

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202514Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Direct-to-Consumer Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 3, 2011
To: Hyun Son, Senior Regulatory Management Officer, DTOP
From: Adora Ndu, Regulatory Review Officer, DDTCP
Subject: NDA 202514
DDTCP comments for ZIOPTAN™ (tafluprost ophthalmic solution)
0.0015%
Patient Package Insert (PPI)

DDMAC has reviewed the proposed Patient Package Insert (PPI) for ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015%, submitted for consult on November 1, 2011, and offers the following comments.

The version of the draft PPI used in this review is titled, "Zioptan PPI (clean)" received from DRISK on November 3rd, 2011.

If you have any questions on the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

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

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/s/

ADORA E NDU
11/03/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **November 3, 2011**

To: Renata Albrecht, MD, Director
**Division of Special Pathogens and Transplant Products
(DSPTP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): ZIOPTAN (tafluprost) 0.0015%

Dosage Form and Route: Ophthalmic solution

Application Type/Number: 202514

Applicant: Merck Sharp and Dohme Corp

OSE RCM #: 2011-4182

1 INTRODUCTION

This review is written in response to a request by the Division of Transplant and Ophthalmology Prodcuts (DTOP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for ZIOPTAN (tafluprost) 0.0015%.

The purpose of the Applicant's submission is to approval of a new drug application for ZIOPTAN (tafluprost) 0.0015% a preservative-free ophthalmic formulation indicated for the treatment of elevated intra-ocular pressure in open angle glaucoma or ocular hypertension.

2 MATERIAL REVIEWED

- Draft ZIOPTAN (tafluprost) 0.0015% Patient Package Insert (PPI) received on January 7, 2011, revised by the Review Division throughout the review cycle and received by DMPP on November 2, 2011
- Draft ZIOPTAN (tafluprost) 0.0015% Prescribing Information (PI) received January 7, 2011, revised by the Review Division throughout the current review cycle and received by DMPP on November 2, 2011

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
11/03/2011

MELISSA I HULETT
11/03/2011

LASHAWN M GRIFFITHS
11/03/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 19, 2011

To: Constantine Markos, B.S., Pharm.D., R.Ph., Regulatory Health
Project Manager
Division of Transplant and Ophthalmology Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)
Division of Professional Promotion (DPP)

Subject: NDA 202514
ZIOPTAN (tafluprost ophthalmic solution) 0.0015%

As requested in your consult dated June 6, 2011, the Office of Prescription Drug Promotion (OPDP) has reviewed the draft labeling for ZIOPTAN (tafluprost ophthalmic solution) 0.0015%.

OPDP's comments are based on the substantially complete version of the labeling titled, "N202514_Label1.doc" which was sent via email from Constantine Markos on October 17, 2011.

OPDP's comments on the PI are attached in the substantially complete version of the labeling. Please note that the Division of Professional Promotion (DPP) reviewed the PI.

If you have any questions about DPP's comments on the PI, please contact Christine Corser at 6-2653 or at christine.corser@fda.hhs.gov.

Thank you for the opportunity to provide comments.

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/s/

CHRISTINE G CORSER
10/19/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: August 23, 2011

Application Type/Number: NDA 202514

Through: Todd Bridges, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Saflutan (Tafluprost) Ophthalmic Solution
0.0015%

Applicant: Merck Sharp & Dohme Corp.

OSE RCM #: 2011-136

1 INTRODUCTION

This review evaluates the labels and labeling of Saflutan (Tafluprost) Ophthalmic Solution for their vulnerability to medication errors in response to a request from the Division of Transplant & Ophthalmologic Products (DTOP).

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis¹, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container label, pouch and carton labeling submitted by the Applicant on January 7, 2011, (See Appendix A; no image of insert labeling). We requested (via correspondence dated March 8, 2011) the Applicant submit a prototype of the proposed LDPE container for our review.

3 DISCUSSION



4 CONCLUSIONS AND RECOMMENDATIONS

The information on the label and labeling can be clarified and improved upon to minimize the potential for re-use of the LDPE vial once opened. Section 4.1 (*Comments to the Division*) contains our recommendations for the insert labeling. Section 4.2 (*Comments to the Applicant*) contains our recommendations for the container labels,

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

carton and pouch labeling. We request these recommendations be communicated to the Applicant prior to approval of this NDA.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

4.1 COMMENTS TO THE DIVISION

Delete the statement, [REDACTED] (b) (4),” in Section 2 (Dosage and Administration) under the heading “Full Prescribing Information” as this may result in patients inappropriately treating both eyes or saving the remaining contents of the container for future doses (which may increase the risk of bacterial contamination of the solution since it is a preservative-free product).

