CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022184Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-184**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**7/2/07 (EDR)**
PRODUCT:	**Bimatoprost Ophthalmic Solution 0.01% (trade name not yet chosen)**
INTENDED CLINICAL POPULATION:	**Patients with open angle glaucoma or ocular hypertension**
SPONSOR:	**Allergan**
DOCUMENTS REVIEWED:	**-000**
REVIEW DIVISION:	**Division of Anti-Infective and Ophthalmology Products**
PHARM/TOX REVIEWER:	**Amy L. Ellis**
ACTING PHARM/TOX TEAM LEADER:	**Wendelyn Schmidt**
ACTING DIVISION DIRECTOR:	**Wiley Chambers**
PROJECT MANAGER:	**Michael Puglisi**

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The pharmacologist has no objection to the approval of this NDA.

B. Recommendation for nonclinical studies

No additional nonclinical studies are recommended.

C. Recommendations on labeling

The labeling that the sponsor proposed for sections 8.1 (Pregnancy), 10 (Overdosage), and 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) is acceptable from the nonclinical standpoint.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Increasing the benzalkonium chloride (BAK) concentration to 200 ppm in conjunction with decreasing the bimatoprost concentration to 0.01% in this Lumigan® reformulation was not associated with ocular irritation or microscopic ocular changes in Dutch-Belted rabbits when administered daily for 6 months. In contrast, when formulations containing 0.015% or 0.02% bimatoprost with 200 ppm BAK were applied to the eyes of New Zealand White rabbits twice daily for one month, ocular findings were observed that were not seen in eyes treated with the original Lumigan®. These included mild to moderate conjunctival congestion, minimal to mild corneal epithelial degeneration/regeneration, and minimal corneal stromal edema. There were no systemic toxic effects in either rabbit species. Pharmacokinetic data suggested that increasing the BAK concentration to 200 ppm increased the ocular bioavailability of bimatoprost.

B. Pharmacologic activity

Prostamides such as bimatoprost are believed to lower intraocular pressure by increasing the outflow of aqueous humor via both the trabecular meshwork and uveoscleral routes.

C. Nonclinical safety issues relevant to clinical use

No.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

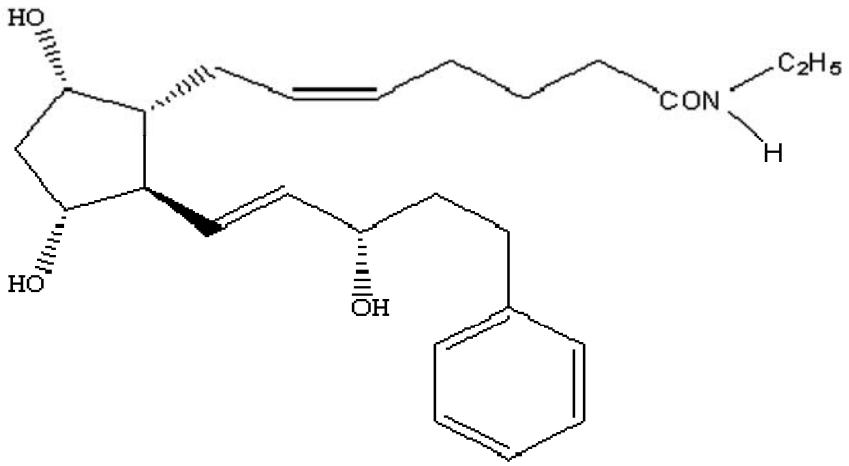
NDA number: 22-184
Review number: 1
Sequence number/date/type of submission: 000/02-JUL-2007/original NDA
Information to sponsor: Yes ( ) No ( )
Sponsor and/or agent: Allergan (Irvine, CA)
Manufacturer for drug substance: (b) (4)

Reviewer name: Amy L. Ellis
Division name: Anti-Infective and Ophthalmology Products
Review completion date: 3/14/08

Drug:

Trade name: not yet chosen
Generic name: Bimatoprost Ophthalmic Solution 0.01%
Code name: AGN 192024
Chemical name: (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide
CAS registry number: 155206-00-1
Molecular formula/molecular weight: $C_{25}H_{37}NO_4$/415.58
Structure: From the NDA:

Figure 3.2.S.1.2-1 Structural Formula of Bimatoprost



Relevant INDs/NDAs/DMFs: IND 48,929; NDAs 21-275 and (b) (4) (NDA 21-275 is for the approved product Lumigan®. It is owned by the sponsor, who has requested that the nonclinical data in this application be incorporated into the current NDA by cross reference.)

Drug class: Prostamide (synthetic prostaglandin analog)

Intended clinical population: Patients with ocular hypertension or open-angle glaucoma

Clinical formulation: From the NDA:

Table 3.2.P.1-1 List of Components and Quantitative Composition

Component	Concentration (% w/v)	Concentration (mg/mL)	Reference of Quality Standard	Function
Bimatoprost	0.01	0.1	In-house standard	Drug Substance
Benzalkonium Chloride [a]	0.02	0.2	NF/Ph Eur	Preservative
Dibasic Sodium Phosphate (b) (4)		(b) (4)	USP	(b) (4)
Citric Acid (b) (4)			USP/Ph Eur	
Sodium Chloride			USP/Ph Eur	
Hydrochloric Acid [b]			NF/Ph Eur	
Sodium Hydroxide [b]			NF/Ph Eur	
Purified Water			USP/Ph Eur	

a (b) (4)

b Pharmaceutical grade hydrochloric acid and sodium hydroxide are prepared into appropriate normality for pH adjustments.

