CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-184

SUMMARY REVIEW

Division Director Review of NDA 22-184

Date	July 13, 2010
From	Wiley A. Chambers, M.D.
NDA#	22-184
Applicant	Allergan
Date of Submission	July 2, 2007
Name	Lumigan (bimatoprost ophthalmic solution) 0.01%
Dosage forms / Strength	ophthalmic solution, 0.01%
Proposed Indication(s)	reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension
Action:	Approval

1. Introduction

Bimatoprost 0.01% was developed from: the marketed product Lumigan (bimatoprost ophthalmic solution) 0.03%, 50 ppm benzalkonium chloride (BAK) with modifications to the levels of both the active substance, bimatoprost, and the preservative, BAK (and decreased sodium chloride for isotonicity). Lumigan (bimatoprost ophthalmic solution) 0.03% has been approved in the United States (US) since March 2001. Bimatoprost ophthalmic solution is a member of the class of prostaglandin analogs.

A clinical development program was conducted by Allergan to evaluate the efficacy and safety of 0.01% bimatoprost/200 ppm BAK Ophthalmic Solution for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension (OHT).

The application demonstrated that bimatoprost 0.01% lowered IOP by a clinically meaningful amount of approximately 5-7 mmHg. The drug product was not equivalent to Lumigan 0.03% in IOP-lowering efficacy as measured by mean IOP. The difference in mean IOP between bimatoprost 0.01% and Lumigan 0.03% was within 1.5 mmHg at all post-baseline timepoints; however, the majority of timepoints were not within 1 mmHg as stipulated in the Division's definition for establishing equivalency.[1]

The types of adverse events seen were consistent with the known adverse event profile of Lumigan 0.03%. However, there were numerically less ocular adverse events reported in the bimatoprost 0.01% (48% vs. 62%) and 0.0125% (49% vs. 62%) arms compared to the Lumigan 0.03% arm.

[1] For equivalence trials, equivalence is attained if the difference in mean IOP between treatment groups is within ±1.5 mmHg at all post-baseline timepoints; and within ±1 mmHg at the majority of post-baseline timepoints. This requirement for equivalence has been consistently used for the approval of several IOP lowering products for approximately twenty years. Products do not necessarily have to be equivalent to another product to be efficacious.

Based on the reported adverse events following approximately 10 years of marketing of Lumigan 0.03% and the IOP lowering effect of both bimatoprost 0.01% and 0.0125% in the clinical trial conducted by Allergan, the risk/benefit profile for both products is favorable. Since it is favorable to expose patients to the lowest effective dose, bimatoprost 0.01% was recommended for approval by the reviewing Medical Officer.

NDA 22-184 has been recommended for approval for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension by the review team. The labeling for the bimatoprost 0.01% should indicate that it is not equivalent to Lumigan 0.03% in its ability to lower intraocular pressure. A combined package insert for both products, Lumigan 0.01% and Lumigan 0.03%, is recommended.

2. Background

Allergan presented a development program to create a new formulation of bimatoprost that would maintain the IOP-lowering efficacy achieved with Lumigan 0.03% and improve the overall safety profile and, in particular, ocular surface tolerability.

Bimatoprost is a synthetic prostaglandin analog which increases aqueous humor outflow. There are currently four products within this class of drugs approved for the reduction of IOP. They include bimatoprost ophthalmic solution 0.03%, travoprost ophthalmic solution 0.004%, latanoprost ophthalmic solution 0.005% and unoprostone isopropyl ophthalmic solution 0.15%.

Safety issues labeled in the ophthalmic prostaglandin analogs include skin and iris pigmentation, eyelash growth, ocular inflammation and cystoid macular edema.

Once-daily dosing was considered the correct dosing frequency for the new formulation of bimatoprost. The once-daily regimen was supported by studies conducted by Allergan with bimatoprost 0.03%, which demonstrated that bimatoprost 0.03% administered once-daily in the evening was more effective than once-daily dosing in the morning and was more effective than twice-daily dosing in lowering IOP. In addition, an evening dose is recommended to achieve greatest IOP-lowering at the times when IOP is at highest in most patients.

At an End-of-Phase 2 meeting with the Division of Anti-Infective and Ophthalmology Products (August 19, 2005), it was agreed that Allergan could file an NDA for a lower strength bimatoprost ophthalmic solution based on a single additional Phase 3 clinical study. Study 192024-031 was designed to show equivalence of either investigational formulation of bimatoprost (0.01% or 0.0125% with 200 ppm BAK) to Lumigan (bimatoprost ophthalmic solution) 0.03%.

The primary efficacy endpoint for the US FDA review as stated in the protocol was mean IOP measured at all timepoints. The primary between-group comparisons were of bimatoprost 0.01% versus Lumigan 0.03% and bimatoprost 0.0125% versus Lumigan 0.03%.

3. CMC

DRUG SUBSTANCE:

Bimatoprost is a synthetic prostaglandin analog with ocular hypotensive activity. Bimatoprost drug substance to be used in the proposed formulation (0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution) is the same drug substance submitted and approved via the original NDA 21-275 for Lumigan (bimatoprost ophthalmic solution, 0.03%). For the chemistry, manufacturing, and controls (CMC) information for the bimatoprost drug substance, reference is made to NDA 21-275.

DRUG PRODUCT:

The 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution was developed from the Lumigan 0.03% product platform with modifications to the levels of the drug substance, bimatoprost, the preservative, benzalkonium chloride, and the tonicity agent, sodium chloride. No new ingredients have been added.

