

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202514Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202514

SUPPL #

HFD # 590

Trade Name ZIOPTAN

Generic Name tafluprost ophthalmic solution

Applicant Name Merck Sharp & Dohme Corp.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES is this approval a result of the studies submitted in response to the Pediatric Written Request? YES NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The Agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 52080 YES ! NO
! Explain:

Investigation #2 N/A !
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1
YES ! NO
Explain: ! Explain:

Investigation #2
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: William M. Boyd, M.D.
Title: Medical Officer
Date: 01/31/2012

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; Formatted 02/15/2005

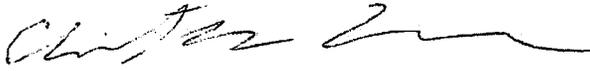
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CONSTANTINE J MARKOS
02/02/2012

RENATA ALBRECHT
02/02/2012

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.



Chitkala Kalidas,
PhD.
Director
WW Reg. Liaison

9 December 2010
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹	
NDA # 202514	If NDA, Efficacy Supplement Type:
Proprietary Name: ZIOPTAN Established/Proper Name: tafluprost 0.0015% Dosage Form: Ophthalmic Solution	Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):
RPM: Constantine J. Markos, B.S., Pharm.D., R.Ph.	Division: Division of Transplant and Ophthalmology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions	
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>03/13/2012</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None CR 11/07/2011

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For re-submissions, (b)(2) applications must be cleared before the action, but it is not necessary to re-submit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Tyson)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>Approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including Approval Letter with final labeling</i>)	Action(s) and date(s) CR 11/07/2011; AP 02/10/2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Enclosed dated 01/23/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Enclosed dated 01/07/2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Enclosed dated 01/23/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Enclosed dated 01/07/2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Enclosed dated 11/04/2011
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	Review 04/15/2011—Denied Letter 04/15/2011—Denied Review 08/31/2011—Accepted Letter 08/31/2011--Accepted Review 02/09/2012—Accepted
<ul style="list-style-type: none"> ❖ Labeling Reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 08/24/2011 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) Consult 11/01/2011; Review 11/03/2011 <input checked="" type="checkbox"/> ODPD (DDMAC) Consult 06/08/2011; Review 10/19/2011; Consult 11/01/2011; Review 11/03/2011 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	07/08/2011
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>Approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>05/25/2011</u> If PeRC review not necessary, explain: <u>Acceptable</u> • Pediatric Page/Record (<i>Approvals only, must be reviewed by PeRC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are co-signed by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing Communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), e-mails, faxes, tele-cons, etc.</i>)	01/28/2011; 02/15/2011; 03/02/2011; 03/08/2011; 03/22/2011; 05/05/2011; 05/10/2011; 05/20/2011; 06/06/2011; 06/17/2011; 07/06/2011; 07/19/2011; 08/04/2011; 08/29/2011; 01/09/2012; 02/08/2012
❖ Internal memoranda, tele-cons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg.</i>)	<input checked="" type="checkbox"/> No mtg.
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg.</i>)	<input type="checkbox"/> N/A or no mtg. None
• Pre-NDA meeting (<i>indicate date of mtg.</i>)	<input type="checkbox"/> No mtg. 08/13/2010
• EOP2 meeting (<i>indicate date of mtg.</i>)	<input type="checkbox"/> No mtg. 08/24/2009
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs.</i>)	Clinical Guidance 10/12/2005
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/07/2011; 02/10/2012
Deputy/Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/07/2011; 11/07/2011; 02/01/2012; 02/10/2012
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/07/2011; 02/01/2012
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	11/07/2011; 02/01/2012
• Clinical Review(s) (<i>indicate date for each review</i>)	02/28/2011; 09/28/2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	09/28/2011 Review on Page 7.

⁶ Filing reviews should be filed with the discipline reviews.

❖ Clinical reviews from immunology and other clinical areas/Divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested Consult 02/24/2011; Letter 06/09/2011; Review 06/27/2011; Letter 07/28/2011
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 03/22/2011; 07/20/2011
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 02/16/2011; 07/20/2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Non-Clinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> AD P/T Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 07/25/2011
<ul style="list-style-type: none"> Supervisory Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Pharm/Tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 03/22/2011; 07/20/2011
❖ Review(s) by other disciplines/Divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc.
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 05/06/2011 Included in P/T review, page N/A
❖ DSI Non-Clinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/07/2011
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product Quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 02/14/2011; 04/25/2011; 08/26/2011; 10/24/2011; 01/31/2012
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 02/18/2011; 09/30/2011; 11/04/2011; 11/04/2011; 01/18/2012
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/Divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	08/26/2011 CMC Review on Page 77.
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 10/13/2011 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

CONSTANTINE J MARKOS
02/16/2012



NDA 202514

**ACKNOWLEDGE --
CLASS 1 COMPLETE RESPONSE**

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY33-204
Rahway, New Jersey 07065-0900

Dear Dr. Kalidas:

We acknowledge receipt on January 13, 2012, of your January 13, 2012, re-submission to your New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZIOPTAN (tafluprost ophthalmic solution) 0.0015%.

We consider this a complete, Class 1 response to our November 7, 2011, action letter. Therefore, the User Fee goal date is March 13, 2012.

If you have any questions, please call me at (301) 796-3871.

Sincerely,

{See appended electronic signature page}

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CONSTANTINE J MARKOS
02/08/2012



NDA 202-514

INFORMATION REQUEST

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zioptan™ ((MK-2452)

We also refer to your December 5, 2011, submission, containing request for Agency feedback on the expiry date.

The actual shelf life will be determined based on the review of the stability data. While extrapolation of the shelf life beyond the period covered by long term data can be proposed, the proposed shelf life should not be more than 12 months beyond the period covered by long-term data (ICH Q1E).

