

Decisional Summary for NDA 22-369, Supplements 8 & 10

Date	September 4, 2014
From	Wiley A .Chambers, M.D.
NDA #	NDA 22-369
Applicant	Allergan, Inc.
Date of Submission	March 4, 2014
Type of Application	Supplement 10 incorporating revisions to Supplement 8
Name	Latisse (bimatoprost ophthalmic solution) 0.03%
Dosage forms / Strength	Topical ophthalmic solution
Indication(s)	For the treatment of hypotrichosis of the eyelashes
Action:	Approval

1. Introduction/Background

Bimatoprost is an ocular hypotensive agent which was first approved for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension in March 2001 (NDA 21-275, Lumigan (bimatoprost ophthalmic solution), 0.03%). In the initial studies which supported the approval of NDA 21-275, increased eyelash growth was observed as an adverse event. In two active-controlled Phase 3 studies, eyelash growth was reported as an adverse event after 3 months of treatment in 17.9% and 25.6% of patients receiving bimatoprost 0.03% ophthalmic solution once daily, applied to the conjunctival sac.

With intentional administration of bimatoprost ophthalmic solution to the eyelid, instead of the conjunctival sac, a new drug application (NDA 22-369) was submitted and subsequently approved . The indication of hypotrichosis of the eyelid had been studied under IND 48,929 with endpoints including eyelash length, progressive eyelash thickness/fullness, and eyelash darkness/intensity. The approval letter included a requirement for a pediatric study under PREA in pediatric patients 0 to 17 years of age. Allergan committed to conduct “A controlled trial of at least 4 months duration with Latisse (bimatoprost ophthalmic solution) 0.03% in at least 30 pediatric subjects less than 18 years of age with hypotrichosis due to a medical condition with the primary endpoint of a 1-grade increase in GEA from baseline.” A pediatric study report in response to the PREA post-marketing requirement was required to be submitted and the findings of the study were to be included in the product labeling. Allergan submitted a proposed protocol. The Agency reviewed and agreed with the protocol. Allergan completed the study.

On March 7, 2013, Allergan submitted supplement 8 to NDA 22-369 proposing to revise a number of sections of the labeling (5.8 Use with Contact Lenses, 6.1 Clinical Studies Experience, 6.2 Postmarketing Experience, 16 How Supplied/ Storage and Handling and 17.8 /Patient Counseling /Use with Contact Lenses). On February 11, 2014, the Agency issued a Complete Response letter for Supplement 8. The Agency suggested revised labeling incorporating some of the changes proposed by Allergan.

The subject of this current review is Supplement S-010 submitted on March 3, 2014, received on March 4, 2014. This supplement proposed revisions to the U.S. Package Insert for Latisse (bimatoprost ophthalmic solution) 0.03% based on the Agency's request to submit labeling based on the completed pediatric study. The supplement also incorporated changes previously submitted as supplement 8.

2. CMC

This supplemental application proposes no revisions to the Chemistry Manufacturing information for the Latisse new drug application.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted with this efficacy supplement. The package insert was revised to describe the exposure margin based on blood levels (AUC), consistent with the Lumigan (bimatoprost ophthalmic solution) 0.03% package insert .

4. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology/biopharmaceutics studies were submitted with this supplemental application.

5. Clinical/Statistical - Efficacy

This supplemental NDA contains the clinical study report of 192024-040: A Multicenter, Double-Masked, Randomized, Parallel-Group Study Assessing the Safety and Efficacy of Once Daily Application of Bimatoprost Solution 0.03% Compared to Vehicle When Applied to the Eyelid Margins of Pediatric Subjects.

Study 192024-040 was a multicenter, double-masked, randomized, vehicle-controlled, parallel-group study consisting of approximately 6 or 7 scheduled visits and 1 telephone visit (screening, baseline [or a single screening/baseline combined visit], telephone visit [week 1], and months 1, 2, 3, 4 [or early exit], and 5 [post treatment follow-up]). A subject was considered to have entered the study at the time of randomization on day 1. Qualified subjects were randomly assigned to daily bilateral application to the upper eyelid margins with either bimatoprost solution 0.03% or vehicle in a 2:1 ratio.

