CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-369

SUMMARY REVIEW

Division Director Review

Date	December 19, 2008
From	Wiley A. Chambers, M.D.
Subject	Summary Review
NDA#	22-369
Applicant	Allergan, Inc.
Date of Submission	June 26, 2008
Name	Latisse (bimatoprost ophthalmic solution) 0.03%
Dosage form	ophthalmic solution for administration to the eyelids
Proposed Indication(s)	Treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness
Regulatory Action:	Approval

1. Introduction/Background

NDA 21-275, Lumigan (bimatoprost ophthalmic solution) 0.03% was approved to reduce ocular hypertension in March 2001. Similar to other prostaglandin analogs it was noted to increased eyelash growth. The applicant (Allergan) has developed the same formulation of bimatoprost ophthalmic solution, 0.03% for a new ophthalmic indication, "to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness."

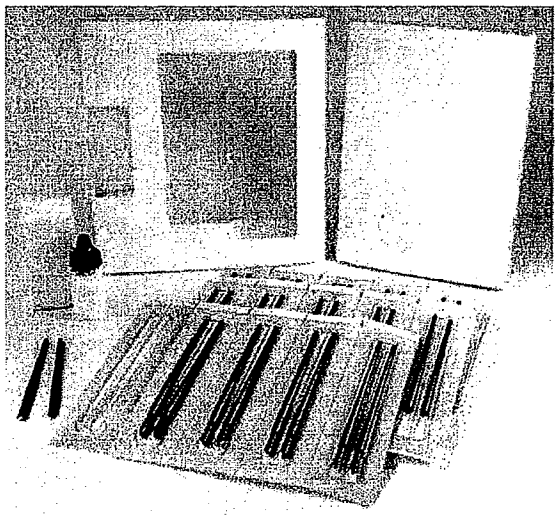
The mechanism of action by which bimatoprost reduces intraocular pressure is thought to occur by increasing aqueous humor outflow through the trabecular meshwork and enhancing uveoscleral outflow. In two active-controlled Phase 3 studies, eyelash growth was reported as an adverse event after 3 months of treatment in 17.9% and 25.6% of patients receiving bimatoprost ophthalmic solution 0.03% once daily. The proportion of subjects reporting eyelash growth increased after 6 and 12 months of treatment. In a proof-of-concept study evaluating the effect of bimatoprost 0.03% on eyelash growth, color, and thickness, bimatoprost was shown to be effective as measured by subjects' assessment of change from baseline. At the end of the 3-month treatment period, 81% (13/16) of subjects who completed the study reported their overall eyelash appearance to be "much improved," and 19% of subjects reported their overall eyelash appearance to be "improved." Lumigan (bimatoprost ophthalmic solution) 0.03% and Latisse (bimatoprost ophthalmic solution) 0.03% studied in the NDA are the same drug product.

The exact mechanism of action by which bimatoprost causes eyelash growth is unknown; bimatoprost-induced eyelash enhancement is believed to occur by 3 mechanisms: by prolonging the growth phase of the hair cycle resulting in longer length; by stimulating the resting follicles resulting in thicker/fuller lashes; and by increasing melanin synthesis resulting in darker hair pigmentation.

2. CMC

Bimatoprost ophthalmic solution 0.03%, a prostaglandin analog is proposed to be applied to the skin of the upper eyelid margin at the base of the eyelashes using the accompanying sterile

disposable applicators. The proposed drug product is a clear, isotonic, colorless, sterile solution. The same formulation as approved in NDA 21-275 under the trade name Lumigan for lowering intraocular pressure (IOP) when instilled directly to the eye. From CMC consideration the 2 drug products' solutions (NDA 21-275 and NDA 22-369) are identical except for the addition of the applicator for NDA 22-369 and the labeling. The proposed drug product specifications are the same as NDA 21-275.