Currently the division requires a one-time extractables/leachables study on container/closure by using appropriate screening methods (HPLC, GC, mass spectrometry, etc) on at least one stability batch through expiry.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
01/09/2012

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Hyun Son, Safety Regulatory Project Manager Division of Transplant and Ophthalmology Products 301-796-1939
------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

REQUEST DATE November 1, 2011	IND NO.	NDA/BLA NO. 202514	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) New NDA submission
----------------------------------	---------	------------------------------	------------------------------------------------------------------

NAME OF DRUG ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015%	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Ophthalmology Product	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) November 3, 2011
------------------------------------------------------------------------------	-------------------------------------------	-------------------------------------------------	-----------------------------------------------------------------------------------------------------

NAME OF FIRM: MERCK	PDUFA Date: November 7, 2011
-------------------------------	-------------------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------

EDR link to submission:
Original NDA submission:
[\\cdsesub1\EVSPROD\NDA202514](http://cdsesub1/EVSPROD/NDA202514)

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:
Merck has submitted a new NDA for ZIOPTAN™ (NDA 202514) on January 7, 2011 for the indication of reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension. In the labeling, the sponsor has submitted a patient package insert (PPI). The review division has revised the proposed PPI (attached). Please review the PPI. I will send the most recently revised PI in a separate email.
Thank you.

SIGNATURE OF REQUESTER
Hyun Son

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS/email <input type="checkbox"/> HAND
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/s/

HYUN J SON
11/01/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE Patient Labeling		FROM: Hyun Son, 301-796-1939 Division of Transplant and Ophthalmology Products		
DATE November 1, 2011	IND NO.	NDA NO. 202514	TYPE OF DOCUMENT New submission (NDA)	DATE OF DOCUMENT January 7, 2011
NAME OF DRUG ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015%		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Ophthalmic product	DESIRED COMPLETION DATE November 3, 2011
NAME OF FIRM: MERCK				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Merck has submitted a new NDA for ZIOPTAN™ (NDA 202514) on January 7, 2011 for the indication of reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension. In the labeling, the sponsor has submitted a patient package insert (PPI). The review division has revised the proposed PPI (attached). Please review the PPI. I will send the most recently revised PI in a separate email. The PDUFA due date is November 7, 2011. Thank you.				
SIGNATURE OF REQUESTER Hyun Son		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

HYUN J SON
11/01/2011



NDA 202514
NDA 202667

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Merck Sharp & Dohme Corp.
126 E. Lincoln Avenue
P.O. Box 2000, RY33-204
Rahway, New Jersey 07065-0900

Dear Applicant:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Product Name/Dosage Form
202514	Zioptan (tafluprost ophthalmic solution), 0.0015%
202667	Cosopt PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution), 2%/0.5%

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b)(4)¹. The pervasiveness and egregious nature of the violative practices by (b)(4) has led FDA to have significant concerns that the bioanalytical data generated at (b)(4), as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented (b)(4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by (b)(4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall

¹ These violations include studies conducted by (b)(4) specific to the (b)(4) facility.

development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [REDACTED] (b) (4) during the time period of concern [REDACTED] (b) (4). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-0833.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
09/29/2011



NDA 202514

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dohme Corp.
126 East Lincoln Avenue
PO Box 2000
Mail Drop: RY33-204
Rahway, New Jersey 07065-0900

ATTENTION: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) dated January 7, 2011, received January 7, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tafluprost Ophthalmic Solution, 0.0015%.

We also refer to your June 9, 2011, correspondence, received June 9, 2011, requesting review of your proposed proprietary name, Zioptan. We have completed our review of the proposed proprietary name, Zioptan, and have concluded that it is acceptable.

The proposed proprietary name, Zioptan, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your June 9, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Constantine Markos at (301) 796-3871.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director, Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
08/31/2011

NDA 202514
Zioptan (tafluprost)
Chitkala Kalidas, Ph.D.

Dear Dr. Kalidas,

Please find below, comments from our Division in regards to NDA 202514:

Microbiology (Sterility)

Please submit the following information as soon as possible, preferably, within the next few business days:

1.  (b) (4)

2. It is not possible to fully assess the bacterial retention studies conducted for the sterilizing ^{(b) (4)} based on the information provided ^{(b) (4)}

Provide a comparison of the routine filtration parameters used for production and the bacterial retention validation studies for the sterilizing ^{(b) (4)}.

3. Provide the following information for the three process validation [REDACTED] (b) (4)
[REDACTED]
4. Revise the [REDACTED] (b) (4) procedure to remove the additional inspection of positive vials after incubation. We refer to the 08 June 2011 amendment answer to question 9. [REDACTED] (b) (4) should mimic production conditions and should not subject positive vials to additional scrutiny above that used for commercial product.
5. Describe the [REDACTED] (b) (4)
[REDACTED]
6. Information found in the 22 August 2011 amendment indicates that the production stability program does not include [REDACTED] (b) (4)
[REDACTED]

Thank you for your time.

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager
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/s/

CONSTANTINE J MARKOS
08/29/2011

Cuff, Althea

From: Kalidas, Chitkala [chitkala_kalidas@merck.com]
Sent: Thursday, August 04, 2011 1:11 PM
To: Cuff, Althea
Cc: Markos, Constantine
Subject: RE: NDA 202-514 - CMC IR

Dear Ms. Cuff-

Thank you for your e-mail. I will contact our CMC team about your request for information and will get back to you shortly.

Best regards,
Chitkala

From: Cuff, Althea [mailto:Althea.Cuff@fda.hhs.gov]
Sent: Thursday, August 04, 2011 1:03 PM
To: Kalidas, Chitkala
Cc: Markos, Constantine
Subject: NDA 202-514 - CMC IR

Dear Chitkala,

Please find below, CMC information request. Please confirm receipt of this e-mail.

- Please clarify if there are differences in the material and dimensions of the (b) (4) pouches used for (b) (4) test batches, stability batches (b) (4) and proposed commercial batches. If there are differences, please provide the (b) (4) pouch dimensions and materials for the above batches, preferably in a tabular format. It is our understanding that the primary container has not changed.
- Your response letter dated 7/26/2011 stated Table 1 and Table 2 represent the analytical validation studies performed at (b) (4) during technical transfer of the analytical methods. The (b) (4) validation study report is not currently submitted to the NDA. Please submit the (b) (4) report or analytical validation information including the data that the original Table 1 and Table 2 were based upon.