As with Lumigan 0.03%, the proposed drug product is a clear, colorless, isotonic, sterile solution containing 0.01% (w/v) bimatoprost as the active ingredient and 0.02% (w/v) benzalkonium chloride as the preservative. The inactive ingredients include sodium chloride, dibasic sodium phosphate (b) (4), citric acid (b) (4), and purified water. The solution pH is adjusted to (b) (4) using either (b) (4) sodium hydroxide or (b) (4) hydrochloric acid. Except for the drug substance, all ingredients are USP/Ph Eur, NF/Ph Eur or USP compendial grade materials.

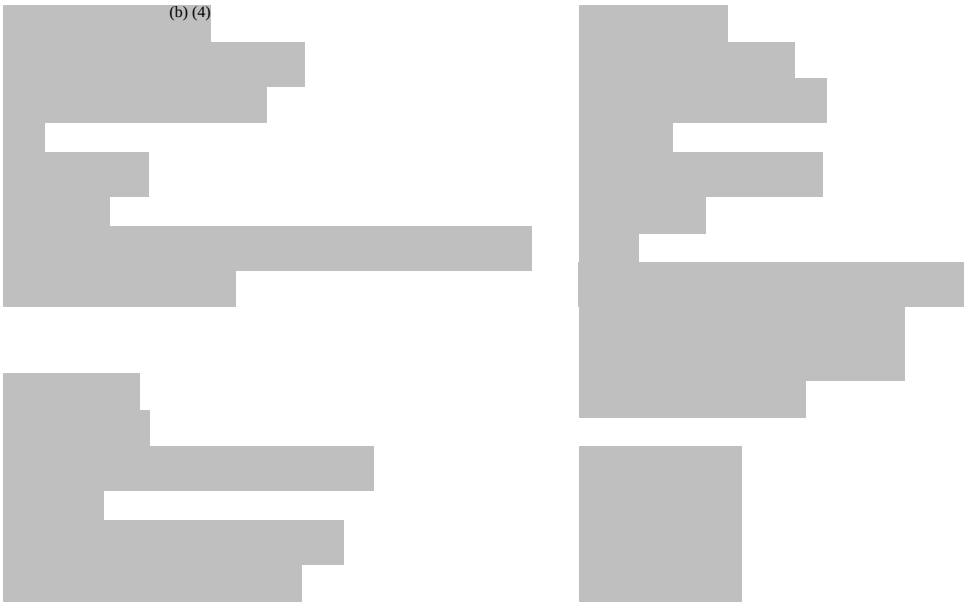
As stated above, all ingredients are identical to those used in the Lumigan 0.03% formulation. The currently proposed formulation of bimatoprost is essentially equivalent to Lumigan 0.03% except for the following small composition differences for the currently proposed drug product versus Lumigan 0.03%: a lower bimatoprost concentration (0.01% versus 0.03%), increased BAK (200 ppm versus 50 ppm), and decreased sodium chloride for isotonicity (0.81% versus 0.83%).

DRUG PRODUCT COMPOSITION:

Bimatoprost	0.1 mg/mL
Benzalkonium Chloride*	0.2 mg/mL
Dibasic sodium phosphate (b) (4)	(b) (4)
Citric Acid (b) (4)	(b) (4)
Sodium Chloride	(b) (4)
Hydrochloric Acid/Sodium hydroxide	(b) (4)
Purified water (b) (4)	

REGULATORY SPECIFICATIONS:

Bimatoprost	(b) (4)



All facilities inspections have been completed and the Office of Compliance and New Drug Quality have determined these facilities are acceptable.

4. Nonclinical Pharmacology/Toxicology

Systemic and ocular toxicology studies were conducted by Allergan and submitted in NDA 21-275 for the original Lumigan 0.03% formulation. Additional ocular toxicity studies with higher concentrations of BAK and lower concentrations of bimatoprost were performed to support the current NDA. Formulations containing 200 ppm BAK (including vehicle) administered twice daily for one month to New Zealand White rabbits were associated with minimal to moderate ocular findings including conjunctival congestion, epithelial degeneration/regeneration, and corneal stromal edema. Single daily doses of 0.01% bimatoprost containing 200 ppm BAK (as in the formulation proposed for marketing) were not associated with any gross or microscopic ocular changes in Dutch-Belted rabbits when administered daily for 6 months.

In monkeys and humans, chronic treatment with bimatoprost is associated with increased pigmentation of the iris and periocular tissues. Increased thickness and pigmentation of eyelashes has also been observed in these species.

Cynomolgus monkeys were topically treated with 0.03% and 0.1% bimatoprost ophthalmic solution once or 2 times a day for 1 year to determine the ocular and systemic toxicity of the drug. Clinical observations and ocular examinations showed increased iridal pigmentation and periocular changes characterized by a prominent upper and/or lower sulcus and/or widening of the palpebral fissure in the treated eyes. No functional or anatomic ocular abnormalities were noted. The periocular findings were completely reversed by-the end of the recovery period, while the increased iridal pigmentation was not reversible. These findings from studies conducted by Allergan were also observed in monkeys with other PG analogues (including latanoprost) and were considered to be related to this pharmacological class. No systemic toxicity was observed at any dose.

Findings in mice (elevated RBC parameters, thymic lymphoid proliferation, increased vaginal acute inflammatory cells) and rats (testicular degeneration, adrenal cortical vacuolation, increased AST/ALT) after repeated oral dosing from 28 days-13 weeks are were not observed at clinically relevant doses (rodent blood AUCs $\geq$ 150-fold higher than that achieved following recommended clinical ocular doses). Ovarian findings (increased ovarian weight, prominently vacuolated corpora lutea) observed in rats beginning at doses about 30-fold higher than those achieved after ocular dosing in humans were not seen in other species including mice, monkeys, rabbits, and dogs. Bimatoprost is believed to have a species-specific effect on the luteal cycle in rats, delaying luteal regression. In naïve rats, PG $F_{2\alpha}$ (in concert with other endogenous compounds) is involved in luteal cycling.

