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APPLICATION NUMBER:

202514Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

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Cross-Discipline Team Leader Review of NDA 202514
Review #2

Date	January 30, 2012
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	202514
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	January 13, 2012
PDUFA Goal Date	March 13, 2012
Type of Application	505(b)(1)
Name	Zioptan (tafluprost ophthalmic solution) 0.0015%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Recommended for Approval

1. Introduction

NDA 202514 for Zioptan (tafluprost ophthalmic solution) 0.0015% received a Complete Response Letter dated November 7, 2011, which cited the following deficiency:

> Your NDA does not provide assurance of the sterility of the final drug product. While you have revised your (b) (4) processing validation protocol in your submission of October 27, 2011, (b) (4) filling procedures using this revised validation protocol. In the absence (b) (4), we cannot determine that the product is sterile and safe for use.
>
> To address this deficiency, provide a report describing three consecutive successful (b) (4) processing simulations (b) (4) that you will use for manufacturing the product using the inspection and accounting procedures provided in the revised (b) (4) processing validation protocol submitted in the October 27, 2011, amendment.

Merck submitted an amendment on January 13, 2012, which constituted a Complete Response.

2. Sterility Assurance

From the original Product Quality Microbiology Review finalized 1/18/2012:

On 13 January 2011 the applicant filed a Class 1 resubmission with the requested data from 3 consecutive (b) (4) processing simulations (b) (4) using the revised validation protocol submitted to the agency on 27 October 2011. (b) (4) batches 10019, 10020, and 10021 were manufactured separately and batch 10019 had a sterile (b) (4)

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(b) (4). A summary of the three (b) (4) is provided in Table 1 below.

Table 1- Summary results from (b) (4) processing simulation studies (Sponsor Table 3.2.P.3.5-2452-ophsln:11)

Batch Number	Mfg. Date	(b) (4)	# of Units Positive for Growth
10019	20Nov2011		0
10020	22Nov2011		0
10021	24Nov2011		0

The revised (b) (4) procedures were summarized in Module 3.5.5.2 and were consistent with data reviewed for the Product Quality Microbiology Reviews #1 and #2. Briefly, (b) (4) ampules were filled with (b) (4) Growth promotion studies are conducted for each batch and must be acceptable.

This application is recommended for approval on the basis of product quality microbiology.

3. Labeling

NDA 202514, Zioptan (tafluprost ophthalmic solution) 0.0015% is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension with the labeling found in this review.

The labeling for Zioptan was finalized prior to the Complete Response letter dated November 7, 2011.

In a January 18, 2012, teleconference with Merck, there was discussion regarding the inclusion of an additional statement in Section 16 (How Supplied/Storage and Handling) of the proposed package insert for Zioptan to maintain consistency between Cosopt PF labeling and Zioptan labeling. The only changes to the proposed Zioptan patient package insert were limited to the revision date, the copyright date and the component number.

The revised package insert and revised patient package insert submitted on 1/23/2012 are acceptable.

The carton and container labeling submitted on 11/4/2011 are acceptable.

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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 202514, Zioptan (tafluprost ophthalmic solution) 0.0015% is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. There is substantial evidence of safety and effectiveness consisting of adequate and well controlled studies which demonstrate that patients receiving Zioptan (tafluprost ophthalmic solution) 0.0015% experienced a statistically and clinically significant reduction in intraocular pressure. The data support Zioptan (tafluprost ophthalmic solution) 0.0015% administered once daily in the evening for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The most common ocular adverse reactions (pooled) were conjunctival hyperemia (10.7%) and ocular stinging/irritation (7.2%). The most common nonocular adverse reaction was headache (5.6%).

RISK BENEFIT ASSESSMENT:
Studies 15-003 and 001 demonstrate that the IOP lowering ability of tafluprost 0.0015% is not inferior to timolol 0.5%. Study 74458 had unequal baselines and is difficult to interpret. The safety profile of tafluprost 0.0015% is similar to other marketed topical prostaglandin analogues.

The benefit of tafluprost 0.0015% for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension has been demonstrated in this NDA application. The risk for using this drug is consistent with the currently marketed prostaglandin analogues.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality 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.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WILLIAM M BOYD
01/30/2012

WILEY A CHAMBERS
02/01/2012

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