Please provide a response within three business days.

Thanks,

Althea Cuff
Regulatory Health Project Manager
Office of New Drugs Quality Assessment
301-796-4061

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/s/

ALTHEA CUFF
08/04/2011

NDA 202514
tafluprost
Chitkala Kalidas, Ph.D.

Dear Dr. Kalidas,

Please find below, comments from our Division in regards to NDA 202514:

CMC

Please submit the following information as soon as possible, preferably, within five business days.

1. Please be advised that the 12-month leachable data that you have provided on 04/28/2011 are insufficient to support the proposed 36-month shelf-life for the drug product.
2. Contact the DMF holder (DMF # (b)(4)) for the revised drug substance specification and update the drug substance specification in the NDA to reflect these changes.
3. In your response letter dated 06/30/2011, you have submitted two validation reports for the drug product HPLC methods (Reference 0002 and Reference 0003). Both reports are dated 10/15/2003. It is noted, that the results provided in the validation reports do not match those of Table 3.2-P.5.3.4-2452-ophsln:1 and Table 3.2.P.5.3.4.-2452-ophsln:2 in the original NDA submission. Please explain the discrepancy. Since the validation, have there been any changes such as changes of the composition of the finished product to require revalidation of the HPLC methods?
4. The explanation provided in your response letter dated 07/11/2011 on the (b)(4) data and test procedures is not clear to us. Please provide a detailed description of the two (b)(4) test procedures used for evaluating (b)(4) batches and indicate which one is the regulatory procedure. In addition, provide the following clarification.
 - (a) The weight loss procedures described in the 07/11/2011 amendment appear to contradict what have been described in the original NDA submission. While the 07/11/2011 amendment states that “the method utilized to test the (b)(4) Please explain the discrepancy.

(b)

(b) (4)

Thank you for your time.

Constantine

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CONSTANTINE J MARKOS
07/19/2011

NDA 202514
tafluprost
Chitkala Kalidas, Ph.D.

Dear Dr. Kalidas,

Please find below, comments from our Division in regards to NDA 202514:

Clinical

In a request dated April 19, 2011, the Agency requested the following information:

Please provide the location of the following analyses for the Intent-to-Treat population with LOCF and Per Protocol population observed cases in Studies 74458, 15-003 and 001:

Upper and lower 95% CI for the mean difference in IOP at each time point (i.e., mean IOP tafluprost minus control).

If they have not been performed, please submit.

In your response dated May 11, 2011, you submitted analyses for the ITT population with LOCF and Per Protocol population with observed cases in Studies 7448, 15-003 and 001 the upper and lower 95% CI for the mean difference in IOP change from baseline at each time point.

We reiterate, the analyses the Agency is requesting are the following:

Upper and lower 95% CI for the difference in mean IOP at each time point and study visit (i.e., mean IOP of tafluprost minus mean IOP of control at each time point and visit).

CMC

1. Please provide data to show that the drug product complies with USP <467>. Please be advised that the FDA can accept (b) (4) test data on components from tests performed by the drug product manufacturer or the drug product manufacturer may provide test data or appropriate statements obtained from properly qualified suppliers as described in 21 CFR 211.84(d)(2).
2. You stated that the validation reports for HPLC methods 54AD10306 and 54AD10406 were described in two appendices. However, we were unable to locate these appendices. Please submit this information.

3. We noted that the Certificate of Analysis (COA) of the [REDACTED] (b) (4) [REDACTED] is not in English. Please provide a copy of the English translation.

Clinical Pharmacology

Regarding the *in vitro* metabolism study report PK032 (Section 4.2.2.4.1), please submit the data for positive-control (i.e., the known substrate for each CYP450 tested) experiments to validate the experimental conditions.

If you could please respond to this new Information Request by the end of June 2011, that would be very helpful.

Thank you for your time.

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
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/s/

CONSTANTINE J MARKOS
06/17/2011

Markos, Constantine

From: Greeley, George
Sent: Friday, June 17, 2011, 2:02 PM
To: Markos, Constantine
Cc: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Albrecht, Renata
Subject: NDA 202-514 Saflutan

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Constantine,

This email serves as confirmation of the review for Saflutan (tafluprost) conducted by the PeRC PREA Subcommittee on May 25, 2011.

The Division presented a full waiver in pediatric patients for the indication of reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.

The PeRC agreed with the Division to grant a full waiver for this product.

The pediatric record is attached for Saflutan.



1_Pediatric_Record
.pdf (62 KB)...

Thanks,

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

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CONSTANTINE J MARKOS
02/02/2012

NDA 202514
tafluprost
Chitkala Kalidas, Ph.D.

Dear Dr. Kalidas,

Please find below, comments from our Division in regards to NDA 202514:

CMC

In Section 2.3.S.4, you state that (1) analytical procedures of tafluprost drug substance are summarized in Sec. 3.2.S.4-2452; (2) method validation results are summarized in Sec. 3.2.S.4.3-2452; (3) batch analysis data for the drug substance are summarized in Sec. 3.2.S.4.4-2452. However, none of the sections that you referred to exist in the submission. Please submit the missing information.

If you could please respond to this information request as soon as possible, or by 06/10/2011, that would be greatly appreciated. There is also one previous pending IR that was e-mailed over to you on 05/20/2011, that included **Clinical, CMC, and Statistics issues**, that I still have not received a response on. Finally, we are also expecting a response from you in regards to some Microbiology/Sterility questions, sometime this first week of June 2011 (per one of your e-mails).

Thank you for your time.

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
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/s/

CONSTANTINE J MARKOS
06/06/2011

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager
Office of Antimicrobial Products
Division of Transplant and Ophthalmology Products
(301) 796-3871

REQUEST DATE
06/06/2011

IND NO.