CARCINOGENICITY:
Oral rodent carcinogenicity studies were conducted by Allergan to support NDA 21-275. There was no evidence of tumorigenic potential in mice and rats given bimatoprost by daily oral gavage for 2 years at doses up to 2 mg/kg/day and 1 mg/kg/day, respectively. These doses are 192 and 291 times higher than human exposure based on AUC levels in blood.

REPRODUCTIVE TOXICOLOGY:
A complete battery of reproductive and developmental toxicity studies was conducted by Allergan to support NDA 21-275. Lumigan 0.03% has been assigned Pregnancy Category C. Bimatoprost did not impair the fertility of male or female rats given at doses up to 0.6 mg/kg/day (about 100 times human exposure based on blood AUC after Lumigan 0.03% administration). Bimatoprost induced late abortions and early delivery following oral administration to mice and rats at 0.3 or 0.6 mg/kg (systemic exposures approximately 30 and100 times greater than those observed in humans using ocular bimatoprost). In rodents, prostaglandins and their analogues are known to induce abortion mediated by their ovarian luteolytic effects; this mechanism is not relevant to humans. In humans, prostaglandins can cause the uterus to contract, but bimatoprost does not cause contraction of human uterine muscle. In a peri/post-natal study in rats, bimatoprost doses of 0.3 mg/kg (approximately 40-fold greater than those observed in humans after Lumigan 0.03% administration) were associated with reduced gestation length, late resorptions, fetal death, and postnatal mortality. The offspring of these bimatoprost-treated dams had lower preweaning body weights and had reproductive impairments. F1 animals reared to maturity had reduced mating performance compared to controls and pregnant females had reduced body weight gains.

Due to species specificity and the much greater systemic exposure of the mice and rats in toxicity studies compared to humans treated with ocular bimatoprost, the reproductive toxicity of bimatoprost in rodents is unlikely to be clinically relevant.

5. Clinical Pharmacology/Biopharmaceutics

The pharmacokinetics of bimatoprost in humans following the administration of Lumigan 0.03% has been characterized in four PK studies and by sparse PK sampling of patients with glaucoma or ocular hypertension in two Phase 3 studies conducted by Allergan. The data from these studies were previously submitted with NDA 21-275 (see Clinical Pharmacology review dated 18 September 2000). No additional clinical pharmacology studies have been conducted

with the proposed 0.01% formulation. Allergan requested a waiver of the in vivo bioavailability requirement for bimatoprost ophthalmic solution, 0.01%, as set forth in 21 CFR 320.22. As the concentration of bimatoprost has been reduced from 0.03% to 0.01% in the new formulation, it is believed that the systemic exposure of bimatoprost will not exceed that observed following the administration of Lumigan 0.03%. The systemic exposure of bimatoprost was below the lower limit of quantitation (0.025 ng/mL) within 1 to 1.5 hours post-dose following 14 days of Lumigan 0.03% administration (1 drop once daily to both eyes). Mean C_{max} and AUC_{0-t} values on Day 14 were 0.082 ng/mL and 0.096 ng•h/mL, respectively. Bimatoprost blood concentrations in patients with glaucoma or ocular hypertension were similar to those observed in healthy subjects, with no systemic accumulation observed over time.

Allergan's request for a waiver of the requirement for submission of evidence of in vivo bioavailability was granted based on the expected low systemic exposure of bimatoprost following ophthalmic administration of bimatoprost ophthalmic solution, 0.01%.

6. Sterility Assurance

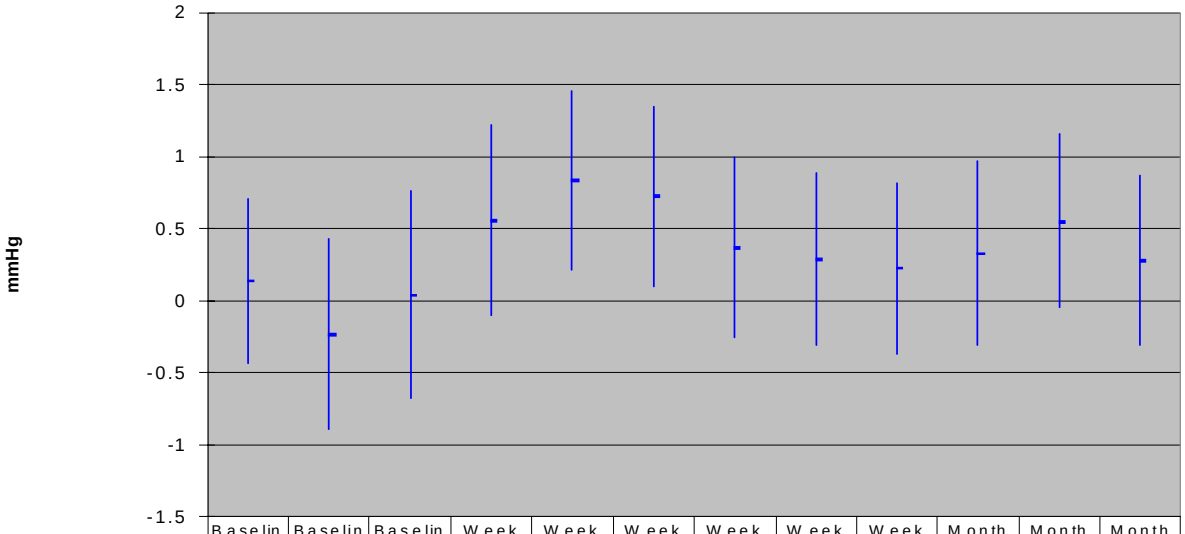
The Product Quality Microbiology Reviewer recommends approval of the application.