Route of administration: Topical ophthalmic

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

New Evidence Supporting the Existence of Unique Prostamide Receptors: Bimatoprost and Prostaglandin $F_{2\alpha}$ Selectively Stimulate Calcium Signaling in Different Cat Iris Sphincter Cells (BIO-03-404)

The Effect of d-Alpha Tocopheryl Polyethylene Glycol 1000 Succinate and Benzalkonium Chloride on Rabbit Ocular Absorption and In-Vitro Corneal Epithelium Penetration of AGN 192024 (PK-04-102)

The Effect of Benzalkonium Chloride and Ethylenediaminetetraacetic Acid on Ocular Absorption of AGN 192024 Following a Single Ocular Administration to Albino Rabbits (PK-04-163)

The Effect of Benzalkonium Chloride and Ethylenediaminetetraacetic Acid on AGN 192024 Cytotoxicity and Permeability Across Primary Culture of Rabbit Corneal Epithelial Cell Layers (PK-04-168)

Studies not reviewed within this submission:

This repeat dose toxicity study was reviewed under IND 48,929-111:

Lumigan Label Enhancement: 1-Month Ocular Toxicity Study in Rabbits (TX05010)

These studies were reviewed under IND 48,929-137:

Primary Pharmacodynamics:

Identification of an Antagonist that Selectively Blocks the Activity of Prostamides (Prostaglandin-Ethanolamides) in the Feline Iris (BIO-06-529)

Second Generation Prostamide Antagonists (BIO-06-546)

Identification and Pharmacological Characterization of Prostaglandin FP Receptor and FP Receptor (BIO-06-555)

Secondary Pharmacodynamics:

Morphological Changes in the Anterior Eye Segment after Long Term Treatment with Different Receptor Selective Prostaglandin Agonists and a Prostamide (BIO-03-402)

Effect of a Second Generation Prostamide Antagonist AGN 211336 in the Beagle Dog Eye: Part 1, Intraocular Pressure (BIO-07-582)

Pharmacokinetic/Toxicokinetic Studies:

Quantitation of AGN 192024 and AGN 191522 in Rabbit Aqueous Humor for Study PK-02-P049, Entitled "Comparison of Ocular Bioavailability of Five 0.03% AGN 192024 Formulations to that of 0.03% Lumigan® in Albino Rabbits" (PK 03-019)
Quantitation of AGN 192024 and its Metabolite, AGN 191522, in Rabbit Aqueous Humor for Study PK-04-P020, Entitled "The Effect of d-Alpha Tocopheryl Polyethylene Glycol 1000 Succinate and Benzalkonium Chloride on Ocular Absorption of AGN 192024 Following a Single Ocular Administration to Albino Rabbits" (PK 04-101)

Quantitation of AGN 192024 (Bimatoprost) and its Metabolite, AGN 191522, in Rabbit Aqueous Humor for Study PK-04-P028, Entitled "The Effect of Benzalkonium Chloride and EDTA on Ocular Absorption of AGN 192024 Following a Single Ocular Administration to Albino Rabbits" (PK 04-165)

Quantitation of AGN 192024 (Bimatoprost) and its Metabolite, AGN 191522, in Buffer Samples for a Study Entitled "The Effect of Benzalkonium Chloride and Ethylenediaminetetraacetic Acid on AGN 192024 Cytotoxicity and Permeability Across Primary Culture of Rabbit Corneal Epithelial Cell Layers" (PK 04-169)

Quantitation of AGN 192024 and AGN 191522 in Rabbit Blood for Study TX 5010, Entitled "Lumigan Label Enhancement: 1-Month Ocular Toxicity Study in Rabbits" (b) (4) 05-025)

Quantitation of AGN 192024 and AGN 191522 in Rabbit Blood for Study TX 06011, Entitled "Lumigan Label Enhancement: Six Month Ocular Toxicity Study in Rabbits with a One Month Recovery" (b) (4) 06-077)

Quantitation of AGN 192024 and AGN 191522 in Rabbit Blood for Study PK-06-P058, Entitled "Comparison of Ocular Absorption of 0.01% and 0.0125% AGN 192024 Formulations to that of 0.03% Lumigan® in Dutch-Belted Rabbits" (b) (4) 06-089)

Quantitation of Bimatoprost and Bimatoprost Acid Metabolite in Rabbit Aqueous Humor for Allergan Study PK 06-P058 Titled "Comparison of Ocular Absorption of 0.01% and 0.0125% AGN 192024 Formulations to that of 0.03% Lumigan® in Dutch-Belted Rabbits" (PK 06-107)

Comparison of Ocular Bioavailability of Five 0.03% AGN 192024 Formulations to that of 0.03% Lumigan® in Albino Rabbits (PK 03-009)

Toxicokinetic Analysis of Allergan Study No. TX05010 Entitled "Lumigan Label Enhancement: 1-Month Ocular Toxicity Study in Rabbits" (PK 05-070)

Toxicokinetic Analysis of AGN 192024 and AGN 191522 For Allergan Study No. TX06011, Titled "Lumigan Label Enhancement: Six Month Ocular Toxicity Study in Rabbits with a One Month Recovery" (PK 06-046)

Comparison of Ocular Absorption of 0.01% and 0.0125% AGN 192024 Formulations to that of 0.03% Lumigan® in Dutch-Belted Rabbits (PK 06-108)

Repeat-Dose Toxicity Study:

Lumigan Label Enhancement: Six Month Ocular Toxicity Study in Rabbits with a One Month Recovery (TX06011)

Special Studies/*In Vitro* Studies:

AGN 192024: *In Vitro* Cytotoxicity Evaluation of Lumigan® Formulations Containing BAK and EDTA Using an Ethidium Bromide Staining Assay (TX04059)

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Bimatoprost is a synthetic structural analog of prostaglandin $F_{2\alpha}$; however, it does not interact with the known prostanoid and cannabinoid receptors. Its activity is believed to be based upon stimulation of prostamide-sensitive receptors. The nature of these receptors has been investigated by the sponsor.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Bimatoprost is a synthetic structural analog of prostaglandin $F_{2\alpha}$.

