

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022184Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-184
Submission Date	July 2, 2007
Brand Name	TBD
Generic Name	Bimatoprost ophthalmic solution, 0.01%
Primary Reviewer	Sarah Robertson, Pharm.D.
Team Leader	Charles R. Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Allergan
Relevant IND(s) / NDA(s)	IND 48,929, NDA 21,275
Submission Type; Code	Original NDA
Formulation; Strength	0.01% ophthalmic solution
Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

EXECUTIVE SUMMARY

Bimatoprost is a synthetic prostamide that reduces intraocular pressure (IOP) by increasing aqueous humor outflow through the trabecular meshwork and enhancing uveoscleral outflow. LUMIGAN[®] (bimatoprost ophthalmic solution, 0.03%) was approved in March 2001 (NDA 21-275) for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. NDA 22-184 is submitted to support the registration of a new formulation of bimatoprost ophthalmic solution for the same indication. The proposed product contains the same ingredients as the currently approved product, except for a lower bimatoprost concentration (0.01% vs. 0.03%), an increase in the preservative benzalkonium chloride (200 ppm vs. 50 ppm), and a decrease in sodium chloride for isotonicity ([REDACTED] ^{(b) (4)}). The concentrations of the other excipients are identical to those of LUMIGAN[®]. The proposed dosage of the new formulation is the same as that of LUMIGAN[®] -- 1 drop in the affected eye(s) once daily at bedtime.

In preclinical studies an increased concentration of benzalkonium chloride was shown to increase the ocular absorption of bimatoprost. By increasing the benzalkonium chloride content, the Sponsor was able to lower the concentration of bimatoprost while maintaining the same efficacy and improving ocular surface tolerability. Benzalkonium chloride is a [REDACTED] ^{(b) (4)}

[REDACTED] One Phase 2 study (192024-030) and one Phase 3 study (192024-031) were conducted in support of the NDA (Table 1). Both studies demonstrated that bimatoprost 0.01% (with 200 ppm benzalkonium chloride) had no difference in IOP lowering effect and improved ocular safety/tolerability compared to LUMIGAN[®].

Table 1. Summary of Clinical Efficacy and Safety Studies

Study No.	Phase	Population (ITT)	Key Features	Results
192024-030	2	OHT or glaucoma	Bimatoprost 0.01% QD, 0.015% QD, 0.015%(w/ EDTA) QD, 0.02% QD (all with 200 ppm BAK) and LUMIGAN [®] QD Double masked, paired-eye 5-day analysis period	Similar decrease in IOP across all treatment groups 0.01% formulation had lowest AE rate and improved macroscopic conjunctival hyperemia
192024-031	3	OHT or glaucoma	Bimatoprost 0.01% QD, 0.0125% QD (both with 200 ppm BAK) vs. LUMIGAN [®] QD Multi-center, double-masked, 3-arm parallel group 3-month primary analysis period, followed by 9-month masked follow-up period	0.01% formulation was equivalent to LUMIGAN [®] in primary and secondary efficacy endpoints at 3-months. 0.0125% did not achieve equivalent efficacy. 0.01% and 0.0125% had significantly less AEs than LUMIGAN [®]

OHT = Ocular hypertension
BAK = Benzalkonium chloride
IOP = Intraocular pressure

The pharmacokinetics of bimatoprost in humans following the administration of LUMIGAN[®] has been characterized in four PK studies and by sparse PK sampling of patients with glaucoma or ocular hypertension in two Phase 3 studies. The data from these studies were previously submitted with NDA 21-275 (please see Clinical Pharmacology review by Dr. Veneeta Tandon, dated 9/18/2000). No additional clinical pharmacology studies have been conducted with the proposed 0.01% formulation. The Sponsor 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[®]. The systemic exposure of bimatoprost was negligible following the ocular administration of LUMIGAN[®] at the recommended dose to healthy subjects and patients. In healthy subjects, blood concentrations of bimatoprost were below the lower limit of quantitation (0.025 ng/mL) within 1 to 1.5 hours post-dose following 14 days of LUMIGAN[®] 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.

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

FORMULATION

Table 2. Composition of LUMIGAN[®] and Proposed Formulation, Bimatoprost Ophthalmic Solution, 0.01%

Ingredient	Concentration (% w/v)	
	LUMIGAN [®]	Proposed Formulation
Bimatoprost	0.03	0.01
Benzalkonium chloride	0.005	0.02
Dibasic Sodium Phosphate (b) (4)	(b) (4)	(b) (4)
Monohydrate Citric Acid	(b) (4)	(b) (4)
Sodium Chloride (b) (4)	(b) (4)	(b) (4)
(b) (4) Disodium	-	-
Sodium Hydroxide or Hydrochloric Acid	(b) (4)	
Purified Water		(b) (4)

RECOMMENDATION

The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant is acceptable. The request for a waiver of the in vivo bioavailability requirement is granted, based on the expected low systemic exposure of bimatoprost following ophthalmic administration of bimatoprost ophthalmic solution, 0.01%.

There are no recommended changes to the Sponsor's proposed label from Clinical Pharmacology.

PHASE IV COMMITMENTS

No Phase IV commitments are recommended.

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

/s/

Sarah M. Robertson
1/23/2008 02:02:58 PM
BIOPHARMACEUTICS

Charles Bonapace
1/24/2008 09:11:10 AM
BIOPHARMACEUTICS