CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	202-514
Submission Date(s):	January 7, 2011
Proposed Brand Name	TBD
Generic Name	Tafluprost
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DTOP
Applicant	MERCK & CO., Inc.
Relevant IND(s)	062690
Submission Type; Code	1S(NME)
Formulation; Strength(s)	Tafluprost 0.0015% Ophthalmic Solution
Indication	For the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
Dosage and Administration	One drop of Tafluprost 0.0015% ophthalmic solution in the conjunctival sac of the affected eye(s) once daily in the evening

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1. EXECUTIVE SUMMARY

Tafluprost (AFP-168, MK-2452) is an ester prodrug of a new synthetic prostaglandin F2α (PGF2α) analogue selective for the FP prostanoid receptor. Converting in vivo into the pharmacologically active tafluprost acid (AFP-172), tafluprost is a new chemical entity drug product developed for the reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension. The proposed product, Tafluprost 0.0015% ophthalmic solution (one eye drop once daily), does not contain any preservative agents, such as benzalkonium chloride, which is commonly used in the approved prostaglandin analogues (e.g., Xalatan®, Travatan®, and Lumigan®) for glaucoma treatment and believed to cause potential toxicity due to chronic use. Tafluprost 0.0015% preservative free (PF) and preservative containing (PC) have been approved for reducing of elevated IOP in open angle glaucoma and ocular hypertension in many countries other than the United States.

In support of the NDA, the Applicant submitted clinical studies including:

- Six Phase 1 dose-escalation studies (Studies 74450, 74451, 74452, 74453, 15005, and 77551) to assess the systemic exposure and tolerability of tafluprost ophthalmic solution in healthy subjects.

- Two Phase 2 dose-ranging studies in patients (Studies P15001 and P15002) to support the selection of tafluprost 0.0015% for further development.

- Five Phase 3 studies in patients to assess the efficacy, safety and tolerability of tafluprost for the treatment of glaucoma, including a comparison to latanoprost (Study 74458 [Latanoprost Non-Inferiority Study]), a comparison to timolol (Studies 15003 [Preservative-containing (PC) Tafluprost vs. PC Timolol Non-Inferiority Study] and 001 [Preservative-free (PF) Tafluprost vs. PF Timolol Non-Inferiority Study]), a study examining tafluprost as adjunctive treatment with timolol (Study 74460 [(Adjunctive Treatment to Timolol]), and a bridging study comparing PC and PF formulations of tafluprost (Study 77550 [PF/PC Comparison Study]).

- In addition, an open-label Phase 3b clinical study (77552 [Open label PF tafluprost /latanoprost switch study]) to investigate changes in ocular signs and symptoms when patients were switched from preservative-containing latanoprost to PF tafluprost.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable.

The reviewer's proposed label changes in *Appendix 4.1* will be forwarded to the sponsor.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Tafluprost is an ester prodrug of tafluprost acid, which is further metabolized in vivo via fatty acid β-oxidation and phase II conjugation. The binding of tafluprost acid to human serum albumin (4%) was >99%. Tafluprost acid is not metabolized by major human CYP450 enzymes. It is unknown if tafluprost or tafluprost acid inhibits or induces any CYP450 enzymes. However, given the low systemic exposure (the systemic C_{max} is about $1/9^{th}$ of EC_{50} value) to tafluprost acid following topical ocular administration of tafluprost 0.0015% ophthalmic solution, clinically relevant interactions based on inhibition of CYP450 enzymes are not to be expected for tafluprost and concomitantly administered drugs.

IOP reduction starts about 2 to 4 hours after topical ocular administration and the maximal effect is reached by 12 hours post instillation. The duration of action for tafluprost was greater than 24 hours, which is consistent with the data obtained on other prostaglandin analogues.

Following topical instillation, tafluprost is absorbed through the cornea and is hydrolyzed to the biologically active tafluprost acid (EC_{50} to the recombinant human FP prostanoid receptor = 217 pg/mL, or 0.5 nM). Following 8-day q.d. administration of tafluprost 0.0015% Preservative-free (PF) ophthalmic solution, mean plasma tafluprost acid C_{max} values were 26 pg/mL and 27 pg/mL on Day 1 and Day 8, respectively; mean plasma tafluprost acid AUC values were 394 pg*min/mL and 432 pg*min/mL on Days 1 and 8, respectively (Study 77551). Mean plasma concentrations of tafluprost acid were below the limit of quantification (10 pg/mL) at 30 minutes. Pharmacokinetic parameters (AUC and C_{max}) of the preservative-containing (PC) and PF formulations of tafluprost were comparable.

The effect of the commonly known intrinsic (e.g., renal impairment, hepatic impairment, age gender) and extrinsic (e.g., drug-drug interactions) factors on the PK of tafluprost following topical administration of tafluprost 0.0015% ophthalmic solution has not been studied. Given the low systemic exposure following topical administration, however, dose adjustment is not warranted in patients based on the commonly known intrinsic or extrinsic factors.

2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

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?

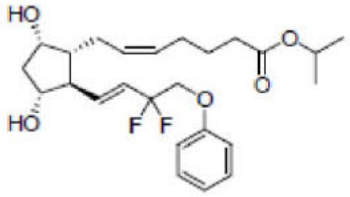
Tafluprost is a colorless to light yellow viscous liquid. It is practically insoluble in water, very soluble in ethanol, diethyl ether, and acetonitrile, sparingly soluble in a mixed solution of phosphate buffer/acetonitrile (1:1).

Structural Formula: $C_{25}H_{34}F_2O_5$

Molecular Weight: 452.53 Dalton

CAS Index Name: 1-methylethyl (5Z)-7-{(1R, 2R, 3R, 5S)-2-[(1E)-3,3-difluoro-4- phenoxy- 1-butenyl]-3,5-dihydroxycyclopentyl}-5-heptenoate

Chemical Structure:



Drug Product:
The drug product, Tafluprost 0.0015% eye drops, is formulated as a sterile, isotonic ophthalmic solution using common excipients and filled (b) (4) into single-dose containers. The solution is clear and colorless with pH of 6.0. The single-dose formulation does not contain benzalkonium chloride (BAC), and the amount of polysorbate 80 is (b) (4). Formulations with preservative BAC, in multidose containers containing 1 to 50 µg/ml tafluprost, were used in most of the clinical studies. **(Table 2.1.1-1)**

Table 2.1.1-1: Composition of the drug product in single-dose and multidose containers

Drug substance	Tafluprost 15 microg/ml eye drops in single-dose container (mg/ml)	Tafluprost 15 microg/ml eye drops in multidose container (mg/ml)
Tafluprost	0.015	0.015
Excipients		
Glycerol	(b) (4)	(b) (4)
Sodium dihydrogen phosphate dihydrate		
Disodium edetate		
(b) (4)		
Polysorbate 80		
Sodium hydroxide and/or Hydrochloric acid		
(b) (4) water (b) (4)		

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