4.2 COMMENTS TO THE APPLICANT

A. Carton and Pouch Labeling (Trade and Professional)

1. Delete the statement, [REDACTED] (b) (4) [REDACTED] from all labeling as this may result in patients inappropriately treating both eyes or saving the remaining contents of the container for future doses (which may increase the risk of bacterial contamination of the solution since it is a preservative-free product).
2. Decrease the size of the pink and orange graphic that appears above the proprietary name.
3. Revise the established name (including dosage form) presentation to be in accordance with 21 CFR 201.10(g)(2) which states “The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast and other printing features.”
4. Follow the statement, ‘Single-Use Container’ with [REDACTED] (b) (4) [REDACTED] This product contains no preservative and must be thrown away after use.
5. Increase the prominence of the product strength so this information is more visible.
6. [REDACTED] (b) (4) [REDACTED]

B. Pouch Labeling (Trade and Professional)

1. Unbold the statements, 'Sterile' and 'Preservative-Free' as these statements are more prominent than the established name.
2. Relocate the entire (b) (4) statement to appear just before the manufactured for statement so that the other statements can move up and have more prominence.

C. Carton Labeling

1. Decrease the size of the orange triangular graphic located in the upper left hand corner and the pink triangular graphic located in the lower right hand corner both of which are located on the principal display panel.
2. Relocate the (b) (4) to the principal display panel beneath the statement, 'Refrigerate'.
3. Relocate the entire (b) (4) statement to the back panel.
4. Un-bold and re-locate the statement, (b) (4) to the back panel.

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

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/s/

DENISE V BAUGH
08/23/2011

TODD D BRIDGES
08/23/2011

CAROL A HOLQUIST
08/24/2011

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA# 202514	
Proprietary Name: Pending Established/Proper Name: tafluprost Dosage Form: Ophthalmic Drops Strengths: 0.0015%	
Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):	
Date of Application: 01/07/2011 Date of Receipt: 01/07/2011 Date clock started after UN: N/A	
PDUFA Goal Date: 11/07/2011	Action Goal Date (if different): 10/07/2011
Filing Date: 03/08/2011	Date of Filing Meeting: 02/16/2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1	
Proposed indication(s)/Proposed change(s): Reduction of elevated intra-ocular pressure (IOP) in open-angle glaucoma or ocular hypertension.	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule post-marketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 062690				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>				
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>			X	
Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>	X			
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</p>	X			
Financial Disclosure	YES	NO	NA	Comment
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	X			
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p>	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>		X		
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 08/24/2009 <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 08/13/2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 02/16/2011

BLA/NDA/Supp #: 202514

PROPRIETARY NAME: Pending

ESTABLISHED/PROPER NAME: tafluprost

DOSAGE FORM/STRENGTH: Ophthalmic Drops, 0.0015%

APPLICANT: Merck Sharp & Dohme Corp.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Reduction of elevated intra-ocular pressure (IOP) in open-angle glaucoma or ocular hypertension.

BACKGROUND: IND 062690; EOP2 Meeting held on 08/24/2009; Pre-NDA Meeting held on 08/13/2010.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Constantine J. Markos	Y
	CPMSs/TLs:	Maureen P. Dillon-Parker Judith Milstein	Y N
Cross-Discipline Team Leader (CDTL)	William M. Boyd		Y
Clinical	Reviewer:	Lucious Lim	Y
	TL:	William M. Boyd	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (for antimicrobial products)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Eric Yongheng Zhang	Y
	TL:	Kim Bergman	Y
Biostatistics	Reviewer:	Yunfan Deng	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jim Wild	Y
	TL:	Wendy Schmidt	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Maotang Zhou	Y
	TL:	Linda L. Ng	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	Y
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	Denise Baugh	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/DCRMS (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (DSI)	Reviewer:	Kassa Ayalew	Y
	TL:	Tejashri Purohit-Sheth	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<p><input checked="" type="checkbox"/> None</p>
<p>CLINICAL</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> 	<p><input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p style="text-align: right;">o Reason: <i>this drug is not the first in its class</i></p>