NDA/BLA NO. 202514

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

Labeling

NAME OF DRUG
tafluprost

PRIORITY CONSIDERATION
NO, STANDARD 505(b)(1)

CLASSIFICATION OF DRUG
Ophthalmic—Prostaglandin
(4042130)

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)

NAME OF FIRM:

MERCK

PDUFA Date: 11/07/2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission:

[\\CDSESUB1\EVSPROD\NDA202514\202514.enx](#)

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: 06/27/2011

Labeling Meetings: [Insert Dates]

Wrap-Up Meeting: 09/12/2011

SIGNATURE OF REQUESTER Constantine J. Markos, B.S., Pharm.D., R.Ph.

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CONSTANTINE J MARKOS
06/08/2011

NDA 202514
Saflutan (tafluprost)
Chitkala Kalidas, Ph.D.

Dear Dr. Kalidas,

Please find below, comments from our Division in regards to NDA 202514:

Clinical

Please provide the location of the following descriptive statistics for Study 001:

Iris color by treatment group

If this information was not collected, please let us know. If it was collected and not included in the NDA submission, please submit.

CMC

1. In the drug product specification, please list impurities/degradation products in the drug product according to ICH Q3B: Each specified identified impurity, Each specified unidentified impurity, Any individual unspecified impurity, and Total impurities.
2. Based on available batch analysis and stability data, we recommend that the acceptance criterion for "Any individual unspecified impurity" be (b) (4) from (b) (4) in the drug product specification table and the acceptance criteria for other degradation products as well as total degradation products be (b) (4) accordingly.
3. For drug product analytical procedure used for identification, assay and related substances (b) (4), provide system suitability to include a standard at the quantitation limit to ensure detectability of impurities observed at that level. Submit representative chromatograms with the impurity peaks appropriately labeled to enable identification.
4. With regard to the stability data, (b) (4) in Table 3.2.P.8.3-2452-ophsln:7.
5. The impurity profile in Table 3.2.P.8.3-2452-ophsln:20 appears to be noticeably different from those in other stability data tables. Please provide a rationale. Do you know the identity of the impurity at (b) (4)?
6. In Section 3.2.P.7.1, you state that LDPE (b) (4) As leachables could be different with different components, how do you propose to ensure a consistent leachable profile?

7. Please note that in support of NDA 202514, a DMF Information Request (IR) letter was issued to the holder of DMF [REDACTED] ^{(b) (4)} on May 10, 2011.

Statistics

- For studies 001, 15-003, and 74458, please analyze the mean change from baseline at each time point for each study by imputing missing data using multiple imputation methods.
- For datasets under the ISE analysis dataset folder (datasets such as iop001, iop15003, iop74458, etc.), please describe clearly what “FAS-LOCF”, ‘FAS-DAO’, ‘PP-LOCF’, and ‘LOCF’ mean for the variable “DTYPE”. Furthermore, we recommend that you create a specific variable as the last observation carried forward flag (LOCF flag). For this LOCF flag, if an IOP value at a certain visit is carried forward from the last visit’s observed value, then the flag sets as ‘Y’, otherwise it sets as ‘N’.

We cannot locate the integrated dataset for efficacy in your April 4th 2011 submission. More specifically, in the definition PDF file for ‘ADSL’ and ‘ADOP’, the variable ‘PROTOCOL’ defined all the following seven studies: 001, P15001, P15002, P15003, P74457, P74458, and P77550; however, the actual ‘ADSL’ and ‘ADOP’ datasets only had data for study 001. Please submit the integrated efficacy dataset that has all seven studies’ efficacy data included in one big dataset. In the integrated efficacy dataset for IOP measurements, please include a variable to indicate whether the data is imputed or not.

If you could please respond to this information request as soon as possible, that would be greatly appreciated.

Thank you for your time.

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
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/s/

CONSTANTINE J MARKOS
05/20/2011

Markos, Constantine

From: Kalidas, Chitkala [chitkala_kalidas@merck.com]
Sent: Friday, May 06, 2011 6:42 PM
To: Markos, Constantine
Subject: RE: NDA 202514 - Saflutan (tafluprost) - MERCK

Hi Constantine-

Thank you for the message. I will discuss these comments with the tafluprost team and get back to you shortly.

Have a good weekend.
Chitkala

From: Markos, Constantine [mailto:Constantine.Markos@fda.hhs.gov]
Sent: Friday, May 06, 2011 6:39 PM
To: Kalidas, Chitkala
Subject: NDA 202514 - Saflutan (tafluprost) - MERCK
Importance: High

Hello Chitkala,

Please find below, comments from our Division in regards to NDA 202514:

Clinical

When we examine the Investigator list for Protocol No. 001, Eugene Protzko, M.D. is listed twice - once as Investigator Site 001-0036 and again as Investigator Site 001-0083. Stacey Ackerman, M.D. is also listed three times - once as Investigator Site 001-0056, as Investigator Site 001-0097, and again as Investigator Site 001-0098.

Please clarify the reason for multiple investigator/site numbers assigned to the same Investigator.

Microbiology (Sterility)

Provide the following information or a reference to its location in the subject submission.

1. Indicate whether the drug substance undergoes microbial limits testing upon receipt.
2. Filter validation studies (b) (4)
3. Describe how your (b) (4)
4. Provide evidence (b) (4)
5. Provide a diagram which provides the location of (b) (4)
6. Provide 3 (b) (4)

5/6/2011

7. Provide a rationale for accepting [REDACTED] (b) (4)
8. Clarify your (b) (4) procedure with respect to product inspection. Provide data to support that [REDACTED] (b) (4)
9. Confirm that (b) (4) units are inspected as would occur during routine production and that if a positive unit is identified no additional inspection will occur to reject that positive unit.
10. Confirm that there is a [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- (b) (4) Clarify these two contradictory descriptions of the manufacturing process.
11. Provide the results from sterility test validation studies which demonstrate the adequacy of your test method for this bactericidal product. We note your previous reference to Ph.Eur.2.6.1 and your failure to submit the product-specific validation studies. Indicate what types of organisms are killed and what types of organisms have reduced growth properties in your product.

If you could please respond to this information request as soon as possible, that would be greatly appreciated.

Please also respond to this e-mail so that I know that you received it. Thank you for your time, and have a nice weekend!