7. Clinical/Statistical - Efficacy

The applicant submitted results from 3 clinical trials: two dose ranging trials, which were supportive, and one twelve month study with a three month analysis for efficacy.

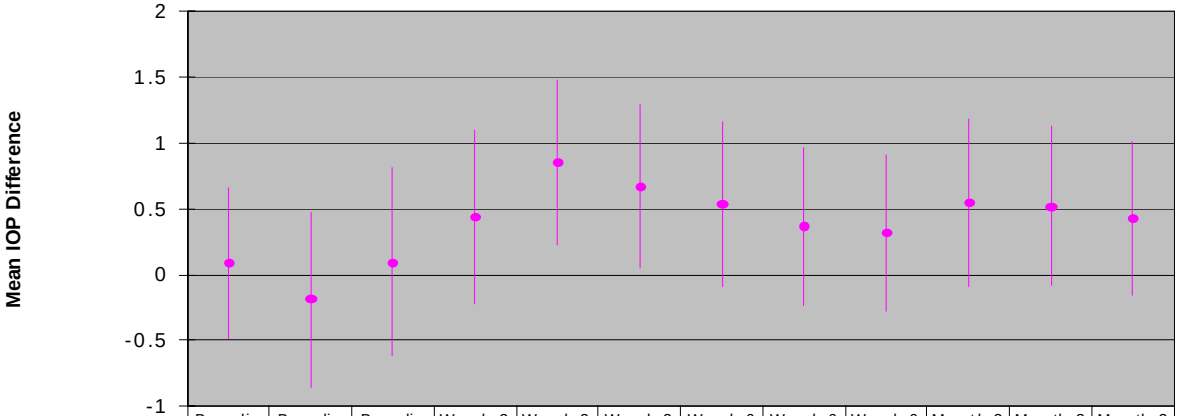
Study 192024-020	N=188	Bimatoprost 0.01% BID, 0.015% BID, 0.02% QD, 0.025% QD compared to Lumigan (all with 50 ppm BAK) and Timolol 0.5%. One month, double-masked, parallel-group.
Study 192024-030	N=249	Bimatoprost 0.01% QD, 0.015% QD, 0.015% QD/EDTA, 0.02% QD (all with 200 BAK) compared to Lumigan (with 50 ppm BAK). Five day, double-masked, paired eye.
Study 192024-031	N=561	Bimatoprost 0.01% QD, 0.0125% QD (with 200 ppm BAK) compared to Lumigan (with 50 ppm BAK). Twelve month study with 3 month efficacy analysis. Double-masked, parallel group, once daily dosing in the evening, designed to show equivalence of either investigational formulation of bimatoprost (0.01% or 0.0125% with 200 ppm BAK) to Lumigan 0.03%.

Mean IOP Difference Bimatoprost 0.01% - Lumigan (ITT LOCF- 95% Confidence Interval) - Study 192024-031



	Baseline (hr 0)	Baseline (hr 4)	Baseline (hr 8)	Week 2 (hr 0)	Week 2 (hr 4)	Week 2 (hr 8)	Week 6 (hr 0)	Week 6 (hr 4)	Week 6 (hr 8)	Month 3 (hr 0)	Month 3 (hr 4)	Month 3 (hr 8)
Lower CI	-0.43	-0.89	-0.68	-0.1	0.21	0.1	-0.25	-0.31	-0.37	-0.31	-0.05	-0.31
Upper CI	0.71	0.43	0.76	1.22	1.46	1.35	1	0.89	0.82	0.97	1.16	0.87
Mean Difference	0.14	-0.23	0.04	0.56	0.84	0.73	0.37	0.29	0.23	0.33	0.55	0.28

Mean IOP Difference Bimatoprost 0.0125% - Lumigan (ITT LOCF- 95% Confidence Interval) - Study 192024-031



	Baseline (hr 0)	Baseline (hr 4)	Baseline (hr 8)	Week 2 (hr 0)	Week 2 (hr 4)	Week 2 (hr 8)	Week 6 (hr 0)	Week 6 (hr 4)	Week 6 (hr 8)	Month 3 (hr 0)	Month 3 (hr 4)	Month 3 (hr 8)
Lower CI	-0.48	-0.85	-0.62	-0.22	0.23	0.05	-0.09	-0.23	-0.28	-0.09	-0.08	-0.16
Upper CI	0.66	0.48	0.81	1.1	1.48	1.29	1.16	0.97	0.91	1.18	1.13	1.01
Mean Difference	0.09	-0.18	0.09	0.44	0.86	0.67	0.54	0.37	0.32	0.55	0.52	0.43

Mean Intraocular Pressure (mm Hg) (ITT with LOCF)

