CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Memo

NDA Number	211911
Submission Date	05/06/2019
Submission Type	505 (b)(1); standard
Brand Name, Drug, Dosage Form and Strength	DURYSTA™ / Bimatoprost SR, intracameral implant containing bimatoprost 10 mcg in the NOVADUR® drug delivery system (DDS®)
Route of Administration	Ophthalmic intracameral administration
Proposed Indication	For the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT)
Applicant	Allergan, Inc
OCP Division	DCP4
OND Division	DTOP
OCP Review Team	Xiaohui (Tracey) Wei, Ph.D.: Clinical Pharmacology Reviewer Philip Colangelo, Pharm. D., Ph.D.: Clinical Pharmacology Team Leader
OCP Final Signatory	Philip Colangelo, Pharm. D., Ph.D.

1. Executive Summary

Allergan Inc. (Applicant) has submitted a 505(b)(1) NDA for DURYSTA™ (referred to by the investigational name as Bimatoprost SR) for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). Bimatoprost SR is a biodegradable, sustained-release, preservative-free bimatoprost implant (using the NOVADUR® drug delivery system [DDS®]) that is preloaded into a single-use applicator for administration into the anterior chamber (AC). The implant is designed to provide (b) (4) sustained release of bimatoprost to the AC of the eye (b) (4) for the reduction of IOP. The biodegradable polymer matrix of Bimatoprost SR slowly degrades so that there is no need to remove the implant once the drug has been released. The drug substance, bimatoprost, was originally developed by Allergan and approved as LUMIGAN® ophthalmic solution (NDA 21-275 and NDA 22-184) for topical administration. Bimatoprost is a synthetic prostamide structurally related to prostaglandin F2α (PGF2α) and has shown ocular hypotensive effect. Bimatoprost SR is proposed for ophthalmic intracameral administration (b) (4) to maintain adequate IOP control, (b) (4). Since Bimatoprost SR is proposed to be administered via intracameral injection locally into the

affected eye, efficacy is not related to systemic exposure of bimatoprost and its metabolites. This review only focuses on evaluating systemic concentrations/exposure of bimatoprost and its metabolites to support the systemic safety of DURYSTA.

Three clinical studies were conducted with Bimatoprost SR including 1 Phase 1/2 dose ranging study (192024-041D) and 2 pivotal Phase 3 registration studies (192024-091 and 192024-092). The systemic pharmacokinetics (PK) of Bimatoprost SR was assessed in Study 192024-041D. In summary, data from patients treated with up to 2 administrations of Bimatoprost SR in Study 192024-041D showed that bimatoprost and bimatoprost acid plasma concentrations were measurable only sporadically, with no correlation to dose strength or generation of implant (Generation 1 or Generation 2). In plasma, concentrations were below the lower limit of quantitation (0.001 to 0.005 ng/mL for bimatoprost and 0.01 to 0.05 ng/mL for bimatoprost acid) in the majority (≥ 91.6%) of the samples. The highest individual bimatoprost plasma concentration observed following administration of Bimatoprost SR 10 µg was 42-fold lower than the mean blood maximum plasma concentration (Cmax 0.08 ng/mL) observed previously following once daily bilateral ocular administration of LUMIGAN 0.03% eyedrops for 14 days in healthy volunteers (LUMIGAN 0.03% label).

2. Recommendations

The Clinical Pharmacology information provided by the Applicant in support of NDA 211911 for DURYSTA™ (Bimatoprost SR) for intracameral administration is acceptable. The Clinical Pharmacology review team recommends approval of this NDA. The Clinical Pharmacology relevant labeling edits are ongoing.

3. Supporting Analyses

Bioanalytical Assay Summary:

Validated liquid chromatography with a tandem mass spectrometric detection (LC-MS/MS) assay was used to determine concentrations of bimatoprost and bimatoprost acid in human plasma. Please refer to Table 1 below for the summary of the analytical method.

Table 1. Summary of Analytical Methods for Quantification of bimatoprost and bimatoprost acid in Human Plasma (Adapted from Summary in the Analytical Method Validation Report AN10039-BM)

Validation Parameters [a]	**Bimatoprost**	**Bimatoprost acid**
Calibration Range	1 pg/mL to 50 pg/mL	10 pg/mL to 500 pg/mL
Inter-run Bias	Low QC (1.5 pg/mL): 0.0% Med QC (7.5 pg/mL): 2.7% High QC (40.0 pg/mL): 2.5%	Low QC (15.0 pg/mL): -4.0% Med QC (75.0 pg/mL): 2.0% High QC (400 pg/mL): -2.0%

