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RESEARCH**

APPLICATION NUMBER:
202667Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review of NDA 202667 Review #2

Date	January 30, 2012
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	202667
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	January 24, 2012
PDUFA Goal Date	March 24, 2012
Type of Application	505(b)(1)
Name	Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone
Recommended:	Recommended for Approval

1. Introduction

NDA 202667 received a Complete Response Letter dated December 16, 2011, which cited 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 January 24, 2012, submission by Merck constitutes a Complete Response.

2. CMC

The regulatory specifications for Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% should include a limit on the unspecified impurities that are not necessarily related to dorzolamide or timolol. These impurities may come from the bottle components, packaging or labeling. The regulatory specification for unspecified impurities should be no more than (b)(4) of the timolol concentration.

In a telephone conversation on December 16, 2011, Merck agreed to amend the specifications.

Table 1

Specification for Dorzolamide Hydrochloride (+) Timolol Maleate Preservative Free
Ophthalmic Solution

Tests	Acceptance Criteria	Test Methods
Appearance (Release and Shelf life)	Clear, colorless to nearly colorless, slightly viscous solution which is practically free from particles.	Visual Sec. 3.2.P.5.2.1
Identity (Release) Dorzolamide Hydrochloride	HPLC [†] - The chromatogram of the sample solution exhibits a peak with essentially the same retention time as the standard reference material. TLC [†] - The R _f value of the spot from the sample preparation corresponds to that obtained from the standard preparation.	HPLC: Sec. 3.2.P.5.2.6 TLC: Sec. 3.2.P.5.2.2
Identity (Release) Timolol Maleate	HPLC [†] - The chromatogram of the sample solution exhibits a peak with essentially the same retention time as the standard reference material. TLC [†] - The R _f value of the spot from the sample preparation corresponds to that obtained from the standard preparation.	HPLC: Sec. 3.2.P.5.2.9 TLC: Sec. 3.2.P.5.2.2
Viscosity	(Release): (b) (4) centipoise (mPa.s) (Shelf Life): (b) (4) centipoise (mPa.s)	Sec. 3.2.P.5.2.3
Deliverable Volume (Release)	Minimum 0.2 mL	Sec. 3.2.P.5.2.
pH (Release and Shelf life)	5.5 - 5.8	Ph. Eur. 2.2.3, Potentiometric Determination of pH, Sec. 3.2.P.5.2.4
Osmolality/Freezing Point Depression (Release)	242 to 323 mOsM	Ph. Eur. 2.2.35, "Osmolality", Sec. 3.2.P.5.2.5
Assay - Dorzolamide Hydrochloride (as base) (Release and Shelf life)	Label Claim: 20.00 mg/mL 90.0 - 110.0% of label claim	HPLC: Sec. 3.2.P.5.2.6

Table 1 (Cont.)

Specification for Dorzolamide Hydrochloride (+) Timolol Maleate Preservative Free
Ophthalmic Solution

Tests	Acceptance Criteria	Test Methods
Degradation Products for Dorzolamide Total Degradates (b) (4)	(b) (4) (Release) (Shelf life) (Shelf life) (Shelf life)	HPLC: Sec. 3.2.P.5.2.6
Any unspecified Impurity	(Release) (Shelf life)	
Total Degradates	(Shelf life)	
Assay Timolol Maleate (as base) (Release and Shelf life)	Label Claim: 5.00 mg/mL 90.0 - 110.0% of label claim	HPLC: Sec. 3.2.P.5.2.9
Degradation Products for Timolol (Release and Shelf life) Total Degradates (b) (4) Any unspecified Impurity Total Degradates	(b) (4) (Release) (Shelf life) (Shelf life) (Shelf life) (Release) (Shelf life) (Shelf life)	HPLC: Sec. 3.2.P.5.2.9
Sterility (Release and End of Shelf Life)	No microbial growth observed	Ph. Eur. 2.6.1, Sterility 3.2.P.5.2.7
Bacterial Endotoxins	(b) (4) (release and end of shelf life)	Sec. 3.2.P.5.2.11, USP <85>, and Ph. Eur. 2.6.14
Particulate Matter (Release and End of Shelf Life)	No more than 50 per mL ($\geq 10 \mu\text{m}$) No more than 5 per mL ($\geq 25 \mu\text{m}$) No more than 2 per mL ($\geq 50 \mu\text{m}$)	USP <789> (Microscopic): Sec.3.2.P.5.2.10

† Identity by TLC may be an alternate test to Identity by HPLC.

In the January 24, 2012, submission, Merck has updated the product specifications to include limits on unspecified impurities. These are now expressed as “impurities” versus the previously proposed “degradents.”

Manufacturing facilities for the drug substance are in compliance with current good manufacturing practice.

3. Labeling

NDA 202667, Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% is recommended for approval for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone.

The labeling submitted in the January 24, 2012, submission, is acceptable. The package insert, patient package insert, carton and container labeling are located in the Appendix at the end of this review.

4. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 202667, Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% is currently recommended for approval for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone.

Merck has adequately addressed the issues listed in the Complete Response Letter dated December 16, 2011.

RISK BENEFIT ASSESSMENT:

The difference between the IOP lowering effect of preservative free dorzolamide 2% / timolol 0.5% ophthalmic solution and dorzolamide 2% / timolol 0.5% ophthalmic solution with preservative at peak and trough around the morning dose were neither clinically relevant nor statistically significant in the All Patients Treated-LOCF or the Per Protocol populations in Study P-081.

Supportive analyses also demonstrate that preservative-free dorzolamide/timolol and preservative-containing dorzolamide/timolol are clinically equivalent.

The data support Cosopt PF (dorzolamide hydrochloride – timolol maleate ophthalmic solution) 2%/0.5% administered twice daily for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone.

The most frequently reported adverse reactions occurring in up to 30% of patients were taste perversion (bitter, sour, or unusual taste) or ocular burning and/or stinging. The following adverse reactions were reported in 5-15% of patients: conjunctival hyperemia, blurred vision, superficial punctate keratitis or eye itching.

Pharmacology/Toxicology, Biostatistics, Clinical, CMC, and Clinical Pharmacology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse reactions.

Appendix

The labeling submitted in Merck's January 24, 2012, submission, is acceptable.

The package insert, patient package insert, carton and container labeling are located in this Appendix.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
01/30/2012

WILEY A CHAMBERS
01/31/2012