CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202667Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action #2

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products[1]
Subject	Division Director Summary Review
NDA Number	NDA 202667
Related IND **Related NDAs**	IND 52080 for COSOPT NDA 20869 for COSOPT NDA 18086 for Timoptic (timolol maleate) NDA 20408 for Trusopt (dorzolamide HCl)
Applicant Name	Merck Sharp & Dohme Corp.
Date of Submission **Date of Receipt**	February 16, 2011 February 16, 2011
Complete Response Letter	December 16, 2011
Date of Resubmission	January 24, 2012
PDUFA Goal Date	March 24, 2012
Proprietary Name / **Established (USAN) Name**	COSOPT PF dorzolamide hydrochloride -timolol maleate ophthalmic solution, 2% / 0.5%
Formulation **Dose**	Topical ophthalmic solution, 2% / 0.5% one drop two times daily
Proposed Indication(s)	reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone
Action for Application	*Approval*

Material Reviewed/Consulted for the resubmission	**Names of discipline reviewers**
Labeling Review	Rhea Lloyd, Bill Boyd, Wiley Chambers 1/27/2012
Chemistry Review	George Lunn, Rapti Madurawe 1/30/2012
CDTL Review	Bill Boyd, 1/31/2012
Deputy Director Review	Wiley Chambers, 1/31/2012
DMEPA proprietary name	Karen Townsend 1/25/2012

[1] The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

Table of Contents:

1. Summary and Recommendations

COSOPT PF is a combination product containing the same active ingredients as the currently marketed COSOPT; the difference between these two products is that the COSOPT PF (preservative-free) formulation does not contain 0.0075% benzalkonium chloride as a preservative. The application was issued a Complete Response letter on December 16, 2011, with the following deficiencies:

- Per 21 CFR 314.125 (a)(8) , the drug product's proposed labeling does not comply with the requirements for labels and labeling in part 201. Specifically, we recommend that you submit draft labeling which is consistent with the package insert, patient package insert, carton and container labeling attached to this letter.

- In addition, there is ambiguity in the terminology of the drug product specifications. To correct this ambiguity, as part of the drug product specifications, please revise the test currently identified as "Any unspecified degradate" to read "Any unspecified impurity."

The applicant responded to these deficiencies on January 24, 2012, and based on review of the information provided, which is summarized below, the application will be approved.

For complete details of the data and information reviewed during the first and second review cycles, the Action package, including primary and secondary reviews should be consulted.

1.1 Deficiencies
None (outstanding labeling and chemistry terminology were resolved with this resubmission)

1.2 Post-Marketing Studies:
None

1.3 Other Issues
None

2. Background

Merck Sharp & Dohme Corp. (Merck) submitted NDA 202667 for COSOPT® PF (preservative-free) ophthalmic solution on February 16, 2011. The product is a combination of dorzolamide hydrochloride 2% and timolol maleate 0.5%, and the same as the currently marketed COSOPT® (NDA 20869 approved April 7, 1998) with the exception of the omission of the preservative, benzalkonium chloride. The proposed indication is the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers. The application is supported by the results of one double-blind, controlled clinical trial done at one center where preservative-free product compared to the preservative containing product. The study was done under Protocol 081 and

completed in 1997. Merck also relied on studies from its other NDAs for the individual component products and the combination COSOPT product.

3. CMC/Product Quality Microbiology

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The January 24, 2012, submission contains the proposed response to the

- In addition, there is ambiguity in the terminology of the drug product specifications. To correct this ambiguity, as part of the drug product specifications, please revise the test currently identified as "Any unspecified degradate" to read "Any unspecified impurity."

Merck submitted an update to section 3.2.P.5.1 Specification(s) to replace the phrase "Any Unspecified Degradate" with "Any Unspecified Impurity," as requested by the Division. Dr. Lunn's review notes that this is acceptable.

Comment:
The application is recommended for approval from the CMC perspective given that the facilities were considered acceptable on December 16, 2011 (until that date the Office of Compliance recommended "withhold.") Merck updated the terminology to Any Unspecified Impurity instead of Any Unspecified Degradate as requested by the Division, to avoid ambiguity and be consistent with terminology in other Merck applications (e.g., tafluprost). I agree with the recommendations from ONDQA for the unspecified impurity limit of (b) (4) *based on their justification, and the CMC recommendation of approval.*

4. Nonclinical Pharmacology/Toxicology

No new information submitted

5. Clinical Pharmacology/Biopharmaceutics

No new information submitted

6. Clinical Microbiology/Immunology

N/A

7. Clinical/Statistical-Efficacy

No new information submitted

8. Safety

No new information submitted

9. Advisory Committee Meeting

N/A

10. Pediatrics

The application does not trigger PREA, because it does not contain a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

No new information submitted

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA, OPDP/DPP and OBP. Dr. Lloyd's review of the Package insert, Patient package insert and Carton and container submitted on January 24, 2012, notes that the applicant has made all labeling revisions requested by the Division and the labeling is acceptable.

- **Package insert (PI):** The PI is written in PLR format. Preliminary format and content comments were reviewed by Leanna Kelly and Maureen-Dillon Parker. DMEPA and OPDP provided labeling recommendations that have been addressed. Labeling has been sent to Merck.

- **Patient package insert (PPI):** The PPI is submitted for this product. The marketed COSOPT (preservative-containing) product has an approved patient package insert. The PPI will be consulted to Office of Medical Policy, per recent procedure change.

- **Carton and Container Labels**: The labels have been reviewed by ONDQA and DMEPA. Requested edits have been communication to Merck.

  Merck has submitted a carton label intended for commercial distribution with 60 single-use containers (4 pouches x 15 single-use containers) and a physician sample containing 30 single-use containers (2 pouches x 15 single-use containers)

- **Proprietary Name**: DMEPA concluded that the proposed proprietary name COSOPT PF was not vulnerable to name confusion and was not found to be promotional in their review of May 13, 2011. A letter stating that the name is acceptable was issued by Dr. Holquist of DMEPA on May 16, 2011, and the pre-action review summarizing these recommendations was finalized October 14, 2011. A follow up email was sent on January 25, 2012, that the name need not be re-reviewed given it's close to the 90-day pre-review.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

With this resubmission to a *Complete Response* letter, the applicant submitted labeling and clarified chemistry terminology. The information was reviewed and found acceptable. An *Approval* letter will be issued.

13.2 Risk Benefit Assessment

The safety and efficacy of preservative-free Cosopt PF was evaluated in one controlled clinical trial comparing the PC and PF formulation of Cosopt, and is supported by information from the approved preservative-containing Cosopt application, as well as safety and efficacy data for the individual components, dorzolamide and timolol. Merck either owns or has right of reference to all these applications.

Labeling has been written in PLR format and summarizes the efficacy and safety of the product. Although companies seek to claim that (b) (4)

The product is packaged in single-use containers with instructions to patients on proper use, including using immediately after opening and discarding remaining contents.

The patient package insert has been reviewed by OMP and is acceptable.

The application will be approved.

13.3 Recommendation for other Postmarketing Requirements and Commitments

N/A

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/s/

RENATA ALBRECHT
01/31/2012