Visit	Timepoint		Mean Intraocular Pressure (mm Hg)	
			Bim 0.01% / LUMIGAN® N = 185/187	**Bim 0.0125% / LUMIGAN® N = 186/187**
Week 2	Hour 0	Difference[a] (95% CI[b])	17.8 / 17.3 0.56 (-0.10 to 1.22)	17.7 / 17.3 0.44 (-0.22 to 1.10)
	Hour 4	Difference[a] (95% CI[b])	17.1 / 16.3 0.84 (0.21 to 1.46)	17.1/ 16.3 0.86 (0.23 to 1.48)
	Hour 8	Difference[a] (95% CI[b])	16.9 / 16.2 0.73 (0.10 to 1.35)	16.9 / 16.2 0.67 (0.05 to 1.29)
Week 6	Hour 0	Difference[a] (95% CI[b])	17.6 / 17.2 0.37 (-0.25 to 1.00)	17.8 / 17.2 0.54 (-0.09 to 1.16)
	Hour 4	Difference[a] (95% CI[b])	16.8 / 16.5 0.29 (-0.31 to 0.89)	16.8 / 16.5 0.37 (-0.23 to 0.97)
	Hour 8	Difference[a] (95% CI[b])	16.7 / 16.4 0.23 (-0.37 to 0.82)	16.8 / 16.4 0.32 (-0.28 to 0.91)
Month 3	Hour 0	Difference[a] (95% CI[b])	17.3 / 17.0 0.33 (-0.31 to 0.97)	17.6 / 17.0 0.55 (-0.09 to 1.18)
	Hour 4	Difference[a] (95% CI[b])	16.7 / 16.1 0.55 (-0.05 to 1.16)	16.6 / 16.1 0.52 (-0.08 to 1.13)
	Hour 8	Difference[a] (95% CI[b])	16.4 / 16.2 0.28 (-0.31 to 0.87)	16.6 / 16.2 0.43 (-0.16 to 1.01)

[a] Calculated as test formulation minus LUMIGAN®; a negative value favored the test formulation.
[b] 95% confidence interval for between-treatment difference based on the one-way ANOVA model with fixed effect of treatment.
Data source: Sponsor's CSR Table 11.4-4.

For the comparison between bimatoprost 0.01% and Lumigan 0.03%, at all the time points, the 2-sided 95% CI for the group difference was within 1.5 mm Hg. At 5/9 time points (Hours 0, 4 and 8 at Week 2 Visit, and Hour 0 at Week 6 Visit, and Hour 4 at Month 3 Visit), the upper limit of the 2-sided 95% CI for the group difference was at or above 1.0 mm Hg. For the comparison between bimatoprost 0.0125% and Lumigan 0.03%, at all the time points, the 2-sided 95% CI for the group difference was within 1.5 mm Hg. At 7/9 time points (Hours 0, 4, and 8 at Week 2 Visit, Hour 0 at Week 6 Visit, Hours 0, 4, and 8 at Month 3 Visit), the upper limit of the 2-sided 95% CI for the group difference was above 1.0 mm Hg.

In the clinical studies of patients with IOP of 26 or above, the mean IOP reduction in patients treated with Lumigan 0.03% was 7-8 mmHg. The natural history of elevated IOP would suggest that IOP either stays the same or increases over the course of a study. Rounding errors may account for changes of 1-2 mmHg. Based on this information, products may be considered to be superior to vehicle (no treatment) if the 95% confidence interval of the difference in IOP is less than 5 mmHg. The maximum confidence interval demonstrated in this trial was 1.46 representing clear superiority to no treatment.

The Ophthalmology group uses a relatively strict definition for clinical equivalence. The definition of equivalence in IOP reduction is that the difference must be within a 95% confidence interval of 1.5 mmHg for all timepoints and with a 95% confidence interval of 1 mmHg for the majority of timepoints. This definition for the largest clinically acceptable difference between test drug and control is a matter of clinical judgment. Lumigan 0.01% is effective in reducing IOP but does not meet the 1 mmHg confidence interval upper bound for the majority of timepoints and is therefore not equivalent in its IOP reduction. Lumigan 0.01% appears to lower IOP slightly less effectively (0.5 mmHg) than does Lumigan 0.03%. Lumigan 0.01% is effective in lowering IOP because it lowers IOP 5 - 7 mmHg from baseline. Some physicians may choose to prescribe Lumigan 0.01% taking into account its IOP lowering potential and its safety profile.

8. Safety

Overall, bimatoprost 0.01% and 0.0125% were safe and well tolerated. The types of adverse events seen were consistent with the known adverse event profile of Lumigan 0.03%. There were less ocular adverse events reported in the bimatoprost 0.01% (47.6% vs. 62%) and 0.0125% (48.9% vs. 62%) arms compared to the Lumigan 0.03% arm. However, in the absence of a second trial that replicates these results, claims of superiority cannot be included in the labeling.

Approximately three times as many subjects discontinued the study due to ocular adverse events in the Lumigan 0.03% group compared to bimatoprost 0.01% (6% vs. 2%) and approximately twice as many compared to bimatoprost 0.0125% (6% vs. 3%). However, more subjects discontinued the study due to non-ocular adverse events in the bimatoprost 0.01% arm compared to the Lumigan 0.03% (3% vs. 2%) and bimatoprost 0.0125% (3% vs. 1%) arms.

Approximately twice as many subjects in the Lumigan group discontinued due to ocular irritation symptoms (i.e. hyperemia, pruritus, irritation) compared to either the bimatoprost 0.01% group or the bimatoprost 0.0125% group. The safety data also suggests that the number of subjects with mild/moderate/severe hyperemia in the Lumigan group is numerically higher for all timepoints in the study compared to bimatoprost 0.01% and for the majority of timepoints compared to bimatoprost 0.0125%. Also, the number of subjects that worsened by at least one severity grade in ocular hyperemia was numerically higher in the Lumigan group compared to bimatoprost 0.01% and 0.0125% for the majority of timepoints.