Drug activity related to proposed indication: Prostamides such as bimatoprost are believed to lower intraocular pressure by increasing the outflow of aqueous humor via both the trabecular meshwork and uveoscleral routes. The sponsor has conducted a number of studies to investigate the endogenous formation of prostamides and the role that they may play in controlling IOP via interaction with the prostamide-sensitive receptors. Studies in feline iris suggest the presence of separate populations of prostamide-sensitive receptors and prostanoid FP receptors. Additional studies in dogs and mice provide evidence regarding the novelty of bimatoprost-sensitive receptors.

New Evidence Supporting the Existence of Unique Prostamide Receptors: Bimatoprost and Prostaglandin $F_{2\alpha}$ Selectively Stimulate Calcium Signaling in Different Cat Iris Sphincter Cells (BIO-03-404)

Summary: Although bimatoprost and prostaglandin (PG) $F_{2\alpha}$ have similar potency to stimulate contractile responses in isolated cat iris sphincter tissue, more selective studies indicate that the 2 compounds act at different receptors. Confocal microscopic imaging of digested cat iris sphincter tissues showed that bimatoprost and PG $F_{2\alpha}$ induced calcium signaling in different cells within the same preparation. Regardless of the order of exposure, the two compounds always acted on different populations of cells without overlap. PF $F_{2\alpha}$ potently induced calcium signaling in HEK cells transfected with the feline or human FP receptor and human dermal fibroblasts that contain natural FP receptors and bimatoprost did not, providing further evidence that the compounds act at different receptors.

2.6.2.3 Secondary pharmacodynamics

In addition to its direct action on prostamide-sensitive receptors, some data from monkeys suggests that chronic bimatoprost treatment is associated with remodeling and morphological changes that increase aqueous outflow by the trabecular and uveoscleral routes.

2.6.2.4 Safety pharmacology

Safety pharmacology studies were not necessary for this NDA.

2.6.2.5 Pharmacodynamic drug interactions

Nothing relevant reported in the nonclinical data.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Copied from the NDA, below:

Primary Pharmacodynamics

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study Number
Iris	Cat	In Vitro	0.1, 1 μM perfused (Ca^{2+} signaling)	54	Using the confocal microscope, results of selective stimulation of different cells in the same cat iris sphincter preparation by bimatoprost and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), along with the absence of observed instances in which the same cells repond to both agonists, suggest the involvement of separate receptor sites for bimatoprost and $PGF_{2\alpha}$.	No	BIO-03-404
Iris; HEK-cells transfected with human prostanoid FP receptors	Cat; Human		10^{-11} – 10^{-5} M (contraction, binding)	3-7			
Iris	Cat	In Vitro	1 – 30 μM (antagonist), 10^{-10} – 10^{-4} M (agonist contraction)	4-6	Prostamide antagonist AGN 204396 antagonized the contractile effects of bimatoprost in the cat isolated iris sphincter, but had no effect on the responses to $PGF_{2\alpha}$, FP receptor agonists, and PGE_2-glyceryl ester. These results using prostamide antagonist AGN 204396 provided further pharmacological evidence that prostamide-sensitive receptors are distinct from prostanoid FP receptors and those that recognize PGE_2-glyceryl ester.	No	BIO-06-529
HEK-cells transfected with human prostanoid FP receptors	Human		10^{-11} – 10^{-5} M (Ca^{2+} signaling)	3			
Iris	Cat	In Vitro	30 μM (antagonist), 10^{-9} – 10^{-5} M (agonist contraction)	4	Prostamide antagonists AGN 211334, AGN 211335, and AGN 211336 antagonized the contractile effects of bimatoprost in the cat isolated iris sphincter, but had no effect on the responses to $PGF_{2\alpha}$. These results using prostamide antagonists provided further pharmacological evidence that prostamide-sensitive receptors are distinct from prostanoid FP receptors.	No	BIO-06-546
HEK-cells transfected with human prostanoid FP receptors	Human		10^{-11} – 10^{-5} M (Ca^{2+} signaling)	3			
HEK -cells tranfected with prostaglandin FP receptors (human) and alternative FP receptor variants (human, monkey)	Human, Monkey/ Cynomolgus	In Vitro	10^{-7} M (agonist) 10^{-8}- 10^{-6} M (antagonist)	3-5	Bimatoprost elicited a second phase of calcium mobilization in HEK-cells co-transfected with prostanoid FP and alternative-FP receptors that was antagonized by prostamide antagonist AGN 211335. The effects of $PGF_{2\alpha}$ on calcium signaling were not antagonized by AGN 211335. These results support one hypothesis that bimatoprost binds to a novel receptor that heterodimerizes with the prostanoid FP receptor.	No	BIO-06-555

HEK– human embryonic kidney

Secondary Pharmacodynamics

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study Number
Anterior eye segment	Monkey/ Cynomolgus	Topical Instillation	0.03%	4F	After 1-year of treatment with bimatoprost, tissues were excised and prepared for morphological studies. The uveoscleral outflow pathways were enlarged and appear organized. Conventional outflow routes were also affected. Long-term treatment with bimatoprost also induces sprouting of nerve fibers.	No	BIO-03-402
Intraocular pressure	Dog/ Beagle	Topical Instillation	5% (multiple drops, antagonist) 0.03% (agonist)	M/F 6	Pretreatment with the prostamide antagonist AGN 211336 attenuated the IOP response to bimatoprost in conscious dogs.	No	BIO-07-582

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The reader is referred to NDA 21-275 for additional details regarding the pharmacokinetics of bimatoprost, including its systemic fate. According to the Lumigan® label, once bimatoprost reaches the systemic circulation in humans, it undergoes oxidation, N-de-ethylation, and glucuronidation. Human males excreted approximately 67% of an intravenous dose in urine and 25% in feces. This is similar to what has been observed in monkeys

Data from rabbits suggests that increasing the benzalkonium chloride concentration in a solution for ocular administration increases the ocular absorption of bimatoprost.

2.6.4.2 Methods of Analysis

A validated HPLC method with tandem MS detection was used to measure bimatoprost and its active C-1 acid metabolite (AGN 191522) in ocular tissues, blood, and buffer samples. Tritiated bimatoprost was used for ocular distribution studies.