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager
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5/6/2011

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CONSTANTINE J MARKOS
05/10/2011

Markos, Constantine

From: Kalidas, Chitkala [chitkala_kalidas@merck.com]
Sent: Tuesday, April 19, 2011 8:53 PM
To: Markos, Constantine
Subject: RE: NDA 202514 - Saflutan (tafluprost) - MERCK
Importance: High

Hi Constantine-

Thank you for your message. I will follow up with members of our Clinical and Biostatistics team regarding your comments and get back to you shortly.

Best regards,
Chitkala

From: Markos, Constantine [mailto:Constantine.Markos@fda.hhs.gov]
Sent: Tuesday, April 19, 2011 8:50 PM
To: Kalidas, Chitkala
Subject: NDA 202514 - Saflutan (tafluprost) - MERCK
Importance: High

Hello Chitkala,

Please find below, comments from our Division in regards to NDA 202514:

Clinical

Please provide the location of the following analyses for the Intent-to-Treat population with LOCF and Per Protocol population observed cases in Studies 74458, 15-003 and 001:

Upper and lower 95% CI for the mean difference in IOP at each time point (i.e., mean IOP tafluprost minus control).

If they have not been performed, please submit them.

Statistics

It seems that the integrated datasets for efficacy were not in your recent April 4, 2011 Gateway e-submission. We are not sure whether some error occurred during the electronic submission process.

Specifically, in the dataset definition PDF file for the ISE, there are two datasets (ADSL and ADOP) defined. However, we cannot find the actual datasets under the folder "metadata." There are datasets named ADSL and ADOP under a different folder for study P001, but they are NOT the true integrated datasets and they are only for Study 001.

These complete datasets will be very helpful in expediting our statistical review and we would like to have the complete datasets for the ISE.

Our original Information Request was as follows:

4/19/2011

Please provide the integrated datasets and the programs used to conduct the analyses according to the integrated SAP for the ISE and ISS reports.

If you could please respond to this information request as soon as possible, that would be greatly appreciated.

Please also respond to this e-mail so that I know that you received it. Thank you for your time.

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager
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4/19/2011

Reference ID: 2942666

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CONSTANTINE J MARKOS
05/05/2011



NDA 202514

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Merck Sharp & Dohme Corp.
PO Box 2000
126 East Lincoln Avenue, RY33-208
Rahway, New Jersey 07065-0900

ATTENTION: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) dated January 7, 2011, received January 7, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tafluprost Ophthalmic Solution, 0.0015%.

We also refer to your January 20, 2011, correspondence, received January 20, 2011, requesting review of your proposed proprietary name, Saflutan. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

The proposed proprietary name, Saflutan, is orthographically similar to, and shares overlapping product characteristics with, Xalatan. The orthographic similarity of this name pair stems from the shared five letters that appear in the same or similar positions and similar positions of upstroke letters giving these names similar shapes. Furthermore, as demonstrated in the handwriting sample below, their first letters may look similar if the cross stroke for the 'X' (in Xalatan) occurs at a lower point on the letter. Given these orthographic similarities, it is possible that a pharmacist or nurse may misinterpret a prescription for Saflutan to be Xalatan even though Saflutan contains the additional letter ('f').

A handwritten sample showing the words "Xalatan" and "Saflutan" written in cursive. The 'X' in "Xalatan" is written with a cross stroke that is lower than the 'f' in "Saflutan", making the two words appear very similar in shape.

A second handwritten sample showing "Xalatan" and "Saflutan" in cursive. In this sample, the 'X' in "Xalatan" has a cross stroke that is higher and more distinct, making it easier to differentiate from the 'f' in "Saflutan".

In addition to the orthographic similarities between the names, Saflutan and Xalatan share overlapping product characteristics such as dosage form (ophthalmic solution), numerically similar strengths (0.015% vs. 0.005%), route of administration (eye), and frequency of administration (once daily at bedtime). Additionally, both products are stored in the refrigerator prior to dispensing and have limited stability at room temperature once opened. Furthermore, they share the same prescriber and patient populations. Finally, since they are both available in single strengths, the strength may be omitted and the product can be dispensed and administered without seeking clarification.

These orthographic similarities between Saflutan and Xalatan combined with the overlapping product characteristics increase the potential for errors to occur during the prescribing and dispensing phases of the medication use process which may result in wrong drug medication errors. Given these similarities and the fact that ‘Xalatan’ is a recognized name in the marketplace, confirmation bias may also play a role in causing confusion between this name pair.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Constantine Markos at (301) 796-3874

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/15/2011



NDA 202514

FILING COMMUNICATION

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY33-204
Rahway, New Jersey 07065-0900

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) dated January 7, 2011, received January 7, 2011, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act, for SAFLUTAN (tafluprost ophthalmic solution) 0.0015%. We also refer to your submissions dated January 20, February 9, 17, and 28, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application was considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 7, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 9, 2011.

During our filing review of your application, we identified the following potential review issues:

1. Sterility test methods and the results of validation studies do not appear to have been submitted. A description of the [REDACTED] (b) (4) [REDACTED] should have been submitted. In addition, process validation information and production parameters [REDACTED] (b) (4) [REDACTED]

- (b) (4)
- should have been submitted.
2. Referenced (b) (4) should have been submitted.
3. Drug product specifications are incomplete. An endotoxin specification, test methods and validation studies should have been submitted. Limits for potential leachables should be included in the drug product specifications.
4. The drug product container closure system is not considered qualified. A one-time freeze-thaw cycling study and a leachable study through expiry using appropriate screening methods for one stability batch should have been submitted.
5. Information on sample orientations in the stability chambers should have been submitted. Data should have been provided for samples stored in the upright, inverted and on-the-side positions to evaluate the impact of product contact with container/closure system on the drug product quality.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you of our decision.