3. Nonclinical Pharmacology/Toxicology

NDA 22-369 cross-references NDA 21-275 for Lumigan and the nonclinical studies conducted by Allergan to support the development and approval of that product are also appropriate to support the current NDA. The sponsor also included a brief report (Effect of Bimatoprost (Lumigan) on the Eyelashes of Mice, Report No. BIO-07-630) for a non-GLP study on the effects of 0.03% bimatoprost on eyelash growth in C57BL/6 mice. According the report (which contained no raw data), bimatoprost increased the thickness and length of short and medium length (but not long) eyelashes and increased the number of eyelash follicles with 2 hairs but did not increase the number of follicles. The NDA also contains reports of a single dose dermal absorption study in mice using an alcoholic gel formulation of bimatoprost (Report No. PK-04-157) as well as a predictive multiple dose PK analysis based on data from that dermal absorption study (Report No. PK-08-038). The gel formulation is not being marketed. The application is recommended for approval by the Pharmacology/Toxicology Reviewer.

4. Clinical Pharmacology/Biopharmaceutics

In support of the NDA, the Sponsor submitted the results of a Phase 3 safety and efficacy study. No new clinical pharmacology data are submitted by the Sponsor. As the formulation of the drug product and dosing frequency are unchanged and the dose administered is less than that for IOP

reduction, the Sponsor was granted a waiver of the requirement to provide evidence of in vivo bioavailability based on 21 CFR 320.22(b)(1). Given the dose and route of administration (application to the upper eyelid), systemic exposure of bimatoprost is expected to be clinically negligible. The application was recommended for approval by the Clinical Pharmacology Reviewer.

5. Sterility Assurance

There are no changes in the previously approved manufacturing process for 0.03% bimatoprost solution [NDA 21-275] except that the newly designated product would be used for external application. An external applicator kit is provided. The application is recommended for approval by the Product Quality Microbiology Reviewer.

The application as submitted did not contain a specification for endotoxin. While the drug product is intended to be applied to the eyelid and therefore unlikely to be significantly affected by endotoxin, it is likely that some small fraction of the drug product may reach the eye. It was therefore recommended that the endotoxin level be monitored and potentially be controlled if needed. In a correspondence dated December 16, 2008, Allergan, Inc. proposes —— b(4)

6. Clinical/Statistical - Efficacy

Clinical Efficacy Studies for Eyelash Growth

Study No.	Study Design	# Pts Treated, Treatment	Duration of Treatment	Key Results
192024-032	Phase 3 multicenter, double-masked, randomized, vehicle-controlled parallel-group study	137 bimatoprost 141 vehicle Bimatoprost or vehicle applied once daily to the upper eyelid margins using a single-use-per-eye applicator	16 weeks (treatment period) followed by a 4-week post-treatment follow-up period	Starting at Week 8, a statistically significant higher percentage of subjects in the bimatoprost group compared with the vehicle group experienced improved eyelash prominence, length, thickness/fullness, and darkness ($p<0.0001$).
192024-MA001	Investigator-sponsored open-label proof-of-concept study	28 subjects All subjects applied bimatoprost once daily to the upper eyelid margins using a sponge-tipped applicator	12 weeks (treatment period) followed by a 4-week post-treatment follow-up period	At the end of the 12-week treatment period, among those 16 respondents who answered the question 81% (13/16) and 19% (3/16) of subjects reported their eyelashes to be "much improved" or "improved," respectively. Most subjects reported that they had noticed growth or darkening of their eyelashes by week 8 (month 2) of the study.