The following tables are from the Medical Officer's review, Section 7.3.3

Overall Profile of Dropouts - Study 192024-031

	0.01% bimatoprost	0.0125% bimatoprost	Lumigan 0.03%
Enrolled	186	188	187
Completed	171 (92%)	171 (91%)	162 (87%)
Discontinued	15 (8%)	17 (9%)	25 (13%)
Adverse Event	8 (4%)	8 (4%)	14 (7%)
Ocular	4 (2%)	6 (3%)	12 (6%)
Non-Ocular	5 (3%)	2 (1%)	3 (2%)
Lost to Follow Up	2 (1%)	5 (3%)	4 (2%)
Personal Reasons	1 (0.5%)	1 (0.5%)	1 (0.5%)
Protocol Violation	0	1 (0.5%)	3 (2%)
Other	4 (2%)	2 (1%)	3 (2%)

Overall Profile of Adverse Events

	Bimatoprost 0.01% N=185	Bimatoprost 0.0125% N=188	Lumigan 0.03% N=187
Adverse events	121(65%)	125 (66%)	145 (77%)
Ocular	88 (48%)	92 (49%)	116 (62%)
Non-ocular	80 (43%)	69 (37%)	77 (41%)
SAEs	17 (9%)	11 (6%)	14 (7%)
Discontinuation due to AEs	8 (4%)	8 (4%)	14 (7%)
Deaths	1 (0.5%)	2 (1%)	0

9. Advisory Committee Meeting

The application was not the subject of an Advisory Committee meeting. No new issues of safety or efficacy have been raised by this application.

10. Pediatrics

Allergan has requested a full waiver for pediatric studies for all pediatric age groups (neonates, infants, children, and adolescents) from birth to 16 years of age. I agree that a full waiver is appropriate.

The principal unanswered questions with respect to bimatoprost in pediatric patients relate to the lifetime safety, i.e. skin and iris pigmentation and eyelash growth. While ten year safety data is already known and considered sufficient for the elderly population in which elevated intraocular pressure is more commonly seen, it is not sufficient for a pediatric population. A long term study in pediatric patients would require at least 20 years of follow-up.

11. History of First Line vs Second Line Indication

Lumigan is being labeled for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. This is considered a first line indication for elevated intraocular pressure and is consistent with the indication originally included on all but five single ingredient ophthalmic drug products for use in patients with ocular hypertension

approved since 1987. The five exceptions are the prostaglandin analogs, namely Xalatan (latanoprost ophthalmic solution), Lumigan (bimatoprost ophthalmic solution) 0.03%, Travatan (travoprost ophthalmic solution), Travatan Z (travoprost ophthalmic solution), and Rescula (unoprostone isopropyl ophthalmic solution). These five products were exceptions because of an adverse event (increased iris pigmentation) initially noted during the development of Xalatan. As part of the development of Xalatan, *in vivo* and *in vitro* work by Pharmacia (the NDA applicant for Xalatan) and submitted as part of the Xalatan application led to the review team concluding that increased iris pigmentation was a pharmacologic response to prostaglandin analogs being placed in the eye. The potential long term consequences of increased iris pigmentation were unknown at the time. From a theoretical prospective, there was the possibility that the cells involved in developing increased pigmentation would eventually act as a neoplastic cells, get too big to survive and/or release pigment that could lead to a type of pigmentary glaucoma.

With the completion of the review of Xalatan in 1996, the Agency concluded that increased iris pigmentation was a class effect of prostaglandin analogs. Xalatan was labeled as a second line product with the understanding that more information was needed to understand the consequences of long term increases in iris pigmentation. Pharmacia agreed to continue studies to investigate the long term consequences of increased iris pigmentation. At the time of the Xalatan approval, it was unclear how long the studies would need to be continued. The Agency initially asked that the studies continue until the iris pigmentation stopped increasing. The Agency also asked all sponsors of prostaglandin analog ophthalmic product INDs to include iris color monitoring in their clinical studies.

With the submission of the Lumigan 0.03% NDA in 2000, there were only two cases of increased iris pigmentation in the Lumigan 0.03% clinical trials. This incidence of iris pigmentation was lower than other prostaglandin analogs reviewed up until that time. The clinical monitoring, application review and labeling of Lumigan 0.03%, was predicated on the knowledge that the increased iris pigmentation was a class effect and that Lumigan was a member of that class. Absent the information about increased iris pigmentation in prostaglandin analogs, there would have been no reason to include the iris monitoring in the Lumigan clinical trials and there were not enough clinical cases of increased iris pigmentation to cause a concern which would have lead to a second line indication.

In 2001, using 21 CFR 201.57(g) of the regulations (now 21 CFR 201.80(g)) and treating increased iris pigmentation as a prostaglandin analog class effect, the adverse events associated with the class of prostaglandin analogs were carried over to the labeling of Lumigan 0.03% at the time of approval. The labeling of Lumigan 0.03% included the second line indication to be consistent with all other prostaglandin analog products. Each of the companies marketing prostaglandin analogs was asked to perform additional follow-up on cases of increased iris pigmentation as a Phase 4 commitment. These companies were also asked to investigate whether patients with increased iris pigmentation had an increase in pigment deposition in the trabecular meshwork.

In 2002, the Agency approved a Xalatan sNDA to change the indication for Xalatan to first line therapy. The sponsor of Xalatan submitted data supporting the conclusion that an

increased risk for ocular melanoma or pigmentary glaucoma associated with prostaglandin analog exposure was unlikely in the population for which the prostaglandin analogs are indicated. Based on the submission of new clinical data necessary for approval, the sponsor of Xalatan was granted 3 years of market exclusivity at the time of approval of this sNDA.