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: Review issues for 74-day letter.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Office Director—Edward M. Cox 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments: MID-CYCLE MEETING 06/27/2011, WRAP-UP MEETING 09/12/2011	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): Please see 74-Day Letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter.
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	filing letter; For NDAs/NDA supplements: see CST for choices) <ul style="list-style-type: none">• notify DMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74.
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter.
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

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

/s/

CONSTANTINE J MARKOS
07/08/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 23, 2011

TO: William Boyd, M.D., Team Leader, DTOPTOP
Division of Transplant and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Jean Mulinde, M.D.
Branch Chief (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 202514

APPLICANT: Merck Sharp & Dohme Corp.
Chitkala Kalidas, Ph.D., Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY33-204
Rahway, NJ 07065
Tel: 732 594 0599
Fax: 732 594 1030
Email: chitkala_kalidas@merck.com

DRUG: SAFLUTAN™ (tafluprost ophthalmic solution)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: For the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.

CONSULTATION REQUEST DATE: February 24, 2011

DIVISION ACTION GOAL DATE: July 15, 2011

PDUFA DATE: November 7, 2011

I. BACKGROUND:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., (Merck), submitted a new drug application NDA 202514 for SAFLUTAN™ (tafluprost) Ophthalmic Solution Single Dose Container, also referred to as MK-2452, for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.

A consult from DAIOP (now DTOP) was received on February 24, 2011 because the below studies are considered pivotal and inspections of the clinical sites are essential to verify the quality of conduct of these studies for this NDA. This was a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of this application. To support the approval, the Applicant provided data from two well controlled clinical trials (1230 subjects) submitted in support of the application. The protocols inspected were:

Protocol No. 15-001: A Phase III, Randomized, Active Comparator-Controlled, Twelve-Week, Double-Masked Clinical Trial to Compare the Efficacy and Safety of Preservative-Free MK-2452 (0.0015%) and Preservative-Free Timolol Maleate (0.5%) in Patients with Open-Angle Glaucoma and Ocular Hypertension. This study was a phase III, multi-center (United States (40 subjects), Spain (6 subjects) and Switzerland (4 subjects)) randomized, double-masked, parallel-group, active comparator-controlled, clinical trial to compare the efficacy and safety of preservative free (PF) tafluprost (0.0015%) and PF timolol maleate (0.5%) in glaucomatous and ocular hypertensive patients over a 12-week treatment period. The total duration of the study for patients was approximately 4.5 months, inclusive of the screening washout period and post-study follow-up phone call. Approximately 620 subjects (310 subjects per treatment group), in the United States and worldwide were to be randomized into the study.

Prototocol No. 15-003: A Randomized, Double-Masked, Parallel-Group, Multicenter, 12-Month Trial Comparing the Efficacy and Safety of Tafluprost 0.0015% with Timolol Maleate 0.5% in Subjects with Open-Angle Glaucoma or Ocular Hypertension. This was a randomized, double-masked, active-controlled, parallel-group, multicenter phase III study comparing the efficacy and safety of

tafluprost 0.0015% eye drops with timolol maleate 0.5% eye drops in patients with primary open-angle glaucoma, pseudoexfoliative glaucoma, pigmentary glaucoma, or ocular hypertension. The study was to be conducted at 26 centers in the United States.

II. RESULTS (by Site):

Name of CI, Location	Protocol # and # of Subjects:	Inspection Date	Preliminary Classification	Final Classification
Douglas Day, MD Omni Eye Services 5505 Peachtree Dunwoody Rd, NE Atlanta, GA 30342	Study 15-003/ 40 subjects	January 19- February 1, 2011.	NAI	NAI
David Wirta, MD 1501 Superior Ave, #303 Newport Beach, CA 92663	Study 15-001/ 67 subjects	May 4-19, 2011	VAI	Pending

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Douglas Day, MD

Omni Eye Services
11205 Alpharetta Highway Suite J3
Atlanta, GA 30076

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between January 19, 2011 and February 1, 2011. At this site, a total of 48 subjects were screened and 40 were randomized into the study. Thirty-three (33) subjects completed the study.