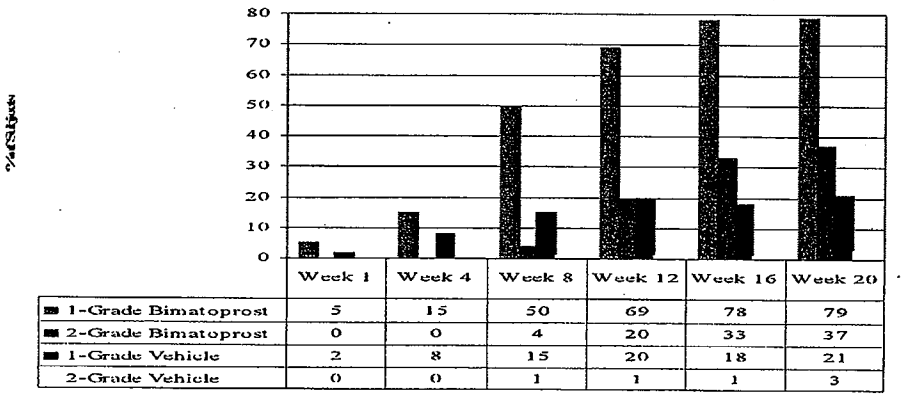
Study No.	Study Design	# Pts Treated, Treatment	Duration of Treatment	Key Results
192024-033	Single-center, randomized study	68 subjects enrolled. Investigational study drug was not administered in this study	No treatment was administered during this 1-day study	The Global Eyelash Assessment Scale with photonumeric guide can be considered to be a reliable instrument in grading overall eyelash prominence.

Study 192024-032

Visit [a]	Bimatoprost 0.03% (N=137)	Vehicle (N=141)	p-value [b]
Week 1	7/137 (5)	3/141 (2)	0.2124 [c]
Week 4	20/137 (15)	11/141 (8)	0.0719
Week 8	69/137 (50)	21/141 (15)	<0.0001
Week 12	95/137 (70)	28/141 (20)	<0.0001
Week 16 (Primary Endpoint)	**107/137 (78)**	**26/141 (18)**	**<0.0001**
Week 20	103/131 (79)	27/126 (21)	<0.0001

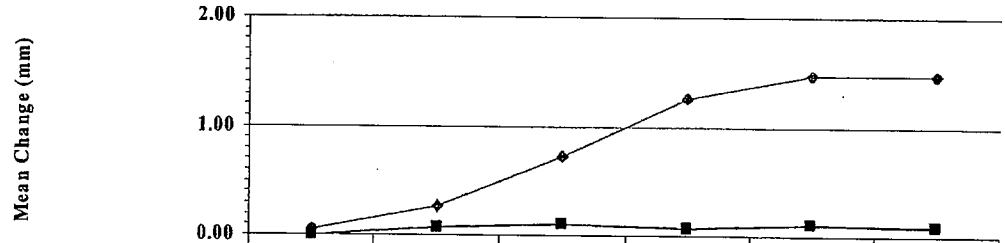
a LOCF was performed on weeks 1 to 16 and week 20 analysis was based only on observed cases.
b p-values are based on Pearson's chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of <5.
c Fisher's exact test was performed.

Percentage of Subjects With at Least a 1- or 2-Grade Increase From Baseline in GEA (ITT Population)



	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20
1-Grade Bimatoprost	5	15	50	69	78	79
2-Grade Bimatoprost	0	0	4	20	33	37
1-Grade Vehicle	2	8	15	20	18	21
2-Grade Vehicle	0	0	1	1	1	3

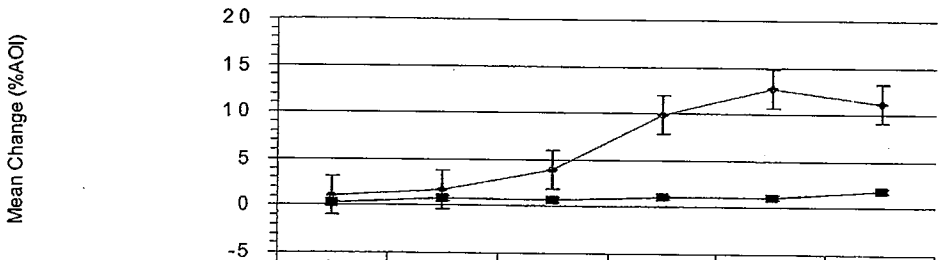
Eyelash Length: Mean Change from Baseline (PP Population)



	1	4	8	12	16	20
Bim 0.03% (mm)	0.06	0.26	0.73	1.25	1.47	1.47
Vehicle (mm)	0.01	0.07	0.11	0.07	0.11	0.08

