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APPLICATION NUMBER:

202667Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 202-667	Submission Date(s): 2/16/2011
Drug	Dorzolamide hydrochloride and timolol maleate (preservative free)
Trade Name	COSOPT PF
OCP Reviewers	Ryan P. Owen, Ph.D.
OCP Team Leader	Phil Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND division	DTOP
Sponsor	Merck Sharp and Dohme Corp
Relevant IND(s)	IND 52,080
Formulation; Strength(s)	COSPOT PF is an ophthalmic solution containing dorzolamide hydrochloride 2.0% and timolol maleate 0.5% supplied in a foil pouch containing 15 low density polyethylene 0.2 mL single-use containers
Indication	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers
Dosage and Administration	Instill one drop of COSPOT PF in the affected eye(s) two times daily

1. EXECUTIVE SUMMARY

COSOPT PF (2.0% dorzolamide hydrochloride and 0.5% timolol maleate) is nearly identical to a previously marketed product (COSOPT, NDA 20-869 approved 4/7/98) with the only difference being the removal of the preservative benzalkonium chloride. The Sponsor has requested a waiver of the requirement for the submission of in vivo bioavailability data on the grounds that there is no strong empirical evidence to expect that removal of the preservative would alter bioavailability. Accordingly, no clinical pharmacology studies of the COSOPT PF formulation were conducted, and no pharmacokinetic samples were obtained in the Phase 3 trial conducted in support of this NDA.

The Reviewer concurs with the Sponsor's request for a waiver of the in vivo bioavailability requirement. The clinical pharmacology program conducted for the approval of the original COSOPT product is sufficient for the approval of the COSOPT PF product.

1.1 Recommendation

The Office of Clinical Pharmacology Division 4 has reviewed NDA 202-667, and it is acceptable from a Clinical Pharmacology perspective.

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Ryan P. Owen, Ph.D.
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

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Concurrence: Phil Colangelo, Pharm.D., Ph.D.
Team Leader

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/s/

RYAN P OWEN
05/27/2011

PHILIP M COLANGELO
05/31/2011

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA:	202-667
Drug Name:	COSOPT PF (Dorzolamide hydrochloride and timolol maleate ophthalmic solution)
Applicant:	Merck Sharp & Dohme Corp.
Submission Date:	February 16, 2011
Filing Date:	April 17, 2011
PDUFA Date:	December 16, 2011
OCP Primary Reviewer:	Ryan P. Owen Ph.D.
OCP Team Leader:	Kimberly Bergman Pharm.D.

QUESTION	***YES***	***NO***	***NA***	***COMMENTS***
Fileability: ***Is the Clinical Pharmacology section of the application fileable?*** ***(if 'NO', please comment as to why it is not fileable)***	***YES***			
Fileability Review Components				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	☐	☐	☒	See additional comment below.
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	☐	☐	☒	No clinical pharmacology studies of PF (preservative-free) dorzolamide/timolol were conducted/submitted.
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	☐	☐	☒	A single, three month Phase 3 study (Protocol 081) was conducted to compare the ocular hypotensive effect and safety profile of PF versus PC (preservative-containing) dorzolamide/timolol. *It is not clear from the submission if the to-be-marketed formulation (COSOPT PF) was studied in Protocol 081.*
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	☐	☐	☒	The marketed product was used as the active control in Protocol 081.
5. Are complete and relevant bioanalytical reports included in the NDA submission?	☐	☐	☒	
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	☒	☐	☐	The proposed formulation is identical to the previously-approved dorzolamide hydrochloride and timolol maleate ophthalmic solution (COSOPT®) formulation, but without the benzalkonium chloride preservative. A waiver is applicable; the applicant contends there is no strong empirical evidence to

				expect that removal of the preservative would alter bioavailability.
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	☐	☐	☒	
Additional comments: For clinical pharmacology information for dorzolamide hydrochloride/timolol maleate, reference is made to the following NDAs previously approved by the FDA: 1. NDA 18,086, TIMOPTIC™, Timolol Maleate (Approval date: August 17, 1978). 2. NDA 20,408, TRUSOPT™, Dorzolamide Hydrochloride (Approval date: December 9, 1994). 3. NDA 20,869, COSOPT™, Dorzolamide Hydrochloride/Timolol Maleate combination (Approval date: April 7, 1998).				

OCP Primary Reviewer — Date

OCP Team Leader — Date

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/s/

RYAN P OWEN
03/25/2011

KIMBERLY L BERGMAN
03/25/2011