Informed consent documents for 20 randomized subjects were reviewed during the inspection, and the consenting process appeared adequate. In addition, in depths audit of the study records for 20 subjects was conducted. Records reviewed included, but were not limited to, source documents, protocol specified blinding/randomization procedures, inclusion/exclusion criteria, adverse events, primary efficacy endpoints, protocol deviations, concomitant therapies, and test article accountability. In addition, IRB correspondence, monitoring logs and correspondence, and financial disclosure documentation were reviewed.

b. General observations/commentary:

No regulatory violations were noted, and a Form FDA 483 was not issued.

c. Assessment of data integrity:

Based on inspectional findings and the observations noted, efficacy and safety data obtained from this site are considered reliable.

2. David Wirta, MD

1501 Superior Ave, #303

Newport Beach, CA 92663

a. What was inspected:

This inspection was conducted in accordance with Compliance Program 7348.811, and it was conducted from May 4 to May 19, 2011.

At this site, a total of 77 subjects were screened, 67 subjects were enrolled and 63 subjects completed the study. Four Subjects discontinued the study (Subject #11362 and #11287 withdrew consent; Subject # 10020 (cough) and #10503 (fatigue) discontinued due to adverse events). Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequate adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

The inspection evaluated records of 66 subjects for the primary efficacy endpoints, 67 subjects for adverse events, 25 subjects for eligibility criteria/randomization, 25 subjects for concomitant medications, and 25 subjects for informed consent. The primary efficacy endpoint was verifiable for all subject records reviewed.

b. General observations/commentary:

The inspection of Dr Wirta's site revealed that he did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation in violation of [21 CFR 312.62 (b)]. A Form FDA 483, Inspectional Observations, was not issued to this investigator but the field inspector addressed seven Discussion Items with Dr. Wirta, including recordkeeping errors regarding adverse events. For example:

- One adverse event on the source document was not reported for Subject #10491. The adverse event was described as ocular irritation and occurred on the same day as the adverse event conjunctival hyperemia. The CI considered ocular irritation as part of the same symptom/event as conjunctival hyperemia so he didn't report it on the eCRF separately.

- Subject #10447 experienced the adverse event of ocular dryness. The causality of this adverse event was inadvertently entered as "Not Related" in the eCRF but as "Related" in the source document. Subject #11420 experienced the adverse events of ocular stinging. Ocular stinging was inadvertently listed as "Not Related" in the eCRF while the source document listed causality as "Related". The CI reported the above errors to the sponsor via email on 5/19/11. Both of these were considered by the investigator to be inadvertent transcription errors.
- Subject #11287 had two adverse events whose severity was upgraded from mild to moderate by the investigator, and updated the eCRF correctly to moderate. The site's paper source document, however, was not updated from mild to moderate.
- Subject #11344, had a subconjunctival hemorrhage recorded in the Ocular History source document which was not included in the eCRF ocular history.

***DSI Reviewer Comments:** These adverse events should have been recorded accurately in the source document and reported in a timely manner to the sponsor. Dr Wirta's written response (submitted on May 25, 2011) to the comments made by the field inspector acknowledged the transcription and reporting errors described above. The transcription and reporting errors of adverse events were minor, and the CI later reported those errors to the sponsor with subsequent submission of the corrections to the NDA. Although regulatory violations were noted at this site, they are relatively isolated in nature, and it is unlikely that these findings would affect subject safety or data integrity.*

c. Assessment of data integrity:

Although minor regulatory violations in recordkeeping of adverse events were observed at this site, the CI later reported the change in causality of adverse events to the sponsor who submitted the corrections to the NDA. Based on inspectional findings and the observations noted, efficacy and safety data obtained from this site are considered reliable.

Note: Observations noted above are based on communications with the field investigator and the draft EIR; an inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites were inspected in support of this application. In general, inspection of Dr. Day's site revealed that he adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations and the final classification for this inspection is No Action Indicated (NAI).

Inspection of Dr. Wirta's site documented regulatory violations and the preliminary classification for this inspection is Voluntary Action Indicated (VAI) for errors in

recordkeeping of adverse events, which were isolated and relatively minor. Incorrect causality of adverse events was corrected and later reported to the sponsor.

The studies at these sites appear to have been conducted adequately, and the data generated may be used in support of the application.