Week

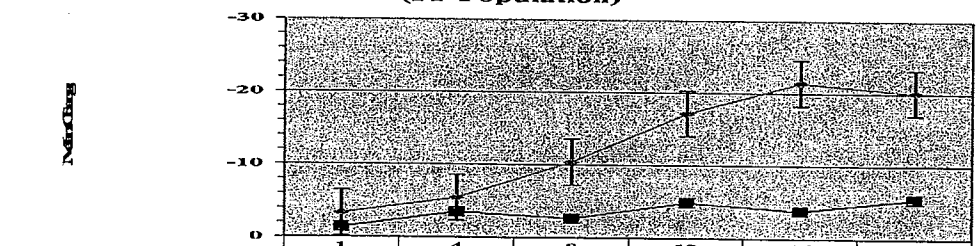
Progressive Eyelash Thickness/Fullness:
Mean Change From Baseline, % AOI (PP Population)



	1	4	8	12	16	20
Bimatoprost 0.03%	1.05	1.76	3.96	9.92	12.75	11.16
Vehicle	0.27	0.84	0.71	1.05	1.08	1.88

Week

Eyelash Darkness: Mean Change from Baseline, Spline (PP Population)



	1	4	8	12	16	20
Bimatoprost 0.03%	-3.35	-5.46	-10.42	-17.15	-21.43	-20.12
Vehicle	-1.44	-3.52	-2.69	-4.94	-3.84	-5.51

Week

Sensitivity Analyses

A sensitivity analysis on the primary efficacy endpoint in which missing values were treated as treatment failures was performed. When missing values were treated as treatment failures, there were no differences in the results of the primary analysis. The subjects in the bimatoprost 0.03% group experienced statistically significantly higher rates of improved eyelash prominence at the week 16 endpoint, as defined by a $\geq$ 1-grade increase on the GEA scale, compared to subjects in the vehicle group ($p < 0.0001$).

192024-032 Efficacy Conclusions

The subjects in the bimatoprost 0.03% group experienced statistically significantly higher rates of improved eyelash prominence which reached statistical significance starting at Week 8 and continuing through the treatment period. Upon discontinue, the effect slowly started to return toward baseline.

VALIDATION STUDY 192024-033

Allergan developed the Global Eyelash Assessment (GEA) score as an objective measure for use as the primary efficacy variable in this clinical study. In order to validate the GEA, _192024-033 was conducted with the objective to evaluate the inter- and intra-rater reliability of the Global Eyelash (GEA) Scale with photonumeric guide.

One response measure was evaluated in this study: overall eyelash prominence as assessed by the GEA scale with photonumeric guide. The scale consisted of 4 categories (1 = minimal, 2 = moderate, 3 = marked, 4 = very marked). The primary efficacy analyses were the agreement between raters (inter-rater reliability) and within raters (intra-rater reliability) based on the GEA scores.

Using the GEA scale with photonumeric guide to assess overall eyelash prominence, there was an adequate degree of agreement within raters. The GEA scale with photonumeric guide has been considered to be a reliable instrument in grading overall eyelash prominence.

7. Safety

EXPOSURE

In Allergan-sponsored clinical studies of any phase, 5848 patients and healthy volunteers have been exposed to bimatoprost, resulting in approximately 3461 patient-years of exposure (10 patient-years in healthy volunteers and 3451 patient-years in glaucomatous patients). Since the initial product launch of Lumigan in 2001, the exposure to bimatoprost has been estimated to be approximately 8.8 million patient-years worldwide with 5 million patient-years in the United States alone.

