Study #550

Type of study:
This was a randomized, double-masked, parallel-group, multicenter study with four arms in pediatric subjects ages 0-6, for the treatment of blepharoconjunctivitis: loteprednol

etabonate and tobramycin ophthalmic suspension, 0.5/0.3% compared to loteprednol etabonate ophthalmic suspension, tobramycin ophthalmic solution, and vehicle. Blepharoconjunctivitis is considered a steroid responsive inflammatory condition for which a corticosteroid is indicated and where the risk of bacterial ocular infection exists.

Indication/Objective:
The objective was to evaluate the safety and efficacy of loteprednol etabonate and tobramycin ophthalmic suspension, 0.5/0.3% compared with loteprednol etabonate ophthalmic suspension, tobramycin ophthalmic solution and vehicle in pediatric subjects ages 0-6, for the treatment of blepharoconjunctivitis.

Male and female subjects clinically diagnosed with blepharoconjunctivitis in at least one eye defined as follows: lid erythema, and bulbar conjunctival injection each of Grade 1 or greater but with the total combination being at least 3 and severity of Grade 1 or greater of any two of the following six ocular signs: lid scaling/crusting, lid edema, lid meibomian plugging, palpebral conjunctival injection, conjunctival discharge, or conjunctival chemosis were enrolled.

Age groups:
137 pediatric subjects (34-35 subjects per treatment group), 0-6 years of age, who had a clinical diagnosis of blepharoconjunctivitis in at least one eye were enrolled into the study. Each treatment group included at least five subjects who were ≥ 1 week of age and < 1 year of age, and at least 25 subjects who were ≥ 1 year of age and ≤ 6 years of age.

Parents/guardians were instructed to instill one or two drops QID at approximately 4-hour intervals for 14 days, starting at Visit 1.

Drug Information:
Loteprednol etabonate and tobramycin ophthalmic suspension, 0.5/0.3% was compared to loteprednol etabonate ophthalmic suspension, tobramycin ophthalmic solution and vehicle.

Subjects in all treatment groups received 1 to 2 drops of the assigned study medication QID in each eye clinically diagnosed with blepharoconjunctivitis starting on day 1 and continuing through day 14.

Drug Specific Safety Concerns:
The study consisted of a 14 day treatment period with evaluations at Days 1 (baseline), 3, 7, and 15. Adverse events, visual acuity, signs of lid edema, lid erythema, palpebral conjunctival injection, and meibomian plugging were evaluated at each study visit.

Statistical Analysis:
Descriptive analyses were performed on the primary safety variables (adverse events) and primary efficacy variable (sum of lid erythema, lid scaling/crusting, lid edema, lid

meibomian plugging, bulbar conjunctival injection, palpebral conjunctival injection, conjunctival discharge, and conjunctival chemosis)

Labeling:
Current Pediatric labeling, (b) (4):

In a trial to evaluate the safety and efficacy of Zylet® in pediatric subjects age zero to six years with lid inflammation, Zylet with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. Patients received warm compress lid treatment plus Zylet or vehicle for 14 days. The majority of patients in both treatment groups showed reduced lid inflammation. There were no differences in safety assessments between the treatment groups.

(b) (4)

Format of Report to be submitted:
A full study report, not previously submitted to the Agency, was submitted.

Pediatric patients were categorized by race as follows: White, Black/African American, American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, and Other, and categorized by ethnicity as follows: Hispanic/Latino and Not Hispanic and Not Latino.

Pediatric Exclusivity Determination Checklist:

Was a formal Written Request made for the pediatric studies submitted?	Y _X_	N ___
Were the studies submitted after the Written Request?	Y _X_	N ___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y _X_	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y _X_	N ___
If there was a written agreement, were the studies conducted according to the written agreement? ***OR*** If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y _X_	N ___
Did the studies fairly respond to the Written Request?	Y _X_	N ___

Reviewer's Comments:

(b) (4)

(b) (4)

Labeling

(b) (4)

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Recommended Regulatory Action:

(b) (4)

Pediatric Exclusivity should be granted for the loteprednol products per the Pediatric Exclusivity Board.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: NDA 50-804
HFD-520/Div Files
HFD-520/CSO/Rodriguez
HFD-520/MO/Lim
HFD-520/CTL/Boyd
HFD-520/Acting Div Director/Chambers

NDA 50-804sdn89 loteprednol etabonate/tobramycin ophthalmic solution

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUCIOUS LIM
03/09/2011

WILLIAM M BOYD
03/09/2011