Follow-up Actions: The preliminary classification for Dr. Wirta's site is based on the preliminary communications with the field investigator and the draft EIR; an inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Jean Mulinde, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

KASSA AYALEW
06/27/2011

SUSAN D THOMPSON
06/27/2011

JEAN M MULINDE
06/27/2011

Executive CAC

Date of Meeting: May 3, 2011

Committee: David Jacobson Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Timothy Robison, Ph.D., DPARP, Alternate Member
Wendelyn Schmidt, Ph.D., DAIP, Supervisor
James Wild, Ph.D., DAIP, Presenting Reviewer

Author of Minutes: James Wild, Ph.D., DAIP

NDA #: 202514

Drug Name: Tafluprost, AFP-168 (proposed trade name Saflutan™)

Sponsor: Merck Sharp & Dohme Corp.

The following information reflects a brief summary of the Committee discussion and its recommendations.

Background

Tafluprost (AFP-168) ophthalmic solution is intended for the treatment of elevated intraocular pressure in open angle glaucoma or ocular hypertension. Tafluprost is a prodrug which is quickly hydrolyzed to form its metabolite, tafluprost acid (AFP-172), the pharmacologically active agent. Tafluprost acid is an analogue of prostaglandin F_{2a} (PGF_{2a}) with high affinity and selectivity for the FP prostanoid receptor. The maximum recommended human dose (MRHD) intended for marketing is expected to be a single daily drop of approximately 30 ul of 0.0015% tafluprost per affected eye, and it is expected that tafluprost will be administered chronically. Currently three other prostaglandin analogues (Lumigan®, Xalatan®, Travatan®) have been marketed for the treatment of glaucoma. All three of these drugs were tested in rodent carcinogenicity studies, and none were shown to increase the incidence of neoplasms in male or female animals. Tafluprost was shown to be non-mutagenic in an *in vitro* Ames test (four strains of *S. typhimurium* and one *E.coli* strain), an *in vitro* chromosome aberration assay in Chinese Hamster lung cells, and an *in vivo* bone marrow micronucleus assay in mice. The FDA did not request the conduct of the 2-years studies in rats and mice.

Rat Carcinogenicity Study

The final study report of a GLP-compliant, two-year, subcutaneous-dose, carcinogenicity study in male and female Crj:CD(SD)IGS rats was reviewed, and the results were discussed at the May 3rd, 2011 meeting of the Executive Carcinogenicity Assessment Committee. The study employed subcutaneous doses of 0, 3, 9, and 30 ug/kg/day tafluprost in a saline vehicle. Two vehicle control groups were included, and 60 animals were included for each study group. The Sponsor did not receive prior FDA dose concurrence. The high-dose was based on plasma AUC exposure levels for tafluprost

acid determined in a prior range-finding study and the rat AUC ratio relative to human exposure levels. Also, serum albumin binding to tafluprost acid and the metabolic profile for tafluprost were shown to be similar for rats and humans.

The high-dose plasma AUC exposure for tafluprost acid was in excess of 500 times the human exposure at the expected MRHD. The survival rates were acceptable, and tafluprost administration was not associated with increased mortality. Appropriate observations and assessments were conducted allowing evaluation of general toxicity and tafluprost-related carcinogenicity.

There was no evidence of tafluprost-related neoplasms in males or females by CDER criteria.

Mouse Carcinogenicity Study

The final study report of a GLP-compliant, 78-week, subcutaneous-dose, carcinogenicity study in male and female Crl:CD-1(ICR)BR mice was reviewed and the results were discussed at the May 3rd, 2011 meeting of the Executive Carcinogenicity Assessment Committee. The study employed subcutaneous doses of 0, 10, 30, and 100 ug/kg/day tafluprost in a saline vehicle. Two vehicle control groups were included, and 51 animals were assigned to each study group. The Sponsor did not receive prior FDA dose concurrence. The high-dose for the study was based on AUC exposure levels for tafluprost acid determined in a prior range-finding study and the AUC ratio relative to human exposure levels.

The study duration was only 1.5 years rather than the standard 2 years. Also the mouse metabolic profile for tafluprost was not determined in previous experiments, thus precluding comparison of mouse and human metabolites. Analysis of AFP-172 binding to mouse plasma proteins was also not performed. However, 99% of AFP-172 was shown to bind to human serum albumin, indicating that a higher percentage of AFP-172 could not practically bind to mouse serum albumin. The high-dose plasma AUC exposure for tafluprost acid was adequate, in excess of 500 times the human exposure at the expected MRHD. The survival rates were acceptable, and tafluprost was not associated with increased mortality at any dose. Appropriate observations and assessments were conducted allowing evaluation of general toxicity and tafluprost-related carcinogenicity.