2.6.4.3 Absorption

Bimatoprost is rapidly absorbed following ocular administration with Cmax concentrations in ocular tissues generally between 0.5 and 2 hours. Increasing the BAK concentration in the dosing solution increased bimatoprost ocular absorption in rabbits.

The Effect of d-Alpha Tocopheryl Polyethylene Glycol 1000 Succinate (TPGS) and Benzalkonium Chloride (BAK) on Rabbit Ocular Absorption and *In-Vitro* Corneal Epithelium Penetration of AGN 192024 (PK-04-102)

Summary: The purpose of the study was to evaluate whether TPGS or BAK would enhance ocular absorption of bimatoprost in female New Zealand White rabbits. An *in vitro* penetration model using primary cultures of rabbit corneal epithelial cells was also used for evaluation.

Each rabbit was given one 28 µl drop of a test article into each eye. The test articles are described in the table below. There were 3 rabbits per test article for an "n" of 6 eyes per formulation and 2 rabbits (4 eyes) in the untreated control group. Rabbits were sacrificed one hour after administration and aqueous humor samples were collected. The levels of the metabolite AGN 191522 were measured in aqueous humor using a validated HPLC assay with tandem MS detection. The level of the metabolite was used as a surrogate for bimatoprost absorption because the parent compound is rapidly converted after its ocular absorption in rabbits. The data in the table below clearly indicate that the ocular absorption of bimatoprost is increased in the presence of 200 ppm BAK. The presence of TPGS reduced the ocular absorption of bimatoprost.

The following table is from the NDA:

Levels of AGN 191522 in Rabbit Aqueous Humor
1 Hour After a Single Ocular Dose of Bimatoprost

Formulation	Aqueous Humor[a] (ng/mL)
1. 0.03% Lumigan® (50 ppm BAK) Control	51.0 ± 9.4
2. 0.03% Lumigan – 200 ppm BAK	87.2 ± 19.0*
3. 0.03% Lumigan – 0.015% TPGS (no preservative)	26.1 ± 3.3*
4. 0.03% Lumigan – 0.2% TPGS (no preservative)	22.9 ± 3.2*
5. 0.03% Lumigan – 0.4% TPGS (no preservative)	19.3 ± 5.6*
6. 0.03% Lumigan – 1.0% TPGS (no preservative)	15.4 ± 3.3*

a Mean ± SD. Per formulation, N=3 rabbits (6 eyes).
* Statistically different ($p<0.05$) compared to 0.03% Lumigan®

Confluent layers of cultured corneal epithelial cells were tested with Lumigan® in comparison with formulations containing 0.03% bimatoprost and 0, 100, or 200 ppm of BAK ± TPGS at concentrations ranging from 0.015-1.0%. Samples of basolateral fluid were taken 30 minutes to 3 hours after the initiation of incubation. These corneal epithelial cell layers demonstrated enhanced penetration of bimatoprost in the presence of 200 ppm BAK, but a concentration-related decrease in penetration when TPGS was added. Transepithelial electrical resistance monitoring (a measure of cell integrity) suggested that BAK caused dose-related cytotoxicity to the layers of corneal epithelial cells, enhancing permeability.

The Effect of Benzalkonium Chloride and Ethylenediaminetetraacetic Acid on Ocular Absorption of AGN 192024 Following a Single Ocular Administration to Albino Rabbits (PK-04-163)

Summary: The purpose of the study was to evaluate whether BAK ± EDTA would enhance ocular absorption of bimatoprost in female New Zealand White rabbits.

Each rabbit was given one 28 µl drop of a test article into each eye. The test articles are described in the table below. There were 3 rabbits per test article for an "n" of 6 eyes per formulation and 2 rabbits (4 eyes) in the untreated control group. Rabbits were sacrificed one hour after administration and aqueous humor samples were collected. The levels of the metabolite AGN 191522 were measured in aqueous humor using a validated HPLC assay with

tandem MS detection. The level of the metabolite was used as a surrogate for bimatoprost absorption because the parent compound is rapidly converted after it ocular absorption in rabbits. The data in the table below show that the ocular absorption of bimatoprost is increased in the presence of 150 ppm BAK. Aqueous humor levels of AGN 191522 were comparable among the treatment groups despite the lower concentration of bimatoprost present in the formulations containing 150 ppm BAK. The addition of 0.1% EDTA to 150 ppm BAK did not significantly enhance the ocular absorption of bimatoprost.

The following table is from the NDA:

Levels of AGN 191522 in Rabbit Aqueous Humor
1 Hour After a Single Ocular Dose of Bimatoprost

Formulation	Aqueous Humor (ng/mL)
1. 0.03% Lumigan® (50 ppm BAK) Control	45.6 ± 10.3
2. 0.015% Lumigan – 150 ppm BAK	32.4 ± 12.4
3. 0.015% Lumigan – 150 ppm BAK, 0.1% EDTA	50.0 ± 21.3

Data are expressed as mean ± SD. Per formulation, N=3 rabbits (6 eyes).

The Effect of Benzalkonium Chloride and Ethylenediaminetetraacetic Acid on AGN 192024 Cytotoxicity and Permeability Across Primary Culture of Rabbit Corneal Epithelial Cell Layers (PK-04-168)

Summary: Primary cultures of New Zealand White rabbit corneal epithelial cells were used to evaluate whether BAK ± EDTA would enhance penetration of bimatoprost *in vitro*.

Confluent layers of cultured corneal epithelial cells were tested with Lumigan® in comparison with formulations containing 0.015% bimatoprost with 0, 50, 125, or 200 ppm of BAK ± EDTA at concentrations ranging from 0.015-0.1%. Bimatoprost alone at a concentration of 0.03% was also tested. Samples of basolateral fluid were taken 30 minutes to 2 hours after the initiation of incubation. The corneal epithelial cell layers demonstrated that BAK enhanced penetration of bimatoprost in a concentration dependant manner. Transepithelial electrical resistance monitoring showed reduced electrical resistance, known to correlate with enhanced permeability of cell layers. Ethidium bromide staining showed minimal cytotoxicity despite the enhanced permeability, although the cytotoxicity correlated with BAK concentration. The presence of EDTA in addition to BAK did not further enhance penetration of bimatoprost in a significant manner. The report stated that these data suggested to the sponsor that increasing the BAK concentration in Lumigan® to 200 ppm would significantly enhance the ocular absorption of bimatoprost, perhaps allowing a lower concentration of the drug substance to be used in a reformulation.