Exposure to Bimatoprost in Studies of IOP Reduction and Eyelash Growth

Study	Number of Patients/Subjects (Bimatoprost Group)	Duration of treatment	Comparator(s)
Phase 3 Studies of Lumigan (bimatoprost ophthalmic solution) 0.03%			
192024-008	240 (bimatoprost QD) 240 (bimatoprost BID)	12 months	Timolol
192024-009	234 (bimatoprost QD) 243 (bimatoprost BID)	12 months	Timolol
Phase 3 Studies of bimatoprost 0.03%/timolol 0.5% ophthalmic solution			

192024-018T [a]	261 (bimatoprost plus timolol) 129 (bimatoprost alone)	12 months	Timolol alone
192024-021T [a]	272 (bimatoprost plus timolol) 136 (bimatoprost alone)	12 months	Timolol alone
Studies of Lumigan in the Published Literature			
Noecker, et al (2003)	133	6 months	Latanoprost plus timolol
Phase 4 Marketing Study of Lumigan			
MA-LUMO1 [b]	131	3 months	Travoprost
Studies of Bimatoprost for Eyelash Growth			
192024-MA001	28	3 months	None
192024-032	137	4 months	Vehicle

a Brandt, et al., 2008; data on file at Allergan
b Data on file at Allergan

The total dose of bimatoprost delivered with topical application to the upper eyelid margins for the enhancement of eyelash growth is much lower than the dose of bimatoprost instilled on the cornea/conjunctiva for the treatment of elevated IOP. In the use of bimatoprost for the treatment of elevated IOP, a drop of bimatoprost ophthalmic solution is instilled directly into the eye leading not only to eye exposure but also eyelid skin and eyelash exposure via a bathing of the eyelid margin and eyelashes in the bimatoprost solution. The applicator for Latisse was designed to deliver a fraction of a 1-drop bimatoprost dose directly to the target treatment area. With a single application, approximately 5-10% of the dose for the treatment of elevated IOP is delivered to the upper eyelid margin.

POSTMARKETING EXPERIENCE

Bimatoprost ophthalmic solution administered by topical dermal administration has not been marketed. Post-marketing experience for the drug product marketed as Lumigan (bimatoprost ophthalmic solution) 0.03% estimated to be 8.8 million patient years collected over a period of 7 years is presented below.

Adverse Event	Number of reports
Conjunctival and ocular hyperemia	596
Eye Irritation	358
Skin hyperpigmentation	285
Eye pain	211
Growth of eyelashes	189
Eye pruritus	171
Headache	130
Vision blurred	119
Eyelid pruritus	75
Eyelid erythema	75

The most frequent adverse reactions reported with Lumigan are similar to those reported in the clinical studies submitted in this NDA.

Adverse Events Reported by Greater than 1% of Subjects in 192024-032

System Organ Class / Preferred Term	Bimatoprost 0.03% (N=137)	Vehicle (N=141)
OVERALL	55 (40.1)	41 (29.1)
EYE DISORDERS		
Eye Pruritus	5 (3.6)	1 (0.7)
Conjunctival hyperemia	5 (3.6)	0 (0.0)
Pinguecula	3 (2.2)	3 (2.1)
Eye irritation	3 (2.2)	2 (1.4)
Dry Eye	3 (2.2)	1 (0.7)
Erythema of eyelid	3 (2.2)	1 (0.7)
Eyelids pruritus	1 (0.7)	2 (1.4)
Conjunctival hemorrhage	0 (0.0)	2 (1.4)
IMMUNE SYSTEM DISORDERS		
Seasonal allergy	2 (1.5)	0 (0.0)
INFECTIONS AND INFESTATIONS		
Upper respiratory tract infection	2 (1.5)	5 (3.5)
Sinusitis	2 (1.5)	2 (1.4)
Influenza	2 (1.5)	0 (0.0)
Urinary tract infection	1 (0.7)	2 (1.4)
BENIGN AND MALIGNANT NEOPLASMS		
Blepharal papilloma	2 (1.5)	0 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Skin hyperpigmentation	4 (2.9)	1 (0.7)
Dermatitis contact	2 (1.5)	0 (0.0)

Note: All adverse events are represented, regardless of relationship to treatment.
Note: Within each system organ class, preferred terms are sorted by descending order of frequencies of treatment groups from left to right. Within each preferred term, a subject is counted at most once.

Conjunctival hyperemia was the only preferred term that was reported by a statistically significantly higher percentage of subjects in the bimatoprost group compared with the vehicle group.

