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RESEARCH**

APPLICATION NUMBER:

202514Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo – Second Review Cycle

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo - Second Review Cycle
NDA/BLA #	NDA 202514
Supplement #	
Applicant Name	Merck Sharpe & Dohme Corp.
Date of re-Submission	January 13, 2012
PDUFA Goal Date	March 13, 2012
Proprietary Name / Established (USAN) Name	Zioptan tafluprost ophthalmic solution
Dosage Forms / Strength	ophthalmic solution, sterile / 0.0015%
Proposed Indication(s)	for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Lucious Lim
Statistical Review	Yunfan Deng, Yan Wang
Pharmacology Toxicology Review	James Wild, Wendelyn Schmidt
CMC Review/OBP Review	Maotang Zhou, Rapti Madurawe
Product Quality Microbiology Review	Jessica Cole, Stephen Langille
Supervisory Product Quality Microbiology Review	David Hussong
Clinical Pharmacology Review	Yongheng Zhang, Phil Colangelo
DSI	Kassa Ayalew, Susan Thompson, Jean Mulinde
CDTL Reviews	William Boyd
Deputy Division Director's Reviews	Wiley Chambers
Division Director's Reviews	Renata Albrecht
OSE/DMEPA	Denise Baugh, Todd Bridges, Carol Holquist

OND=Office of New Drugs

DSI=Division of Scientific Investigations

CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

Tafluprost is an analog of prostaglandin F_{2α} developed for the treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Other members of this class (prostaglandin F_{2α} analogs) have been previously approved for this indication. Tafluprost 0.0015% has been approved in a number of other countries outside of

the US in preservative-free or preservative containing formulations. The formulation that the applicant is seeking approval of in NDA 202514 is a preservative free formulation.

The review team has reviewed the issues in detail in their respective disciplines with regards to the safety and efficacy of Zioptan (tafluprost ophthalmic solution) 0.0015%. For a detailed discussion of NDA 202514, the reader is referred to the individual discipline specific reviews. In addition Dr. Boyd's Cross-Discipline Team Leader Memorandums from the first and second review cycles and Dr. Chambers' Deputy Division Director Reviews from the first and second review cycles, Dr. Albrecht's Division Director Reviews from the first and second review cycles and my review from the first cycle also summarize key issues in the NDA submission. This memorandum will focus on the deficiency from the first cycle. For a more detailed discussion of the issue, the reader is referred to the Product Quality Microbiology Review of January 17, 2012, and the reviews from the first cycle discussing this issue.

This is the second review cycle for tafluprost. On November 7, 2011, a complete response letter was issued that noted the following product quality microbiology 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.

The product quality microbiology reviewer has evaluated the data from the 3 consecutive (b) (4) processing simulations using the revised validation protocol that are provided in the January 13, 2012, re-submission. The product quality microbiology assessment is that the results are acceptable and the deficiency has been adequately addressed. They recommend approval from the product quality microbiology standpoint.

The proposed proprietary name, Zioptan, has been re-assessed by the Division of Medication Error Prevention and Analysis (DMEPA). As described in the DMEPA review of February 9, 2012, the proprietary name Zioptan is found to be acceptable.

The application for Zioptan (tafluprost ophthalmic solution) 0.0015% was not referred to an FDA advisory committee because it is a member of the class of ophthalmic prostaglandin analogs with similar potential risks and benefits as other members in this class. The benefits and risks of using prostaglandin analogs to treat elevated intraocular pressure have been previously discussed at a meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee on December 8, 1995, and the safety profile of tafluprost did not raise any new significant safety issues. The design of the clinical studies was similar to other approved drugs

in this class and we are not aware of any controversial issues that would benefit from further advisory committee discussion.

With regard to the Pediatric Research Equity Act (PREA), the pediatric study requirement for this application is being waived because necessary studies are impossible or highly impracticable as there are too few children with this disease/condition to study.

In summary, the deficiency from the first cycle regarding inadequate assurance of sterility has been adequately addressed. The review team recommends approval. I agree with the review team's recommendation. The application for Zioptan (tafluprost ophthalmic solution) 0.0015% for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension should be issued an Approval letter.

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/s/

EDWARD M COX
02/10/2012