2.6.4.4 Distribution

Additional studies on bimatoprost distribution were not conducted to support the current NDA. Higher bimatoprost/metabolite concentrations have been found in the eyelid, conjunctiva, and sclera, than in the cornea, iris, and ciliary body. Data from monkeys suggested accumulation in ocular tissues after repeated dosing.

2.6.4.5 Metabolism

Additional studies on bimatoprost metabolism were not conducted to support the current NDA. In rabbits, but not in monkeys, bimatoprost is rapidly converted to its active C-1 acid metabolite (AGN 191522) after ocular absorption. This conversion does not occur to as great an extent in human ocular tissues as it does in rabbits. In rats, monkeys, and humans, bimatoprost undergoes glucuronidation, hydroxylation, deamidation and N-deethylation.

2.6.4.6 Excretion

Additional studies on bimatoprost excretion were not conducted to support the current NDA. Human males excreted approximately 67% of an intravenous dose of bimatoprost in the urine and about 25% in the feces. These data are similar to those obtained from male and female monkeys (58-64% in urine and 24-31% in feces).

2.6.4.7 Pharmacokinetic drug interactions

Nothing in the NDA.

2.6.4.8 Other Pharmacokinetic Studies

Nothing in the NDA.

2.6.4.9 Discussion and Conclusions

Increasing the BAK concentration in the dosing solution increased bimatoprost ocular absorption in rabbits.

2.6.4.10 Tables and figures to include comparative TK summary

Nothing to add beyond the 2 tables directly below.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

From the NDA:

Table 2.6.4.3.1-1 Summary of aqueous humor pharmacokinetics of bimatoprost acid (AGN 191522) in rabbits after topical ocular administration of bimatoprost

Species n/timepoint or formulation	Formulations	Dose (% w/v)	Cmax or 1 hr postdose (ng/mL)	Tmax (hr)	AUC (ng·hr/mL)	Allergan Report
Rabbits (NZW) 2F (4 eyes)	LUMIGAN® (50 ppm BAK)	0.03	21.0 (6.86)	1	50.1 (9.01)	PK-03-009
	Refresh LiquiGel, pH 7.3	0.03	56.1 (7.98)*	1	97.3 (10.1)*	
	LiquiGel/Cyclodextrin, pH 7.3	0.03	16.2 (3.91)	1	28.3 (5.03)	
	LiquiGel/High Calcium, pH 7.3	0.03	32.6 (5.47)	1	51.9 (7.60)	
	Emulsion, pH 7.07	0.03	18.8 (2.99)	3	46.0 (5.73)	
	TSP Gel, pH 7.3	0.03	39.8 (15.6)	1	72.4 (19.8)	
Rabbits (NZW) 3F (6 eyes)	LUMIGAN® (50 ppm BAK)	0.03	51.0 (9.4)	ND	ND	PK-04-102
	Bimatoprost (0.015% TPGS)	0.03	26.1 (3.3)*	ND	ND	
	Bimatoprost (0.2% TPGS)	0.03	22.9 (3.2)*	ND	ND	
	Bimatoprost (0.4% TPGS)	0.03	19.3 (5.6)*	ND	ND	
	Bimatoprost (1.0% TPGS)	0.03	15.4 (3.3)*	ND	ND	
	Bimatoprost (200 ppm BAK)	0.03	87.2 (19.0)*	ND	ND	
Rabbits (NZW) 3F (6 eyes)	LUMIGAN® (50 ppm BAK)	0.03	45.6 (10.3)	ND	ND	PK-04-163
	Bimatoprost (150 ppm BAK)	0.015	32.4 (12.4)	ND	ND	
	Bimatoprost (150 ppm BAK, 0.1% EDTA)	0.015	50.0 (21.3)	ND	ND	
Rabbits (DB) 6F (6 eyes)	LUMIGAN® (50 ppm BAK)	0.03	34.8 (18.5)	ND	ND	PK-06-108
	Bimatoprost (200 ppm BAK)	0.01	11.1 (5.8)*	ND	ND	
	Bimatoprost (200 ppm BAK)	0.0125	16.4 (15.0)	ND	ND	

All values are mean (SD for C_{max} or SE for AUC) when applicable.

NZW: New Zealand White rabbits; DB: Dutch Belted rabbits; TSP Gel: Tamarind polysaccharide

BAK: benzalkonium chloride; TPGS: d-Alpha Tocopheryl Polyethylene Glycol 1000 Succinate.

ND: not determined.

* Statistically significant ($p<0.05$) compared to LUMIGAN® control.

Table 2.6.4.3.2-1 Summary of blood pharmacokinetics of bimatoprost in rabbits after topical ocular administration of bimatoprost

