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APPLICATION NUMBER:

21-994

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

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA#	21-994
PRODUCT	Travoprost (TRAVATAN® Z/AP/AF; TBD)
FORMULATION	Ophthalmic solution, 0.004%, benzalkonium chloride (BAC) free formulation
SUBMISSION DATE(S)	18NOV2005
SUBMISSION TYPE	505(b)(2) application
SPONSOR	Alcon Research, Ltd.
OCPB DIVISION	DCP4
OND DIVISION	DAIOP
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1. EXECUTIVE SUMMARY

Travoprost is the isopropyl ester prodrug of a potent and selective FP prostaglandin receptor agonist. It is in the pharmacological class of PGF_{2α} agonists that includes the IOP-lowering agents latanoprost and bimatoprost, marketed in the United States as XALATAN® and LUMIGAN®, respectively. Prostaglandin analogues are believed to lower intraocular pressure by increasing the outflow of aqueous humor via trabecular meshwork and uveoscleral pathways.

TRAVATAN® BAC-free is an ophthalmic solution composed of travoprost (AL-6221) at a concentration of 0.004%. This is the same active ingredient and at the same concentration as in TRAVATAN® (NDA 21-257), which was approved by the FDA in March 2001. Unlike

TRAVATAN, which contains 0.015% benzalkonium chloride (BAC) as a preservative, TRAVATAN BAC-free is preserved in the bottle with a buffered ionic system. TRAVATAN BAC-free is proposed to be marketed as an alternate formulation to TRAVATAN.

The proposed dosage and indication for TRAVATAN BAC-free is the same as that approved for TRAVATAN: once-daily topical ocular therapy for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

The current submission for TRAVATAN BAC-free is a 505b(2) NDA and is based on the previously approved NDA for TRAVATAN, which included two Phase II pivotal clinical trials, dose-response studies, an adjunctive-use study, and clinical pharmacology and pharmacokinetic studies. The clinical development plan for TRAVATAN® BAC-free ophthalmic solution included one Phase III safety and efficacy study (C-04-17) designed to demonstrate therapeutic bioequivalence of the BAC-free formulation of travoprost ophthalmic solution, 0.004% to the marketed formulation of travoprost ophthalmic solution, 0.004% (TRAVATAN), both dosed once-daily in the evening in patients with open-angle glaucoma or ocular hypertension. The Sponsor's request for a waiver from the requirements for submission of in vivo pharmacokinetic bioavailability/ bioequivalence data is acceptable based on the consideration that the differences in formulation between TRAVATAN and TRAVATAN BAC-free formulations are not expected to influence the limited systemic availability of travoprost, and the therapeutic bioequivalence established in Alcon Study C-04-17.

1.1. Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant is acceptable.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The active component of TRAVATAN BAC-free, travoprost, is an approved therapeutic agent for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The clinical pharmacology, safety, and efficacy of travoprost have been established in NDA 21-257 [TRAVATAN (travoprost ophthalmic solution), 0.004%]. The current NDA for TRAVATAN® BAC-free ophthalmic solution included one Phase III safety and efficacy study (C-04-17) designed to demonstrate therapeutic bioequivalence of the BAC-free formulation of travoprost ophthalmic solution, 0.004% to the marketed formulation of travoprost ophthalmic solution, 0.004% (TRAVATAN), with both dosed once-daily in the evening in patients with open-angle glaucoma or ocular hypertension. The concentration of travoprost in TRAVATAN BAC-free formulation is the same as that of the previously approved and marketed product TRAVATAN. Alterations in formulation were made to TRAVATAN to develop a formulation that meets USP preservation criteria and does not contain a conventional preservative, specifically BAC.

The Sponsor has not performed any clinical pharmacology assessments of TRAVATAN BAC-free Ophthalmic Solution, as differences between TRAVATAN and TRAVATAN BAC-free formulations are not expected to influence the systemic availability of travoprost. During development of TRAVATAN, the Sponsor conducted 4 Phase I trials to fully characterize the steady-state plasma pharmacokinetics of travoprost (AL-6221) and AL-5848 (the active acid metabolite of travoprost) in healthy Caucasian (C-99-08) and male Japanese (C-00-15) subjects, as well as in patients with renal (C-99-97) or hepatic (C-00-05) impairment. In addition, the Sponsor conducted a pharmacokinetic and drug-drug interaction trial with TRAVATAN, travoprost 0.004%/timolol 0.5% ophthalmic solution and timolol 0.5% ophthalmic solution (C-02-35). For additional information on the clinical pharmacology of TRAVATAN and detailed assessments of these Phase I studies, please refer to the Clinical Pharmacology and Biopharmaceutics reviews under NDA 21-257 (original submissions dated 07JUL2000, 26DEC2000, and 28JUN2002) and NDA 21-699 (original submission dated 13NOV2003).

From a Clinical Pharmacology perspective, the requirements for submission of in vivo pharmacokinetic bioavailability/bioequivalence data can be waived based on:

- 1) consideration that the alterations between TRAVATAN and TRAVATAN BAC-free formulations are minor and not expected to significantly influence the limited systemic exposure of travoprost that was observed with the original approved formulation, and
- 2) therapeutic bioequivalence established in the safety and efficacy study of TRAVATAN BAC-free Ophthalmic Solution versus TRAVATAN Ophthalmic Solution (Alcon Study C-04-17).