In 2006, following the end of the exclusivity period, the Agency approved a Lumigan 0.03% sNDA to change the indication to first line therapy. This sNDA was submitted as a 505(b)(2) application referencing the findings of safety for Xalatan. The Agency relied in part upon the conclusions of safety for the intended prescription population for Xalatan and product specific literature for Xalatan to support the change in indication for Lumigan 0.03%. Data submitted by Allergan scientifically justified this partial reliance. These data included a primate iris histology study of animals exposed to bimatoprost which, similar to studies with Xalatan, showed no proliferation of melanocytes associated with iris pigmentation change. In addition, Allergan had completed the post-marketing studies requested by the Agency. The first study included following patients treated with Lumigan 0.03% for up to 5 years. The second study included an evaluation of the trabecular meshwork of patients who had increased iris pigmentation. No complications as a consequence of increased iris pigmentation were reported in these studies. Lumigan 0.03% had been labeled with a second line indication for consistency with the Agency's original conclusions about prostaglandin analogs including Xalatan. It therefore seemed reasonable from a scientific perspective to continue to use the Agency's conclusions about prostaglandin analogs including Xalatan after the agency better understood the longer term consequences of increased iris pigmenation. However, since the Agency's new understandings were based in part on findings of safety related to Xalatan, the Agency did not rely on those new findings during the exclusivity period granted to Pfizer for conducting the studies. Following the end of the exclusivity period, the Agency relied upon these findings of safety, published scientific literature, and data submitted by Allergan to support the change in indication for Lumigan 0.03%.

Pfizer has argued in a citizen's petition submitted to the Agency, that the use of the Agency's findings was not correct and that Agency's conclusions concerning increased iris pigmentation, based in part on the Agency's findings related Xalatan, were not applicable to other prostaglandin analogs. Were the Lumigan 0.03% sNDA to be submitted in 2010, reliance in part upon the findings of safety for Xalatan and product specific literature for Xalatan to support the change in indication to first line therapy would no longer be necessary. Lumigan 0.03% is now in its tenth year of marketing. During that time there have been approximately (b) (4) distributed worldwide each year (except first year when there were approximately (b) (4)). Based on patients using approximately (b) (4) treated per year over each of the last eight years. There have been no reports of pigmented irides releasing pigment to cause pigmentary glaucoma and only two reports of ocular melanomas. Neither of which is believe to be related to Lumigan use. While it is not always possible to use postmarketing reports or lack thereof to support the safety of an application, it is appropriate to rely in part on the postmarketing reports in this case to reassure ourselves that the hypothesized concerns that led to the initial limitation to second line therapy were not seen with sufficient frequency to justify this continued limitation. Further, patients treated for glaucoma or ocular hypertension are regularly followed by ophthalmologists using the magnification provided by biomicroscopes.

Intraocular pressure is measured at these follow-up visits. This type of exam would be expected to detect cases of pigmentary glaucoma or neoplasia. The two cases of ocular melanomas occurred in patients over the age of 50. Considering the natural incidence of ocular melanoma in individuals over the age of 50 is 20 per million per year, it is unlikely that these cases are necessarily related to Lumigan. This absence of significant safety problems related to increased iris pigmentation after better than 4 million patient years in patients routinely followed with biomicroscopes, together with the clinical trials conducted and submitted by Allergan in support of Lumigan 0.03%, would be sufficient in 2010 to support a first line indication without reference to any other information.

The Lumigan 0.01% clinical trials did not have any reported cases of increased iris pigmentation. A first line indication for Lumigan 0.01% is supported by the absence of any cases of increased iris pigmentation in Lumigan 0.01%, the post-marketing and other studies conducted by Allergan, and the nine year marketing history of Lumigan 0.03% as noted above. The revised labeling for Lumigan does not rely on the Agency findings regarding the safety of Xalatan or literature.

12. Lumigan 0.03% Postmarketing Studies

Study #1
Commitment Date: 01 March 2001
Commitment: Allergan committed to conduct a post-marketing study or continue current studies to evaluate increased iris pigmentation and the potential for changes in eyelash length and density over time.
Study/Commitment Status: Submitted/Reviewed
Explanation of the Study Status: Allergan conducted clinical study 192024-014 titled, "A multicenter, double-masked, randomized, parallel, six-month extension study of protocols 192024-008 and 192024-009 evaluating the safety and efficacy of AGN 192024 0.03% ophthalmic solution QD or BID, compared with timolol 0.5% ophthalmic solution BID, in patients with glaucoma or ocular hypertension." The study protocol was submitted to IND 48,929 in Serial No. 067 on 24 July 2001. The 24-month and 36-month study reports were submitted in S-013 on 01 July 2003, and the 48-month study report was submitted on 28 October 2004. Protocol MM-HTL-001 continued follow-up for a fifth year. All patients were switched to LUMIGAN during the fifth year. The study report for the fifth year was submitted December 20, 2005. Approximately 600 patients who completed Studies 192024-008 or 192024-009 were offered the opportunity to enroll in the extension study. A total of 379 patients entered the first extension period (months 12 to 24). Of the 284 patients who completed the Month 24 visit, 183 were enrolled in the post Month 24 to Month 36 extension period. Of these patients, 162 completed the Month 36 visit, and 152 of them were enrolled in the post Month 36 based on the site's willingness to participate and the patient's eligibility and willingness to continue. There were no objective findings or adverse event reports by the investigators of increased iris pigmentation for any patient during 3rd to 5th years of the assessment study. During the original 192024-008 and 192024-009 studies, a total of 957 patients received bimatoprost treatment (QD or BID) for up to 12 months (Months 0 to 12).

Adverse events of increased iris pigmentation were reported by investigators for a combined

total of 16 patients during these studies (1.67%, 16/957). Four of these 16 patients were enrolled in the extension study 192024-014, during which patients received bimatoprost treatment for up to an additional 48 months (Months 12 to 60). There were no reports of increased iris pigmentation for any of these 4 patients or for any of the other patients enrolled in study 192024-014. Only one of the 16 patients with investigator reported adverse events of increased iris pigmentation in studies 192024-008 and 192024-009 was enrolled in the 5th year assessment study (Months 48 to 60). This patient (2821-1457) did not have any adverse event reports by the investigator of increased iris pigmentation during the current 5th year of the assessment study. A total of 7 patients who had received treatment with Timolol during the 192024-008/192024-009, and 192024-014 studies, received bimatoprost treatment in the current 5th year assessment. None of these 7 patients had any reports by the investigator of increased iris pigmentation during the previous studies or in the current study. The results demonstrated that, after two, three, and four years of dosing, Lumigan has had 1 case of cystoid macular edema and no new cases of iris pigmentation, uveitis, or iritis between months 12 to 48 of dosing.