No deaths occurred during the course of Study 192024-032.

A total of three subjects (1 bimatoprost, 2 vehicle) reported serious adverse events during the course of the study.

- Subject 10010-1035 (bimatoprost) was diagnosed with squamous cell carcinoma of the skin (on back)
- Subject 11302-1102 (vehicle) was diagnosed with lymphoma during the treatment period
- Subject 10011-1277 (vehicle) was diagnosed with recurrent metastatic breast cancer during the post-treatment period.

Four subjects in each treatment group discontinued the study (192024-032) due to an adverse event. The adverse events that led to study discontinuation by the 4 subjects in the vehicle group were lymphoma, eyelid erythema, conjunctival hemorrhage (all mild or moderate severity), and low IOP (severe). The adverse events that led to study discontinuation by the four subjects in the bimatoprost group were eczema, dry eye, eye inflammation, and contact dermatitis, all of which were of mild or moderate severity.

Subject 10005-1159 discontinued study medication on day 16 on the advice of her private ophthalmologist due to suspected post-cataract cystoid macular edema (CME).

Subject 10012-1125 reported the adverse event of xerostomia at day 34 of the study. The subject discontinued use of the study treatment but remained in the study for follow-up through month 5/ study exit.

Demographics and Baseline Characteristics (ITT Population) in 192024-032

	Bimatoprost 0.03% N=137	Vehicle N=141	p-value [a]
Age (years)			***0.904***
Mean	49.9	49.7	
SD	11.67	11.27	
Median	50.0	50.0	
Min, Max	22, 77	22, 78	
> 65, N (%)	11 (8.0)	10 (7.1)	
Sex, N (%)			***0.499***
Male	3 (2.2)	5 (3.5)	
Female	134 (97.8)	136 (96.5)	
Race, N (%)			***0.566*** [b]
Caucasian	109 (79.6)	116 (82.3)	
Black	0 (0.0)	1 (0.7)	
Asian	18 (13.1)	16 (11.3)	
Hispanic	6 (4.4)	5 (3.5)	
Other	4 (2.9)	3 (2.1)	
Iris Color, N (%)			***0.677***
Dark [c]	53 (38.7)	58 (41.1)	
Light [c]	84 (61.3)	83 (58.9)	
GEA Score, N (%)			***0.675***
Minimal (1)	29 (21.2)	27 (19.1)	
Moderate (2)	108 (78.8)	114 (80.9)	
Marked (3)	0 (0.0)	0 (0.0)	
Very Marked (4)	0 (0.0)	0 (0.0)	

a For continuous variables, a 1-way ANOVA model was used. For categorical variables, Pearson's chi-square test was used or Fisher's exact test (if ≥ 25% of the expected cell count is < 5).
b P-value for race is for Caucasian vs. non-Caucasian
c Light irides included the colors blue, blue-gray, blue/gray-brown, green, green-brown, hazel, and other, and dark irides included the colors brown, dark brown, and black.

Sixteen African American subjects were screened for enrollment. One subject was randomized to the study in the vehicle group. The applicant indicated that many of these patients failed screening due to an inability to obtain and/or analyze acceptable digital image photographs.

An adequate safety database in men and African Americans has been established for bimatoprost ophthalmic solution 0.03% with Lumigan (bimatoprost ophthalmic solution) 0.03% [NDA 21-275]. However, Non-Caucasians were under-represented in the 192024-032 study (i.e., 79.6% of the treated subjects were Caucasian, 13% Asian, 4.4% Hispanic and 0.0% black). In a correspondence dated December 16, 2008, Allergan, Inc. proposes a postmarketing commitment to address this issue.

Intraocular Pressure Changes

Since Lumigan is approved for the treatment of elevated IOP in patients diagnosed with glaucoma or ocular hypertension, IOP measurements were performed as a part of the overall safety assessment in 192024-032. Whereas statistically significant differences in mean IOP reduction were observed

between the bimatoprost and vehicle treatment groups at weeks 1 through 16, the magnitude of this reduction was small and was often not clinically meaningful, with the mean difference between the groups usually being less than 1 mmHg. The range of individual changes was between -8.5 (decrease of 8.5 mmHg) and 5 (increase of 5 mmHg).