Species n/timepoint or formulation	Study Day	Formulations	Bimatoprost Dose (% w/v)	C_{max} or 1 hr postdose (ng/mL)	T_{max} (hr)	AUC (ng·hr/mL)	Allergan Report
Rabbits (NZW) 4F	7	LUMIGAN® (50 ppm BAK)	0.03	0.571 (0.071)	0.167	0.179 (0.009)	PK-05-070 (TX05010)
		Bimatoprost (200 ppm BAK)	0.015	0.737 (0.617)	0.083	0.132 (0.028)	
		Bimatoprost (200 ppm BAK)	0.02	0.523 (0.107)	0.083	0.139 (0.008)	
		Bimatoprost (200 ppm BAK+0.03% EDTA)	0.015	0.326 (0.138)	0.083	0.049 (0.006)	
	28	LUMIGAN® (50 ppm BAK)	0.03	0.649 (0.181)	0.083	0.208 (0.012)	
		Bimatoprost (200 ppm BAK)	0.015	0.539 (0.134)	0.083	0.094 (0.008)	
		Bimatoprost (200 ppm BAK)	0.02	0.901 (0.293)	0.083	0.191 (0.013)	
		Bimatoprost (200 ppm BAK+0.03% EDTA)	0.015	0.451 (0.135)	0.083	0.095 (0.009)	
Rabbits (DB) 6M/ 6F	7	200 ppm BAK, 1 drop 1x daily	0.01	BLQ	NC	NC	PK-06-046 (TX06011)
		200 ppm BAK, 1 drop 3 x daily	0.01	BLQ	NC	NC	
		200 ppm BAK, 1 drop 1x daily	0.0125	0.135 (0.110)	0.083	0.006 (0.002)	
		200 ppm BAK, 1 drop 3 x daily	0.0125	0.198 (0.116)	0.083	0.008 (0.002)	
	29	200 ppm BAK, 1 drop 1x daily	0.01	0.098 (0.077)	0.083	0.004 (0.001)	
		200 ppm BAK, 1 drop 3 x daily	0.01	0.276 (0.110)	0.083	0.012 (0.002)	
		200 ppm BAK, 1 drop 1x daily	0.0125	0.222 (0.123)	0.083	0.027 (0.005)	
		200 ppm BAK, 1 drop 3 x daily	0.0125	0.364 (0.092)	0.083	0.040 (0.004)	
	85	200 ppm BAK, 1 drop 1x daily	0.01	0.366 (0.227)	0.083	0.015 (0.004)	
		200 ppm BAK, 1 drop 3 x daily	0.01	0.211 (0.147)	0.083	0.009 (0.003)	
		200 ppm BAK, 1 drop 1x daily	0.0125	0.317 (0.145)	0.083	0.031 (0.005)	
		200 ppm BAK, 1 drop 3 x daily	0.0125	0.276 (0.152)	0.083	0.026 (0.005)	
	180	200 ppm BAK, 1 drop 1x daily	0.01	0.333 (0.152)	0.083	0.031 (0.005)	
		200 ppm BAK, 1 drop 3 x daily	0.01	0.178 (0.092)	0.083	0.007 (0.002)	
		200 ppm BAK, 1 drop 1x daily	0.0125	0.289 (0.249)	0.083	0.012 (0.004)	
		200 ppm BAK, 1 drop 3 x daily	0.0125	0.372 (0.167)	0.083	0.039 (0.006)	
Rabbits (DB) 6F	1	LUMIGAN® (50 ppm BAK)	0.03	0.369 (0.343)	ND	ND	PK-06-108
		Bimatoprost (200 ppm BAK)	0.0125	BLQ	ND	ND	
		Bimatoprost (200 ppm BAK)	0.01	BLQ	ND	ND	

All values are mean (SD) when applicable. AUC interval was from 0-0.25 to 0.50 hr for PK-05-070 study.
AUC interval was from 0-0.083 or 0.167 hr for PK-06-046 study.
BLQ: Below the limit of quantitation (<0.125 ng/mL for bimatoprost and <0.250 ng/mL for AGN 191522).
NC: not calculable; ND: not determined.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Systemic and ocular toxicology studies were submitted in NDA 21-275 for the original Lumigan® 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.

Monkeys have demonstrated widening of the palpebral fissure and increased prominence of ocular sulci following ocular or intravenous treatment with bimatoprost.

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.

2.6.6.2 Single-dose toxicity

No additional single dose toxicity studies with bimatoprost were conducted to support the current NDA.

2.6.6.3 Repeat-dose toxicity

Two repeat dose toxicity studies with bimatoprost formulations containing higher levels of BAK than Lumigan® were conducted to support the current NDA. Increasing the benzalkonium chloride (BAK) concentration to 200 ppm in conjunction with decreasing the bimatoprost concentration to 0.01% in this Lumigan® reformulation was not associated with ocular irritation or microscopic ocular changes in Dutch-Belted rabbits when administered daily for 6 months. In contrast, when formulations containing 0.015% or 0.02% bimatoprost with 200 ppm BAK were applied to the eyes of New Zealand White rabbits twice daily for one month, ocular findings were observed that were not seen in eyes treated with the original Lumigan®. These included mild to moderate conjunctival congestion, minimal to mild corneal epithelial degeneration/regeneration, and minimal corneal stromal edema. There were no systemic toxic effects observed in either of these ocular rabbit studies.

2.6.6.4 Genetic toxicology

A complete battery of genotoxicity studies was conducted to support NDA 21-275. Bimatoprost did not induce reverse mutations in *S. typhimurium* at concentrations up to 5000 µg/plate in the Ames assay regardless of metabolic activation. It did not cause mutations in L5178Y/TK +/- mouse lymphoma cells $\pm$ S-9 at concentrations up to 900 µg/ml. *In vivo*,

bimatoprost did not induce micronuclei formation in polychromatic erythrocytes in mouse bone marrow at a dose of 20 mg/kg.

2.6.6.5 Carcinogenicity

Oral rodent carcinogenicity studies were conducted 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.

2.6.6.6 Reproductive and developmental toxicology

A complete battery of reproductive and developmental toxicity studies was conducted to support NDA 21-275. Lumigan® 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® 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® 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.

2.6.6.7 Local tolerance

As seen in numerous ocular toxicity studies, bimatoprost concentrations used for clinical treatment are generally well tolerated in a variety of animal species including rabbits, dogs, and monkeys. Signs of ocular irritation have been observed in some animals and conjunctival hyperemia has been reported in the clinic.

2.6.6.8 Special toxicology studies

Nothing additional to report.