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2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

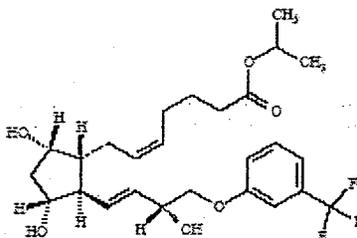
Since this submission is a 505b(2) NDA with changes in preservative to the approved formulation, only relevant questions from the OCP question-based review (QBR) format are addressed below.

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

Travoprost, the active ingredient in TRAVATAN® BAC-free, has been previously approved in Alcon's NDA 21-257 for TRAVATAN® (travoprost ophthalmic solution) 0.004%. The chemical structure and physical-chemical properties of travoprost are shown below:

Structural Formula: C₂₆H₃₅F₃O₆

Chemical Structure:



Chemical Names:

1. [1R-[1 α (Z),2 β (1E,3R*),3 α ,5 α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester
2. (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(α , α , α -trifluoro-m-isopropyltolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate

Relative Molecular Mass: 500.55

The physical and chemical properties of travoprost are described in NDA 21-257 for TRAVATAN [Volume 2; Section 4.A.1 (Drug Substance)].

2.1.2. *What is the proposed mechanism of drug action and therapeutic indication?*

Travoprost is the isopropyl ester prodrug of a potent and selective FP prostaglandin receptor agonist. It is in the pharmacological class of PGF_{2 α} agonists that includes the IOP-lowering agents latanoprost and bimatoprost, marketed in the United States as XALATAN® and LUMIGAN®, respectively. Prostaglandin analogues are believed to lower intraocular pressure by increasing the outflow of aqueous humor via trabecular meshwork and uveoscleral pathways.

The proposed indication for TRAVATAN BAC-free is the same as that approved for TRAVATAN: once-daily topical ocular therapy for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

2.1.3. *What is the proposed dosage and route of administration?*

The proposed dosage for TRAVATAN BAC-free is the same as that approved for TRAVATAN: the recommended dosage is one drop in the affected eye(s) once-daily in the evening. The dosage of TRAVATAN® Z ophthalmic solution should not exceed once-daily since it has been shown that more frequent administration of travoprost may decrease the intraocular pressure lowering effect. Reduction of intraocular pressure starts approximately 2 hours after administration of travoprost. The maximum effect is observed 12 hours after administration and is maintained throughout the day.

2.2. General Biopharmaceutics

TRAVATAN BAC-free (travoprost ophthalmic solution) 0.004% (i.e., TRAVATAN BAC-free) is a sterile, preserved aqueous solution formulated for topical ophthalmic application. The formulation contains 0.004% travoprost, which is the same concentration approved in TRAVATAN (travoprost ophthalmic solution) 0.004% (NDA 21-257). TRAVATAN BAC-free is formulated such that it does not contain the quaternary ammonium compound benzalkonium chloride and preservative aid disodium edetate that are present in TRAVATAN.

The quantitative composition of the proposed product is shown in the following table (Table 2.2-1):

Table 2.2-1 Composition of TRAVATAN BAC-free Ophthalmic Solution

Component	Percent W/V	Compendial Designation	Purpose
Travoprost (AL06221)	0.004 ^a	Non-compendial	Active
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)		JPE	
Propylene Glycol		Alternate: Alcon Global Monograph	
Boric Acid		USP	
Sorbitol		NF	
Zinc Chloride		NF	
Sodium Hydroxide and/or Hydrochloric Acid		USP	
Purified Water		NF	
		USP	

^a Adjust to — based on purity of the raw material.

^b The combination of — provide the — capacity. Preservation of the drug product in the container is achieved by the —

2.2.1. What data support or do not support a waiver of in vivo BE data?

The Sponsor requested a waiver from the requirements for submission of in vivo pharmacokinetic bioavailability/bioequivalence data. This request is supported by the following rationale:

1. The drug product is an ophthalmic solution applied topically to the eye and is intended only for local therapeutic effect. The drug product contains the same active ingredient, travoprost, in the same concentration, 0.004% that is the basis of an approved full New Drug Application, 21-257 [TRAVATAN (travoprost ophthalmic solution) 0.004%]. Differences between TRAVATAN and TRAVATAN BAC-free formulations are not expected to influence the systemic availability of travoprost.
2. Bioequivalence was established in an vivo therapeutic bioequivalence study of TRAVATAN BAC-free Ophthalmic Solution versus TRAVATAN (Alcon study C-04-17) designed to compare the IOP-lowering efficacy of TRAVATAN BAC-free Ophthalmic Solution (dosed once-daily) to TRAVATAN (dosed once-daily) using an accepted criterion of clinical relevance, 1.5 mmHg.