Iris Pigmentation Changes
Iris pigmentation changes have been noted with bimatoprost ophthalmic solution 0.03% administered to the eye for the treatment of elevated intraocular pressure. In the original clinical trials for IOP reduction, two cases of iris pigmentation were noted to occur. Post-marketing adverse event reporting has also included cases of iris pigmentation. In the clinical trials for eyelash growth, no cases have been observed. While the sponsor recorded one case of increased iris pigmentation during the first month of use based on an investigator rating of iris color, subsequent months recorded the iris color as being the same as baseline and the individual patient in question denied a change in iris color. Increases in iris pigmentation remain a possibility in spite of the lower exposure (5-10%) of the eye to the drug product from lid administration than from cornea/conjunctiva administration and therefore it is an important feature of the labeling particularly since any changes would be expected to be permanent. No cases of increased iris pigmentation have been noted to result in any clinical harm beyond the change in appearance.

8. Advisory Committee Meeting

The Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration met on December 5, 2008 at the Hilton Washington/Rockville 1750 Rockville Pike, Rockville, Maryland. Michael X. Repka, M.D., chaired the meeting. After discussion, the committee unanimously agreed that safety and efficacy was demonstrated by the data presented. Committee members also recommended performing Phase 4 studies in pediatric patients with systemic conditions resulting in a loss of eyelashes.

9. Pediatrics

Safety and efficacy of bimatoprost in pediatric patients has not been studied. Based on the mechanism of action of bimatoprost in eyelash growth and the fact that ocular development is generally complete by adolescence, the expected effect on lashes would be similar to that in adults.

On December 16, 2008, Allergan Inc. submitted a pediatric plan which committed to conduct a post-marketing study of Latisse in pediatric subjects consisting of a controlled trial of — with Latisse (bimatoprost ophthalmic solution) 0.03% in — pediatric subjects less than 18 years of age with hypotrichosis — b(4)

Protocol Submission: November 30, 2009
Study Start: June 30, 2010
Final Report Submission: December 31, 2012.

10. Statistical

Per the Statistical Review and Evaluation completed by the Office of Biostatistics on November 7, 2008, there were no major statistical issues identified for this submission. For the submitted pivotal study C-192024-032, bimatoprost ophthalmic solution 0.03% was statistically superior to vehicle in eyelash prominence using the global eyelash assessment (GEA) scale; bimatoprost ophthalmic solution 0.03% was also statistically superior to vehicle in the three secondary efficacy variables: change from baseline in eyelash length, in progressive eyelash thickness/fullness, and in eyelash darkness/intensity.

11. Scientific Investigations Audit

A Division of Scientific Investigations (DSI) audit was requested. The sites requested for inspection are the domestic centers that were among the highest enrollers in the study 192024-032. Three clinical investigator inspections were completed for this NDA. Based on the results of these inspections, the study appears to have been conducted adequately and the data in support of the NDA appear reliable. No regulatory violations were noted for Dr. Werschler or Dr. Smith. Although regulatory violations were noted and Form FDA 483 was issued to Dr. Yoelin, the nature of the violations makes it unlikely that they significantly affect overall reliability of safety and efficacy data from this site. Based on the provided Establishment Inspection Report (EIR) for this site and Dr. Yoelin's written response to the Form FDA 483 observations, dated November 7, 2008, data derived from Dr. Yoelin's site were considered acceptable.

Allergan, Inc. has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There is no evidence to suggest that the results of the study were impacted by any financial payments.

A consult was requested from the Office of Surveillance and Epidemiology regarding a trade name review for the proposed name "Latisse." The results of the Proprietary Name Risk Assessment found that the proposed name, Latisse, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Latisse, for this product.

12. Drug Marketing, Advertising and Communications

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed Allergan's proposed product labeling (PI) for this application submitted to the Agency on 26 June 2008.