2.6.6.9 Discussion and Conclusions

This product is a reformulation of Lumigan® that contains a lower concentration of the drug substance bimatoprost (0.01% vs. 0.03%), but a higher concentration of benzalkonium

chloride (0.02% vs. 0.005%) to allow greater penetration of bimatoprost into the aqueous humor. The original Lumigan® formulation has been marketed in the U.S. since March 2001. The sponsor believes that using a lower concentration of bimatoprost may improve the ocular surface tolerability and safety of the product to humans without sacrificing efficacy. Ocular solutions containing 200 ppm bimatoprost (including vehicle) were associated with minimal to moderate conjunctival congestion, epithelial degeneration/regeneration, and corneal stromal edema in New Zealand White rabbits dosed twice daily for one month; these ocular findings were reversible. Other approved ophthalmic drug products intended for chronic use contain 200 ppm bimatoprost, and there were no ocular changes in the eyes of Dutch-Belted rabbits that were dosed daily with 0.01% bimatoprost and 200 ppm BAK for 6 months. Thus, the proposed bimatoprost reformulation appears reasonably safe.

2.6.6.10 Tables and Figures

All tables and figures relevant to this NDA have been included in other sections of this review.

2.6.7 TOXICOLOGY TABULATED SUMMARY

From the NDA:

2.6.7.7-1 Repeat-Dose Toxicity **Report Title:** Lumigan Label Enhancement: 1-Month Ocular Toxicity Study In Rabbits
Test Article: Bimatoprost

Species/Strain: Rabbits/New Zealand White **Duration of Dosing:** 30 Days **Study Number:** TX05010
Initial Age: Approximately 3 to 5 Months **Duration of Postdose:** 28 Days
Date of First Dose: 15 Mar 05 **Method of Administration:** Topical Ocular
Special Features: None **Vehicle/Formulation:** N/A **GLP Compliance:** Yes
No Observed Adverse-Effect Level: None

Daily Dose (1 drop (30µL/drop) 2X/day)	Bimatoprost placebo w/ 200 ppm BAK	LUMIGAN® (AGN 192024 0.03% w/ 50 ppm BAK)	Bimatoprost 0.015% w/ 200 ppm BAK	Bimatoprost 0.02% w/ 200 ppm BAK	Bimatoprost 0.015% w/ 200 ppm BAK and 0.03% EDTA
Number of Animals	**F:8**	**F:8**	**F:8**	**F:8**	**F:8**
Toxicokinetics: AUC_{0-t} (ng·hr/mL Day 28)	BLQ	0.208	0.094	0.191	0.095
Noteworthy Findings					
Died or Sacrificed Moribund	0	0	0	0	0
Clinical Observations	-	-	-	-	-
Ocular Observations					
Gross Ocular					
Congestion	+	-	+	+	+
Slit Lamp Examination	-	-	-	-	-
Pupillary Reflex	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-
Intraocular Pressure	-	-	-	-	-

BLQ – Below limit of quantitation
- No noteworthy findings
+ = mild

2.6.7.7-1 Repeat-Dose Toxicity **Study No. TX05010 (Continued)**

Daily Dose (1 drop (30µL/drop) 2X/day)	Bimatoprost placebo w/ 200 ppm BAK	LUMIGAN® (AGN 192024 0.03% w/ 50 ppm BAK)	Bimatoprost 0.015% w/ 200 ppm BAK	Bimatoprost 0.02% w/ 200 ppm BAK	Bimatoprost 0.015% w/ 200 ppm BAK and 0.03% EDTA
Number of Animals	**F:8**	**F:8**	**F:8**	**F:8**	**F:8**
Noteworthy Findings					
Body Weight	-	-	-	-	-
Food Consumption	-	-	-	-	-
Gross Pathology (ocular tissues only)					
Number Examined	6	6	6	6	6
Microscopic Pathology (ocular tissues only)					
Number Examined	6	6	6	6	6
Corneal Epithelial Degeneration					
Minimal	3/6	-	2/6	5/6	3/6
Mild	3/6	-	4/6	1/6	1/6
Corneal Epithelial Regeneration					
Minimal	5/6	3/6	4/6	-	1/6
Mild	1/6	-	-	-	-
Corneal Stroma Edema					
Minimal	3/6	-	2/6	4/6	1/6
Goblet Cell Depletion					
Minimal	4/6	-	5/6	4/6	3/6
Mixed Inflammatory Cell Infiltrates					
Minimal	-	-	1/6	1/6	1/6
Mild	-	-	-	1/6	-
Postdose Evaluation					
Number Evaluated	2	2	2	2	2

- No noteworthy findings

2.6.7.7-2 Repeat-Dose Toxicity **Report Title:** Lumigan® Label Enhancement: Six-Month Ocular Toxicity Study in Rabbits with a One Month Recovery **Test Article: Bimatoprost**

Species/Strain: Rabbits/Dutch Belted
Initial Age: Approximately 3.5 to 4.5 Months
Date of First Dose: 15-16 Mar 06 (M-F)
Special Features: None
Duration of Dosing: 181 Days
Duration of Post-Dose: 30 Days
Method of Administration: Topical Ocular
Vehicle/Formulation: N/A
Test Article: Bimatoprost/200 BAK Ophthalmic Solution (0.01% and 0.0125%)
Study Number: TX06011
GLP Compliance: Yes
No Observed Adverse-Effect Level: None