Study #2
Commitment Date: 01 March 2001
Commitment: Allergan committed to conduct a study to evaluate pigmentation in the trabecular meshwork after patients have been treated with bimatoprost ophthalmic solution 0.03% for over two years.
Study/Commitment Status: Submitted/Reviewed
Explanation of the Study Status: Allergan conducted clinical study 192024-029 titled, "A Masked Histological Evaluation of Trabecular Meshwork Specimens Collected from Trabeculectomy Patients with Primary Open-Angle Glaucoma Treated with Bimatoprost 0.03% Ophthalmic Solution Once-Daily (QD) for at Least Two Years Compared with Primary Open-Angle Glaucoma Patients Treated with Other Topical Ophthalmic IOP-Lowering Drugs." The protocol was submitted to IND 48,929 in Serial No.094 on 29 October 2003. The study started in January 2004. This study has been completed. A preliminary report for study 192024-029 was submitted to the Agency on 20 December 2005, as a part of the complete response to the FDA Action Letter for S-013. The final report for this clinical study was submitted to this NDA on July 25, 2008. The overall pigmentation evaluation of the trabecular specimens from patients treated with bimatoprost for at least 2 years (without exposure to ocular prostaglandins or with exposure of no more than 6 weeks) was similar to that obtained from patients treated with other topical, ophthalmic IOP-lowering therapies (without exposure to ocular prostaglandins or with exposure of no more than 6 weeks). The results of this study provide no evidence of a bimatoprost-induced hyperpigmentation in the trabecular meshwork.

13. 505(b)(1) vs 505(b)(2)

NDA 22-184 was submitted as an NDA under 505(b)(1) and relies only on clinical studies and/or postmarketing data conducted/collected by Allergan. While NDA 22-184 references some information submitted to NDA 21-275, it only references studies or marketing data submitted to NDA 21-275 which were conducted/collected by Allergan.

One of the efficacy supplements for NDA 21-275 was submitted as a 505(b)(2) application. As discussed above, were that efficacy supplement to be submitted in 2010, it would not be necessary to submit it as a 505(b)(2) application. The review of NDA 22-184 does not rely upon studies which were not conducted by or for Allergan, product-specific literature for Xalatan, the Agency's prior findings regarding the safety of Xalatan or other literature.

14. Other Relevant Regulatory Issues

A Division of Scientific Investigations (DSI) audit was requested. This inspection audited one study, Study #192024-031-00 at two domestic sites, those of Investigators #2078 and #3761. The data from the #2078 site are considered acceptable in support of the respective indication. However, the safety data at the #3761 site were interpreted as being incomplete. At the #3761 site, the major finding was related to under-reporting of adverse events in 5 subjects (see the DSI consult dated 5 March 2008). There was a separate section of the Case Report Form in this trial for reporting hyperemia; this separate section led to hyperemia being reported as a pharmacological event instead of an adverse event. While the DSI audit cites this as possibly underreporting some adverse events, the Review Division does not believe interpretation of the reported events is correct.

Allergan 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 "Lumigan RC." They recommended managing the proposed product under the existing product name, Lumigan, with an educational program to increase awareness among the practitioners of the new strength.

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 2 July 2007. Their suggestions regarding the Highlights section of the labeling and adverse reactions have been incorporated in the revised labeling.

15. Labeling

NDA 22-184 is labeled for approval for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension with the labeling submitted by Allergan on 29 April 2008 and the most recent version was revised in March 9, 2010. The proposed labeling is acceptable.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

16. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 22-184 is to be approved for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. The labeling for the bimatoprost 0.01% indicates that it is not equivalent to Lumigan 0.03% in its ability to lower intraocular pressure. The package insert is a combined package insert for Lumigan 0.01% and Lumigan 0.03%. The labeling submitted by Allergan on March 9, 2010, is acceptable for approval.

RISK BENEFIT ASSESSMENT:
The application demonstrated that bimatoprost 0.01% lowered IOP by approximately (b) (4) mmHg; this amount is clinically meaningful. The drug product was not equivalent to Lumigan 0.03% in IOP-lowering efficacy as measured by mean IOP. The difference in mean IOP between bimatoprost 0.01% and Lumigan 0.03% was within 1.5mmHg at all post-baseline timepoints; however, the 95% confidence interval for the majority of timepoints were not within 1 mmHg as stipulated in the Division's definition for establishing equivalency.

The application supports the safety of bimatoprost 0.01% in the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. Overall, bimatoprost 0.01% and 0.0125% were safe and well tolerated. The types of adverse events seen were consistent with the known adverse event profile of Lumigan 0.03%. There were less ocular adverse events reported in the bimatoprost 0.01% (48% vs. 62%) and 0.0125% (49% vs. 62%) arms compared to the Lumigan 0.03% arm. However, there is no second trial and without a second trial that replicates these results, the lower frequency of ocular adverse events has not been included in the labeling.

Clinical, CMC, Pharmacology/Toxicology, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application. The Statistical review states that study 031 failed to demonstrate equivalency of efficacy of bimatoprost 0.01% or bimatoprost 0.0125% to Lumigan 0.03% in reducing elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. This will be noted in the labeling of the products.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22184	ORIG-1	ALLERGAN INC	Lumigan (bimatoprost ophthalmic solution) 0.01%

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/s/

WILEY A CHAMBERS
08/31/2010