Approximately 70 subjects (approximately 30 medical-need post chemotherapy or alopecia areata pediatric subjects and approximately 40 nonmedical-need¹ adolescents) were planned to be enrolled at approximately 15 investigational sites. At the time of randomization, eligible subjects were stratified by age group (5 to 11 versus 12 to 17 years). Seventy-one subjects were randomized and enrolled in the study. There were 40 nonmedical-need adolescent subjects, 16 post chemotherapy subjects, and 15 subjects with alopecia areata. The mean age overall was 14.5 years (range 5 to 17 years). There were imbalances in the patient population by age group and by etiology which were caused by difficulty enrolling postchemotherapy and alopecia areata

¹ Nonmedical need is defined as hypotrichosis with no identifiable causal related medical condition

patients. In order to increase enrollment, non-medical need adolescent subjects were enrolled. Thus, the majority of the resulting study population was age 15 to 17 (n=52, 73.2%).

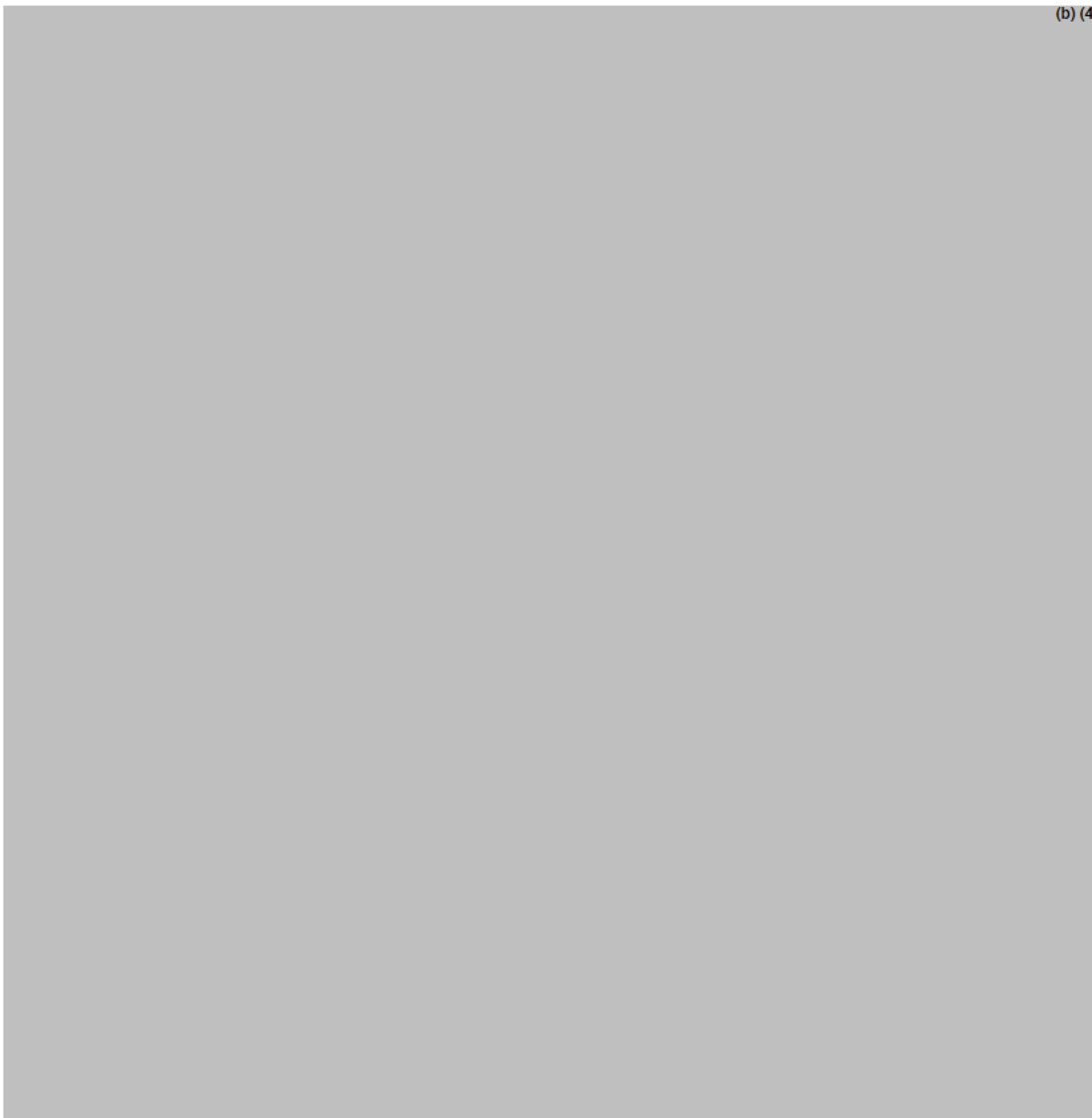


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	Age Range (years)	LATISSE®	Vehicle	Difference (95% CI)
Adolescents with hypotrichosis (N=40)	15 – 17	19/26 (73%)	1/14 (7%)	66% (44%, 88%)
Post Chemotherapy Pediatric Patients (N=16)	5 – 17	11/13 (85%)	3/3 (100%)	-15% (-35%, 4%)
Alopecia Areata Pediatric Patients (N=15)	5 – 17	4/9 (44%)	2/6 (33%)	11% (-39%, 61%)