Inter-run Precision	Low QC (1.5 pg/mL): 8.0% Med QC (7.5 pg/mL): 6.0% High QC (40.0 pg/mL): 6.3%	Low QC (15.0 pg/mL): 10.4% Med QC (75.0 pg/mL): 5.6% High QC (400 pg/mL): 2.7%
Processed Sample Stability	171 hours at 1 to 8°C	1011 hours at 5°C
Stock Solution Stability	466 days at 1 to 8°C	
Freeze-thaw Stability	3 cycles at -20°C	
Short-term Stability	24 hours at room temperature	
Long-term Stability	1122 days at -20°C	

[a]: The original concentration range validated was 0.5 – 50 pg/mL for bimatoprost and 5 – 500 pg/mL for bimatoprost acid. The LLOQ was raised to 1 pg/mL for bimatoprost and 10 pg/mL for bimatoprost acid to ensure assay ruggedness.

Reviewer's comments: The bioanalytical assay is acceptable.

Individual Study Summary

Systemic Pharmacokinetics in Study 192024-041D

Study title: An Open-label (Stage 1) and Randomized (Stage 2), 24-Month Study of Safety and Efficacy of Bimatoprost Drug Delivery System in Patients With Open-Angle Glaucoma or Ocular Hypertension

Study design: Study 192024-041D evaluated the safety and efficacy of 4 dose strengths of Bimatoprost SR (6, 10, 15, or 20 µg [2 ×10 µg implants]) in 1 eye versus the daily use of topical LUMIGAN 0.03% eyedrops in the fellow eye (non-study eye). Two implant formulations of Bimatoprost SR were used in this clinical study: Generation 1 and Generation 2 (used for pivotal Phase 3 studies and for initial registration). Patients implanted with ≤ 15 µg dose strength Generation 2 implants were eligible to receive a second administration of the same dose strength of Generation 2 Bimatoprost SR after a minimum of 90 days and up to 12 months following the first administration if they had not already received rescue medication in either eye, and the study eye met re-administration requirements. A total of 109 patients received at least 1 implant of Bimatoprost SR: 34 patients received a Generation 1 implant and 75 patients received a Generation 2 implant. A total of 24 patients received repeat administration of Generation 2 Bimatoprost SR (6, 10, and 15 µg dose groups). Blood samples for PK evaluation were collected from a total of 107 patients receiving at least 1 administration of Bimatoprost SR. Blood samples were collected at baseline; Weeks 4, 8, 12, 16, and 20; and Months 6, 12, and 24/Early Exit.

PK results: Of the 653 samples with reportable bimatoprost concentrations, only 8.4% (55/653) had measurable plasma concentrations while the remaining 91.6% (598/653) were below the LLOQ (< 0.001 to 0.005 ng/mL). The highest plasma concentration of bimatoprost observed after a single implant administration was 0.00502 ng/mL (15 µg Generation 2 implant). No

patient had measurable bimatoprost concentrations following repeat administration of Bimatoprost SR. Because of the use of LUMIGAN in the fellow eye, blood samples were collected the morning after the daily topical dose that was administered the prior evening. All drug from the LUMIGAN dose was expected to have been cleared from the systemic circulation within approximately 3 hours (LUMIGAN 0.03% label; Study 192024-006 Report PK-98-119).

Of the 659 samples with reportable bimatoprost acid concentrations, only 1.1% (7/659) had detectable plasma concentrations, while the remaining 98.9% (652/659) were below the LLOQ (< 0.01 to 0.05 ng/mL). Those patients with measurable bimatoprost acid plasma concentrations were all treated with Generation 2 implants, and the concentrations of bimatoprost acid ranged from 0.0105 to 0.0245 ng/mL. Two patients had measurable bimatoprost acid plasma concentrations at baseline. These concentrations were near the lower limit of detection and likely represent variability in the assay. No patient had measurable bimatoprost acid concentrations following repeat administration of Bimatoprost SR.

Reviewer's Comments:

- *The reviewer agrees with the Applicant's conclusion / interpretation of the PK results from this study.*
- *The Applicant provided a LLOQ range of 0.001 to 0.005 ng/mL and 0.01 to 0.05 ng/mL, for bimatoprost and bimatoprost acid, respectively. According to the bioanalytical method validation report AN10039-BM and report of Study 192024-041D, LLOQ is 0.001 and 0.01 ng/mL for bimatoprost and bimatoprost acid, respectively, for most samples (> 99%) from study 192024-041D; LLOQ was reported to be 0.005 and 0.05 ng/mL for bimatoprost and bimatoprost acid, respectively, from LUMIGAN 0.03% Study 192024-006 (Report PK-98-119). Therefore, it is more appropriate to report LLOQ of bimatoprost and bimatoprost acid to be 0.001 ng/mL and 0.01 ng/mL, respectively, for Bimatoprost SR from study 192024-041D.*

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/s/

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