2.2.1.1. Comparative Composition in Support of a Waiver of In Vivo BE Data

The comparative composition of the proposed product TRAVATAN BAC-free and the previously approved formulation TRAVATAN is shown in the following table (Table 2.2.1-1):

Table 2.2.1-1 Comparative Composition of TRAVATAN BAC-free and TRAVATAN Ophthalmic Solutions (W/V%)

Component	TRAVATAN® BAC-free	TRAVATAN®
Travoprost (AL06221)	0.004	0.004
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)		
Tromethamine		
Propylene Glycol		
Boric Acid		
Sorbitol		
Mannitol		
Edetate disodium		
Benzalkonium chloride (BAC)		
Zinc Chloride		
Sodium Hydroxide and/or Hydrochloric Acid		
Purified Water		

The concentration of travoprost (the active ingredient) in TRAVATAN BAC-free formulation is the same as that of the previously approved and marketed product TRAVATAN. Alterations in formulation were made to TRAVATAN to develop a formulation that meets USP preservation criteria and does not contain a conventional preservative, specifically BAC. In addition, the formulation was modified to remove EDTA and mannitol, and to include propylene glycol, zinc chloride and sorbitol. Also, ~~similar to TRAVATAN, this formulation contains~~ polyoxyl 40 hydrogenated castor oil for

Although differences between the composition of TRAVATAN BAC-free and TRAVATAN may alter the ocular penetration of travoprost, the differences in excipients are not expected to influence the limited systemic availability of travoprost that was observed with the original approved formulation. This assessment is further supported by the safety and efficacy findings from Alcon Study C-04-17.

2.2.1.2. In Vivo Therapeutic Bioequivalence Study in Support of a Waiver of In Vivo BE Data

The Sponsor has conducted an in vivo therapeutic bioequivalence study of TRAVATAN BAC-free Ophthalmic Solution versus TRAVATAN (Alcon Study C-04-17) to compare the IOP-lowering efficacy of the two formulations (dosed once-daily in the evening). This study was designed as an equivalence trial with statistical power to demonstrate equivalence in IOP lowering efficacy between TRAVATAN BAC-free and TRAVATAN using an accepted criterion of clinical relevance, 1.5 mmHg. This multicenter, randomized, double-masked, parallel group, active-controlled study enrolled 690 patients with open-angle glaucoma or ocular hypertension, age 18 years or older, which included a total of 344 patients exposed to once daily TRAVATAN BAC-free for a duration of 3 months. Efficacy and safety data were collected at Week 2, Week 6, and Month 3. IOP was assessed at 8 AM, 10 AM, and 4 PM at all study visits. All enrolled patients were followed for up to three months.

Efficacy results from Alcon Study C-04-17 indicated that the 95% confidence limits for differences in mean IOP were <1.5 mmHg, demonstrating that TRAVATAN BAC-free is equivalent to TRAVATAN in IOP-lowering efficacy. Differences in mean IOP between TRAVATAN BAC-free and TRAVATAN ranged from -0.3 to $+0.2$ mmHg in both the per protocol and intent-to-treat analyses. There were no statistically significant differences in mean IOP at baseline between treatment groups. Mean IOP reductions in the per protocol and intent-to-treat analyses ranged from 7.3 to 8.5 mmHg for TRAVATAN BAC-free and from 7.4 to 8.4 mmHg for TRAVATAN. The maximum mean IOP reductions for TRAVATAN BAC-free (8.5 mmHg) and TRAVATAN (8.4 mmHg) correspond to approximate 31% IOP reductions in each group. Confidence limits for the treatment group differences were within ± 0.8 mmHg at 9 of 9 study visits and times in both the per protocol and intent-to-treat analyses.

Safety data from Alcon Study C-04-17 demonstrated a similar safety profile comparing therapy with TRAVATAN BAC-free to TRAVATAN based upon a review of adverse events and an assessment of ocular safety parameters. In both the TRAVATAN BAC-free and the TRAVATAN treatment groups, the most frequently reported, treatment-related adverse event was ocular hyperemia, occurring at incidences of 6.1% and 9.0%, respectively. A comparison of the adverse events observed with TRAVATAN BAC-free to those observed with TRAVATAN revealed no unexpected types of events.

Overall, efficacy and safety findings from Alcon Study C-04-17 indicate that the two formulations are therapeutically bioequivalent. For a detailed assessment of safety and efficacy results from Study C-04-17, please refer to the Clinical review of the NDA.

In summary, from a Clinical Pharmacology perspective, a waiver from the requirements for submission of in vivo pharmacokinetic bioavailability/bioequivalence data is acceptable based on:

- 1) consideration that the alterations in formulation between TRAVATAN and TRAVATAN

BAC-free formulations are not expected to influence the limited systemic availability of travoprost, and 2) therapeutic bioequivalence established in the safety and efficacy study of TRAVATAN BAC-free Ophthalmic Solution versus TRAVATAN Ophthalmic Solution (Alcon Study C-04-17).

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4. APPENDICES

For additional information on the clinical pharmacology of TRAVATAN, please refer to the Clinical Pharmacology and Biopharmaceutics reviews of submissions under NDA 21-257 (original submissions dated 07JUL2000, 26DEC2000, and 28JUN2002) and NDA 21-699 (original submission dated 13NOV2003).

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