If you have any questions, call Constantine J. Markos, B.S., Pharm.D., R.Ph., Regulatory Health Project Manager, at (301) 796-3871.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Division Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

WILEY A CHAMBERS
03/22/2011

Markos, Constantine

From: Markos, Constantine
Sent: Monday, March 07, 2011 8:18 PM
To: 'Kalidas, Chitkala'
Subject: NDA 202514 - Saflutan (tafluprost) - MERCK
Importance: High
Attachments: Industry Site Level Data Request For Site Selection Tool.doc

Hello Chitkala,

Please find below, comments from our Division in regards to NDA 202514:

Microbiology (sterility)

1. Provide the sterility test method and the results of validation studies. A detailed summary would also be acceptable.
2. Provide a description [redacted] (b) (4)
[redacted]
[redacted]
[redacted]
[redacted]
3. Provide the referenced [redacted] (b) (4)
[redacted]
4. Please establish an endotoxin specification and submit the test method and validation studies.

DSI

Reference ID: 2915484

3/7/2011

5. Please provide a site level data set. We have provided to you (attached) for your convenience the document entitled,

"Industry Site Level Data Request For Site Selection Tool," to help you prepare the data.

DMEPA

6. Please submit prototypes of the following two items for review by the Division of Medication Error Prevention and Analysis (DMEPA):

1) Foil pouch with label attached

2) Single-use LDPE container

Both items should reflect how they would be presented in the marketplace.

Statistics

7. Please provide the integrated datasets and the programs used to conduct the analyses according to the integrated SAP for the ISE and ISS reports.

If you could please respond to this information request as soon as possible, that would be greatly appreciated.

Please also respond to this e-mail so that I know that you received it. Thank you for your time.

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager
FDA/CDER/OND/OAP/DAIOP
P--301-796-3871
F--301-796-9881
Constantine.Markos@FDA.HHS.GOV

Markos, Constantine

From: Kalidas, Chitkala [chitkala_kalidas@merck.com]
Sent: Monday, March 07, 2011 8:44 PM
To: Markos, Constantine
Subject: RE: NDA 202514 - Saflutan (tafluprost) - MERCK
Importance: High

Hi Constantine-
Thank you for the e-mail. Could you please clarify whether the NDA will be filed tomorrow or if acceptance of the NDA will occur only after a response is submitted to these comments from the Agency.
Best regards,
Chitkala

From: Markos, Constantine [mailto:Constantine.Markos@fda.hhs.gov]
Sent: Monday, March 07, 2011 8:18 PM
To: Kalidas, Chitkala
Subject: NDA 202514 - Saflutan (tafluprost) - MERCK
Importance: High

Hello Chitkala,

Please find below, comments from our Division in regards to NDA 202514:

Microbiology (sterility)

1. Provide the sterility test method and the results of validation studies. A detailed summary would also be acceptable.

2. Provide a description [redacted] (b) (4)
[redacted]
[redacted]
[redacted]
[redacted]

3. Provide the referenced [redacted] of the 9 day hold time from (b) (4)
[redacted]

4. Please establish an endotoxin specification and submit the test method and validation studies.

DSI

5. Please provide a site level data set. We have provided to you (attached) for your convenience the document entitled,

"Industry Site Level Data Request For Site Selection Tool," to help you prepare the data.

DMEPA

6. Please submit prototypes of the following two items for review by the Division of Medication Error Prevention and Analysis (DMEPA):

- 1) Foil pouch with label attached
- 2) Single-use LDPE container

Both items should reflect how they would be presented in the marketplace.

Statistics

7. Please provide the integrated datasets and the programs used to conduct the analyses according to the integrated SAP for the ISE and ISS reports.

If you could please respond to this information request as soon as possible, that would be greatly appreciated.

Please also respond to this e-mail so that I know that you received it. Thank you for your time.

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager

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/s/

CONSTANTINE J MARKOS
03/08/2011

Markos, Constantine

From: Markos, Constantine
Sent: Wednesday, February 16, 2011 12:22 PM
To: 'Kalidas, Chitkala'
Subject: NDA 202514 - Saflutan (tafluprost) - MERCK
Importance: High
Attachments: p15003 71.pdf

Hello Chitkala,

Please find below, comments from our Division in regards to NDA 202514:

Clinical

Regarding 5.3.5.1. Reference P001 (A Phase 3, 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):

We are unable to locate the number of subjects randomized to PF tafluprost or PF timolol at each investigational site for P001.

Please provide the location of this information within the submission or provide a new Table with this information. For an example of what we are requesting, see Study 15-003, Table 14.1.1 where each investigational site has its number of randomized patients listed (see attached file). We do not need the number of PG naive subjects for P001 if this information is not readily available.

If you could please respond to this information request as soon as possible, that would be greatly appreciated.

Please also respond to this e-mail so that I know that you received it. Thank you for your time.

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager
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F--301-796-9881
Constantine.Markos@FDA.HHS.GOV

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Markos, Constantine

From: Kalidas, Chitkala [chitkala_kalidas@merck.com]
Sent: Wednesday, February 16, 2011 1:01 PM
To: Markos, Constantine
Subject: RE: NDA 202514 - Saflutan (tafluprost) - MERCK

Hi Constantine-

Thank you for this message. I would like to acknowledge receipt of your request for information on NDA 202514. I will contact the team about this request and get back to you as soon as possible.

Best regards,
Chitkala

From: Markos, Constantine [mailto:Constantine.Markos@fda.hhs.gov]
Sent: Wednesday, February 16, 2011 12:22 PM
To: Kalidas, Chitkala
Subject: NDA 202514 - § (b) (4) (tafluprost) - MERCK
Importance: High

Hello Chitkala,

Please find below, comments from our Division in regards to NDA 202514:

Clinical

Regarding 5.3.5.1. Reference P001 (A Phase 3, 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):

We are unable to locate the number of subjects randomized to PF tafluprost or PF timolol at each investigational site for P001.

Please provide the location of this information within the submission or provide a new Table with this information. For an example of what we are requesting, see Study 15-003, Table 14.1.1 where each investigational site has its number of randomized patients listed (see attached file). We do not need the number of PG naive subjects for P001 if this information is not readily available.

If you could please respond to this information request as soon as possible, that would be greatly appreciated.

Please also respond to this e-mail so that I know that you received it. Thank you for your time.