6. Safety

Study 192024-040 is the only study of pediatric subjects with bimatoprost ophthalmic solution 0.03%. Bimatoprost ophthalmic solution has been studied extensively during its clinical development program for the reduction of intraocular pressure and for the treatment of hypotrichosis in adults.

Common Adverse Events

**Table 7.4.1-1 All Adverse Events with Incidence > 1 Subject in Either Treatment Group
Treatment and Posttreatment Periods Combined
(Safety Population)**

Adverse Event (Preferred Term ^a)	System Organ Class	Bimatoprost 0.03% (N=48)	Vehicle (N=23)
Conjunctival hyperemia	Eye Disorders	2 (4.2%)	0 (0.0)
Conjunctivitis	Eye Disorders	2 (4.2%)	0 (0.0)
Eczema	Skin and subcutaneous tissue disorders	2 (4.2%)	0 (0.0)
Erythema of eyelid	Eye Disorders	2 (4.2%)	0 (0.0)
Nasopharyngitis	Infections and Infestations	2 (4.2%)	0 (0.0)
Sinusitis	Infections and Infestations	2 (4.2%)	0 (0.0)

Note: All adverse events, regardless of relationship to treatment, with incidence >1 subject in either treatment group, are presented. Preferred terms are sorted by descending frequency in treatment groups from left to right. Within each preferred term, a subject is counted at most once.

^a MedDRA Version 15.1

Source: Table 14.3-5.1

Safety Summary- While the number of study subjects is small, the adverse event profile is consistent with those reported in previous studies of bimatoprost ophthalmic solution. There were no reports of iris hyperpigmentation or skin hyperpigmentation.

7. Advisory Committee Meeting

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

8. Other Relevant Regulatory Issues

An Office of Scientific Investigations (OSI) audit was requested. The clinical site of Dr. Baumann was selected for inspection because it was among the highest enrolling sites. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of a regulatory action.

The applicant has adequately disclosed the financial interests/arrangements with clinical investigators. None of those with significant financial interests are sponsor employees. There was no evidence suggesting problems with the integrity of the submitted data.

9. Application Discussion

The study supporting this supplement was completed to fulfill a postmarketing requirement. The applicant received a Fulfillment of Postmarketing Requirement letter dated April 21, 2014, which stated that postmarketing requirement 501-1 (Deferred pediatric study under PREA for the treatment of hypotrichosis in pediatric patients ages 0 to 17 years) had been fulfilled. Based on the low enrollment in the lower age groups, studies in pediatric patients less than 5 years would be impossible or highly impractical.

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[REDACTED] Differences in these interpretations and opinions lead to differences of opinion with respect to the wording that should be included in the labeling.

This supplemental application was discussed at the Pediatric Regulatory Committee (PeRC) on Wednesday, August 20, 2014. It was the opinion of the members present that the Section 8.4 of the Latisse package insert be revised to include a description of the efficacy findings for the different populations based on their underlying medical condition from Study 192024-040 without providing interpretations or definitive conclusions. There was a consensus agreement among PeRC members and the Review team to accept this approach. The package insert has been revised based on this recommendation.

10. Labeling

Previous recommendations from the review of NDA 22-369/S-008 have been incorporated in the labeling for supplement NDA 22-369/S-010. The revised labeling received on September 3, 2014, it includes the revisions to Section 8.4 for supplement S-010 and revisions to Sections 5.8, 6.1, 6.2, 16 and 17.8 requested for supplement S-008. This labeling is included below and will be approved.

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11. Regulatory Action

NDA 22-369/S-008 and S-010 will be approved with the labeling submitted on September 3, 2014. The requirement for studies in pediatric patients less than 5 years of age will be waived because such studies would be impossible or highly impractical. Studies in pediatric patients aged 5 years and above are considered complete.

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Deputy Division Director

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/s/

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09/04/2014