There was no evidence of tafluprost-related tumorigenicity in males and females. In the tafluprost high-dose group, no unusual tumors or significantly increased tumor incidence suggestive of tafluprost-related carcinogenesis was observed compared to the vehicle control groups.

Executive CAC Recommendations and Conclusions:

Rat

- The Committee concurred that there were no tafluprost-related neoplasms.
- The Committee concurred that the study was adequate.

Mouse

- The Committee concurred that there were no tafluprost-related neoplasms.
- However, the Committee concluded that the study was not adequate due to its non-standard duration of only 1.5 years and incomplete evaluation of the low and mid dose group for many tissues.

Despite the inadequate design of the mouse carcinogenicity study, the Committee concurred that sufficient carcinogenicity testing had been conducted for tafluprost administered in the clinical setting by the topical ocular route at the expected MRHD. Factors influencing this decision were the very low systemic exposure associated with the expected MRHD, negative genetic toxicology findings, and the lack of neoplasm findings in carcinogenicity studies for three other marketed drugs in the same pharmacological class.

The Committee recommended that due to the inadequate design of the mouse carcinogenicity study, the drug label for tafluprost ophthalmic solution should not include mention of the mouse carcinogenicity study in Section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DAIP
/WSchmidt, DAIP
/JWild, DAIP
/CMarkos, DAIP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
05/06/2011

DAVID JACOBSON KRAM
05/06/2011

DSI CONSULT: Request for Clinical Inspections

Date: February 24, 2011

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP 2
Jean M. Mulinde, M.D., Acting Team Leader, GCP 2
Kassa Ayalew, M.D. Medical Officer
Division of Scientific Investigation
Office of Compliance/CDER

Through: William Boyd, MD, Clinical Team Leader, 301-796-0686
Division of Anti-Infective and Ophthalmology Products

From: Constantine Markos, Regulatory Health Project Manager, 301-796-3871
Division of Anti-Infective and Ophthalmology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-202514

Applicant/ Applicant contact information:

Chitkala Kalidas, Ph.D
Director, Worldwide Regulatory Affairs
Merck Sharp & Dohme Corp.
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tel 732-594-0599

Drug Proprietary Name: Saflutan (tafluprost ophthalmic solution)

NME: No

Review Priority: No

Study Population includes < 17 years of age: No

Is this for Pediatric Exclusivity: No

Proposed Indication:

For the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.

PDUFA: November 7, 2011
Action Goal Date: October 7, 2011
Inspection Summary Goal Date: August 15, 2011

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Randomized	Indication
DSI Choice	001	320	reduction of IOP in patients with open angle glaucoma or ocular hypertension
DSI Choice	15-003	458	reduction of IOP in patients with open angle glaucoma or ocular hypertension

An inspection is requested for at least one site for each of these clinical trials only as your resources permit. See rationale below

III. Site Selection/Rationale

The clinical portion of the application has been preliminarily reviewed, and no issues have been identified to date to suggest a problem with data integrity.

Protocols 001 and 15-003 are large, multicenter, randomized, double-masked trials of adequate duration which use appropriate FDA recommended endpoints for the evaluation of intraocular pressure.

Protocol 001 utilizes the preservative-free tafluprost formulation with timolol as the active comparator. Protocol 15-003 Protocol 001 utilizes the preservative-containing tafluprost formulation with timolol as the active comparator.

Note that the highest enrollers in Study 001 are Eugene B. McLaurin, MD (49 subjects) and David Wirta, MD (67 subjects).

Not that the highest enrollers in Study 15-003 are Sall Eye Research Center, Artesia, CA (40 subjects), and Omni Eye Services, Atlanta, GA (40 subjects).

An inspection is requested for at least one site for each of these clinical trials only as your resources permit.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Routine Inspections

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Goal Date for Completion:

If routine inspections are completed the Inspection Summary Results should be provided by August 15, 2011. **We intend to issue an action letter on this application October 7, 2011.**

Should you require any additional information, please contact Constantine Markos at 301-796-3871 or William Boyd, MD at 301-796-0686.

Additional Information:

This is an electronic NDA. The clinical portion of the application has been preliminarily reviewed and no issues have been identified to date to suggest a problem with data integrity.

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

/s/

MAUREEN P DILLON PARKER
02/24/2011
DSI Consult - NDA 202514

WILLIAM M BOYD
02/24/2011