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager
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Constantine.Markos@FDA.HHS.GOV

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/s/

CONSTANTINE J MARKOS
03/02/2011



NDA 202514

NDA ACKNOWLEDGMENT

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY33-204
Rahway, New Jersey 07065-0900

Dear Dr. Kalidas:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act (FDCA) for the following:

Name of Drug Product: SAFLUTAN (tafluprost) 0.0015% Ophthalmic Solution Single Dose Container (MK-2452)

Date of Application: January 7, 2011

Date of Receipt: January 7, 2011

Our Reference Number: NDA 202514

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 8, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Constantine J. Markos, B.S., Pharm.D., R.Ph., Regulatory Health Project Manager, at (301) 796-3871.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
02/15/2011



NDA 202-514

INFORMATION REQUEST

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 200, RY33-204
Rahway, NJ 07065-0900

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tafluprost (MK-2452) Ophthalmic Solution.

We also refer to your January 7, 2011, New Drug Application submission.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Although you are referencing DMF (b)(4) for drug substance information, in order to facilitate our review, please provide important CMC information in Sections 2.3.S and 3.2.S of the NDA. Please include established name, structure, acceptance specification for the drug substance, and information about drug substance attributes which are important for the drug product manufacture and product performance.

If you have any questions, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely

{See appended electronic signature page}

Stephen Miller, Ph.D.
Acting Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN P MILLER
01/28/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 062690

MEETING MINUTES

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs
Sumneytown Pike
P.O. Box 1000, UG2CD-48
North Wales, PA 19454-1099

Dear Dr. Kalidas:

Please refer to your Investigational New Drug Application (IND) file for Tafluprost (MK-2452).

Please also refer to the teleconference between representatives of your firm and the FDA on August 13, 2010. The purpose of the teleconference was to discuss your planned NDA submission.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Constantine J. Markos, Pharm.D., R.Ph., Regulatory Health Project Manager at (301) 796-3871.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Division Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

DATE: August 13, 2010
TIME: 1:00 p.m. EST
APPLICATION: IND 062690
PRODUCT NAME: Tafluprost (MK-2452)
TYPE OF DISCUSSION: Type B – Pre-NDA
MEETING CHAIR: Wiley A. Chambers, M.D.
MEETING RECORDER: Constantine J. Markos, Pharm.D., R.Ph.

FDA/Attendees:

Division of Anti-Infective and Ophthalmology Products (Division)

William M. Boyd, M.D.	Clinical Team Leader
Wiley A. Chambers, M.D.	Acting Division Director
Yunfan Deng, Ph.D.	Statistical Reviewer
Constantine J. Markos, Pharm.D.	Regulatory Health Project Manager
Martin Nevitt, M.D., M.P.H.	Clinical Reviewer
Linda L. Ng, Ph.D.	Product Quality (CMC) Team Leader
Victor Ng	Regulatory Health Project Manager
Yan Wang, Ph.D.	Statistical Team Leader
James Wild, Ph.D.	Pharmacology/Toxicology Reviewer

Sponsor/Attendees:

Merck Sharp & Dohme Corp. (Merck)

Almira Chabi, M.D.	Associate Director, Clinical Research
Richard Entsuaah, Ph.D.	Executive Director, Biostatistics
Tamra Goodrow, Ph.D.	Senior Director, Worldwide Regulatory Affairs
Chitkala Kalidas, Ph.D.	Director, Worldwide Regulatory Affairs
Robert Lupinacci, M.S.	Senior Biometrician, Biostatistics
Duane Snaveley, M.A.	Director, Clinical Biostatistics
Gretchen Trout, M.S.	U.S. Regulatory Policy Lead

BACKGROUND:

On April 20, 2010, Merck submitted a Pre-NDA meeting request. On August 10, 2010, the Division provided Merck via e-mail with responses to the questions outlined in the briefing package dated July 9, 2010.

The questions from the briefing package are restated below in bold followed in italics by the comments provided by the Division to Merck. The meeting comments then follow in plain text.

MEETING OBJECTIVES:

To clarify the Division's responses to the questions outlined in the briefing package.

OPENING COMMENTS:

At the start of the meeting, Merck commented that they found the comments provided by the Division very helpful; however, they would like some clarification in regards to certain questions.

DISCUSSION POINTS:

Questions Grouped by Discipline

Clinical

Question 1

The Table of Contents for Modules 2.5 and 2.7 of the CTD are included in Section 6 of this Background Package. Does the Agency concur that the clinical data from the four pivotal clinical trials as outlined in the Table of Contents for Modules 2.5 and 2.7 of the CTD, would be adequate to support review of the NDA for preservative-free tafluprost?

FDA Response: Concur.

However, the proposed Section 2.5.6.7 references proposed tafluprost prescribing information and glaucoma treatment. There are no approved drug products for the treatment of glaucoma; the trials conducted with tafluprost would not be expected to support a treatment of glaucoma indication.

Meeting Comments: There was no further discussion of this issue.

IND 062690

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Page 3

Question 2

Does the FDA concur with the proposed plan for submission of data from the Japanese studies to support review of the NDA for preservative-free tafluprost?

FDA Response: Concur, provided the overview of results describes each of the Japanese studies individually.

Meeting Comments: There was no further discussion of this issue.

Question 3

Can FDA provide an update on the status of the [REDACTED] ^{(b) (4)}? Does the Agency anticipate that it will be able to provide an action on the NDA for preservative-free tafluprost, assuming that the data submitted are adequate to support the review and approval of the NDA?

FDA Response: The [REDACTED] ^{(b) (4)} is still under consideration by the Agency. At this time, the Agency is not able to respond to the second part of this question.

Meeting Comments: There was no further discussion of this issue.

Question 4

Merck believes that the format of the two CSRs included in this Background Package will be acceptable to support the review of the NDA. Does the Agency concur?

FDA Response: The formats of the two CSRs are acceptable with the revisions suggested below. Because the CSRs for 15-003 and the Prototype CSR are incomplete (e.g. missing a linked table of contents, case report forms (CRFs) for discontinued patients, some appendices), we may have additional comments or questions after NDA submission.