Daily Dose (1 drop/left eye)	Bimatoprost Placebo Ophthalmic Solution with 200 ppm BAK (3x daily)		0.01% Bimatoprost/200 BAK Ophthalmic Solution (1x Daily)		0.01% Bimatoprost/200 BAK Ophthalmic Solution (3x Daily)		0.0125% Bimatoprost/200 BAK Ophthalmic Solution (1x Daily)		0.0125% Bimatoprost/200 BAK Ophthalmic Solution (3x Daily)	
Number of Animals	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**
Toxicokinetics (Day 7):										
C_{Max} (ng/mL)			BLQ		BLQ		0.135		0.198	
T_{max} (min)			NC		NC		5		5	
AUC_{0-t} (ng·min/mL)			NC		NC		0.338		0.495	
AUC Interval (min)			NC		NC		0-5		0-5	
Toxicokinetics (Day 29):										
C_{Max} (ng/mL)			0.098		0.276		0.222		0.364	
T_{max} (min)			5		5		5		5	
AUC_{0-t} (ng·min/mL)			0.245		0.690		1.61		2.37	
AUC Interval (min)			0-5		0-5		0-10		0-10	
Toxicokinetics (Day 84):										
C_{Max} (ng/mL)			0.366		0.211		0.317		0.276	
T_{max} (min)			5		5		5		5	
AUC_{0-t} (ng·min/mL)			0.915		0.528		1.84		1.58	
AUC Interval (min)			0-5		0-5		0-10		0-10	
Toxicokinetics (Day 176):										
C_{Max} (ng/mL)			0.333		0.178		0.289		0.372	
T_{max} (min)			5		5		5		5	
AUC_{0-t} (ng·min/mL)			1.87		0.445		0.723		2.31	
AUC Interval (min)			0-10		0-5		0-5		0-10	

BLQ= Below the limit of quantitation; NC= Not calculable

2.6.7.7-2 Repeat-Dose Toxicity **Study No. TX06011 (Continued)**

Daily Dose (1 drop/left eye)	Bimatoprost Placebo Ophthalmic Solution with 200 ppm BAK (3x daily)		0.01% Bimatoprost/200 BAK Ophthalmic Solution (1x Daily)		0.01% Bimatoprost/200 BAK Ophthalmic Solution (3x Daily)		0.0125% Bimatoprost/200 BAK Ophthalmic Solution (1x Daily)		0.0125% Bimatoprost/200 BAK Ophthalmic Solution (3x Daily)	
Number of Animals	M:6	F:6	M:6	F:6	M:6	F:6	M:6	F:6	M:6	F:6
Noteworthy Findings										
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0	0	0
Clinical Observations	-	-	-	-	-	-	-	-	-	-
Body Weights	-	-	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-	-	-
Ocular Observations										
Gross Ocular Congestion	-	-	-	-	-	-	-	-	-	-
Gross Ocular Swelling	-	-	-	-	-	-	-	-	-	-
Gross Ocular Discharge	-	-	-	-	-	-	-	-	-	-
Slit Lamp Biomicroscopy	-	-	-	-	-	-	-	-	-	-
Pupillary Reflex	-	-	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-	-	-
Intraocular Pressure	-	-	-	-	-	-	-	-	-	-
Gross Pathology (ocular tissues only)	-	-	-	-	-	-	-	-	-	-
Number Examined	4	4	4	4	4	4	4	4	4	4
Microscopic Pathology (ocular tissues only)	-	-	-	-	-	-	-	-	-	-
Number Examined	4	4	4	4	4	4	4	4	4	4
Postdose Evaluation										
Number Evaluated	2	2	2	2	2	2	2	2	2	2

- = No Noteworthy Findings

2.6.7.17 Other Toxicity Studies **Test Article: Bimatoprost**

Species/Strain	Method of Administration (Vehicle/ Formulation)	Doses	Gender and No. per Group	Noteworthy Findings	Study Number
Rabbit Corneal Epithelial Cell Layer (RCECL)	NA	0.015% bimatoprost with 0, 50, 125, 150, or 200 ppm BAK	NA	Bimatoprost formulations containing 0.015% bimatoprost with 50-200 ppm BAK caused ethidium bromide staining of RCECL in a dose-dependent manner related to BAK concentration from 50-200 ppm with a maximal effect on cell viability at 200 ppm, and no additive effect by EDTA up to 0.03%. Bimatoprost at 0.015 or 0.03% without BAK or EDTA did not cause ethidium bromide staining greater than the negative control suggesting no effect of bimatoprost on RCECL viability.	TX04059
		0.015% bimatoprost with 50, 125, or 200 ppm BAK with 0.015% or 0.03% EDTA.			
		0.015% bimatoprost with 150 ppm BAK with 0.01% EDTA.			
		0.03% bimatoprost with no BAK and no EDTA			
		LUMIGAN® control (0.03% bimatoprost, 50 ppm BAK and no EDTA)			
		Vehicle control and Methanol control			

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: This reformulated drug product, 0.01% bimatoprost with 200 ppm BAK does not appear to cause greater ocular irritation in Dutch-Belted rabbits than the original Lumigan®. Ocular findings in New Zealand White rabbits that appeared mediated by BAK were reversible. Other approved ophthalmic solutions intended for chronic human use contain 200 ppm BAK. The pharmacology/toxicology reviewer has no objection to the approval of this NDA.

Unresolved toxicology issues: None.

Recommendations: There are no recommendations for additional nonclinical studies.

Suggested labeling: The labeling that the sponsor proposed for sections 8.1 (Pregnancy), 10 (Overdosage), and 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) is acceptable from the nonclinical standpoint. It is very similar to the labeling for Lumigan®, which is appropriate. The sponsor has added the qualifier "at least" to the dose multiples between the animal and human data discussed in these sections because the topical dose of bimatoprost is lower in the new formulation. The Division agreed with the sponsor that systemic exposure to bimatoprost for patients using the new formulation is unlikely to be greater than the exposure to bimatoprost during Lumigan® use, so clinical PK studies with the new bimatoprost formulation were not required. It was acceptable for the sponsor to add the qualifier "at least" for dose comparison purposes because there are no new PK data to use to make new comparisons. Additionally, the sponsor changed the dose multiple in the Overdosage section to reflect the lower amount of bimatoprost that would be present in a container of the new drug product. This was also acceptable.

Signatures (optional):

Reviewer Signature _____

Acting Team Leader Signature_____ Concurrence Yes ___ No ___

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

/s/

Amy Ellis
3/21/2008 04:32:18 PM
PHARMACOLOGIST
The pharm/tox reviewer has no objection to the approval of this NDA.
Wendy- You previously signed the paper copy of this review.

Wendelyn Schmidt
3/26/2008 09:52:30 AM
PHARMACOLOGIST