13. Labeling

After discussions with the Division of Anti-Infective and Ophthalmology Products, revised labeling for NDA 22-369, Latisse (bimatoprost ophthalmic solution) for the treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness was submitted by Allergan, Inc. on 18 December 2008 and found to be acceptable by the review team.

14. Recommendations/Risk Benefit Assessment

The labeling submitted by Allergan, Inc. on 18 December 2008 and found in this Cross-Discipline Team Leader Review (see Appendix 1) is acceptable for approval.

The proposed postmarketing studies/clinical trials listed below are acceptable.

In a December 16, 2008, submission, Allergan, Inc. commits to:

- A four month randomized, controlled comparative study of Latisse (bimatoprost ophthalmic solution) 0.03% versus vehicle in at least 50 African American subjects — b(4)

  Protocol Submission: September 30, 2009
  Study Start: May 31, 2010
  Final Report Submission: December 31, 2011

- A controlled trial of at least — with Latisse (bimatoprost ophthalmic solution) 0.03% ir — pediatric subjects less than 18 years of age with hypotrichosis b(4)

  Protocol Submission: November 30, 2009
  Study Start: June 30, 2010
  Final Report Submission: December 31, 2012.

RISK BENEFIT ASSESSMENT:
Findings from Study 192024-032 together with clinical studies submitted in NDA 21-275 and the postmarketing information from NDA 21-275 provide adequate evidence of safety and efficacy for bimatoprost ophthalmic solution in the QD dosing regimen for the treatment of hypotrichosis of the eyelashes. Overall findings from these studies include analysis of 'the percentage of subjects with at least a 1-grade increase from baseline on the Global Eyelash Assessment scale'. This endpoint was found to be clinically relevant and statistically significant in Study 192024-032. Study 192024-032 also showed significance in three key secondary endpoints which measured the overall change from baseline by week 16 after QD dosing in three different measures: eyelash length, progressive eyelash thickness/fullness, and eyelash darkness/intensity. These endpoints were considered clinically relevant and statistically significant. Based on the FDA recommended primary and secondary analysis results and other considerations, there was adequate overall evidence presented for the QD regimen as an effective treatment in subjects with hypotrichosis of the eyelashes.

The same studies and postmarketing information in the application supports the safety of Latisse (bimatoprost ophthalmic solution) 0.03% for the treatment of hypotrichosis of the eyelashes. The

safety of bimatoprost ophthalmic solution 0.03% for the treatment of elevated intraocular pressure was demonstrated in NDA 21-275 Lumigan (bimatoprost ophthalmic solution) 0.03% and the dose administered is considered to exceed the dose that will be administered with Latisse. Overall, Latisse (bimatoprost ophthalmic solution) 0.03% was well tolerated in Study 192024-032. Adverse reactions most frequently associated with bimatoprost ophthalmic solution include eye pruritus, conjunctival hyperemia, skin hyperpigmentation, eye irritation, dry eye and erythema of the eyelid. These are consistent with the reactions noted to occur with the use of Lumigan and Latisse.

The total dose of bimatoprost delivered with topical application to the upper eyelid margins for the enhancement of eyelash growth is much lower than the dose of bimatoprost for the treatment of elevated IOP. The clinical studies and marketing history of NDA 21-275 support this application by providing an example of relatively safe use following an exacerbation of the clinical exposure expected with topical skin application with the potential for bimatoprost-related effects on intraocular pressure, iris and eyelid pigmentation, and hair growth outside the treatment area being adequately described in the proposed prescribing information.

Clinical, CMC, Pharmacology/Toxicology, Product Quality Microbiology, Statistics, and Clinical Pharmacology have recommended approval for this application. In summary, the potential benefits are believed to outweigh the potential risks associated with the use of Latisse for the proposed indication with the proposed labeling.

15. Regulatory Action

NDA 22-369 is considered adequate for approval for the treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness.

The new drug application, NDA 22-369 as amended, Latisse (bimatoprost ophthalmic solution) should be approved to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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/s/

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12/24/2008 12:28:09 PM
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