The CRFs for all Phase 3 discontinued patients, regardless of reason, should be submitted to the NDA.

Cited References should be provided in their entirety.

Regarding the Protocol 001 CSR Prototype, iris pigmentation can influence reductions in intraocular pressure; Section 11.4 of the Protocol should include iris color as a classification variable. The investigator information should include the name of the principle investigator and his/her address, number of patients enrolled at each site, and the assigned investigator identification number.

IND 062690

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Page 4

For Protocol 15-003, we cannot locate the results for the treatment comparisons of IOP reduction at each of the time points on Week 2, Week 6, Month 3, Month 6, and Month 9.

It is recommended that the treatment difference of the mean change from baseline at each of the time points (including its 95% CI) be presented separately in each of the five studies that are going to be included in the integrated efficacy and safety analyses. We recommend that the analysis strategy be similar as that proposed in Table X on page 27 of the Protocol 001 CSR Prototype. We expect the mean change from baseline at each time point for each study is analyzed with and without adjusting for the baseline IOP and ocular diagnosis, with and without repeated measurement method, and in both per-protocol and the full analysis sets. We also recommend that you analyze the data for worst eye, fellow eye, and the average of both eyes.

Meeting Comments: Merck responded that they will provide the CRFs for Phase 3 discontinued patients, regardless of cause. Links and cited references will also be provided in the NDA submission. The Division stated that as a general rule, a patient's IOP should not differ by more than 5 mm Hg between eyes at baseline if the IOPs are to be averaged.

Question 5

Does the Agency concur with the proposed plan for analysis and presentation of pooled efficacy and safety results from the two Phase II and three Phase III pivotal studies, as described in the statistical analysis plan for the Integrated Summary of Efficacy and for the Integrated Summary of Safety?

FDA Response: The proposed plan for the ISE and ISS are acceptable. A table with information regarding treatment exposure (i.e. treatment duration) for the pooled safety population should be provided.

We expect the analysis strategy for the ISE is similar as that proposed in Table X on page 27 of the Protocol 001 CSR Prototype. Please also include a flag to indicate the values that were imputed using the LOCF method for the integrated dataset.

Meeting Comments: There was no further discussion of this issue.

Question 6

As preservative-free tafluprost has been marketed in the EU and other parts of the world since 2008, Merck proposes to provide a summary of available post-marketing safety data as part of Module 2.7. The post marketing safety data for tafluprost are collected together for both the preservative-containing and preservative-free formulations and cannot be consistently separated by the type of formulation. Therefore, Merck proposes to submit the integrated post marketing safety data as part of Module 2.7 for the preservative-free tafluprost NDA. Does the Agency concur with this approach?

FDA Response: Concur, although an attempt should be made to summarize the data according to the formulation type when known.

Meeting Comments: There was no further discussion of this issue.

Question 7

Does the Agency agree that the organization of the pre-clinical studies as shown in Table of Contents for Module 4 will support review of the NDA for preservative-free tafluprost?

FDA Response: Agreed.

Meeting Comments: There was no further discussion of this issue.

Quality

Question 8

We believe that the proposed contents of the chemistry, manufacturing and controls section of the CTD, as outlined in Section 6 of this Background Package will be adequate to allow the review of the NDA to support approval of preservative-free tafluprost. Does the Agency concur?

FDA Response: There is not enough information present in the submission to answer this question. While we note that Section 6 lists the titles of the CTD sections, the determination of whether sufficient quality information is present to allow substantive review will occur after submission of the NDA and review of the data present in Module 3.

Meeting Comments: There was no further discussion of this issue.

Pediatric Population

Question 9

Merck would like to request Agency feedback on the possibility of issuing a Pediatric Written Request in response to the PPSR.

FDA Response: The Agency is amenable to issuing a Pediatric Written Request for this drug product. An adequate pediatric study for this product would be expected to have a duration of at least 20 years to satisfactorily answer questions of safety due to the long term increases in iris pigmentation in this population.

Meeting Comments: There was no further discussion of this issue.

Risk Evaluation and Mitigation Strategies (REMS)

Question 10

The safety profile of preservative-free and preservative-containing formulations of tafluprost has been closely monitored by Santen and Merck as part of routine pharmacovigilance since their first approval in 2008. No safety concerns have been identified that would warrant consideration of a Risk Evaluation and Mitigation Strategies (REMS) plan. The Company proposes that routine pharmacovigilance measures (labeling and spontaneous adverse event reporting) are appropriate for the management of the product's risks. Does the Agency concur?

FDA Response: Concur, provided review of the application reveals no unexpected safety concerns with this product.

Meeting Comments: There was no further discussion of this issue.

Plans for Electronic Submission

Question 11

MRL proposes to submit the Statistical Review Aids for only the 3 pivotal, Phase III studies (Protocols 001, 15-003 and 74458) as part of the eCTD submission for the preservative-free tafluprost NDA. Does the Agency concur that the proposed strategy is acceptable?

IND 062690

Teleconference Minutes 08-13-10

Page 7

FDA Response: No. If datasets and source code are available for the Phase 2 studies, it is recommended that the datasets and source code be submitted for these studies in addition to the datasets and source code for all programs used in the analysis of the Phase 3 studies.

Meeting Comments: Merck agreed to provide the completed SAS code datasets including those from their Japanese studies.

Question 12

MRL proposes to submit the Division of Scientific Investigations (DSI) files for only the 3 pivotal, Phase III studies (Protocols 001, 15-003 and 74458). Does the Agency concur that the proposed strategy is acceptable?

FDA Response: Concur.

Meeting Comments: There was no further discussion of this issue.

Question 13

MRL believes that the detailed derived variables document along with the statistical review aids, defined.pdf and the annotated case report forms would provide adequate information to the Reviewer on how the derived variables were obtained. Does the Agency agree with this proposal?

FDA Response: No. All SAS programs are potentially useful because they describe the process used in the analysis. It is recommended that all SAS programs used in the analysis of Phase 2 and Phase 3 studies be submitted.

We cannot locate the statistical review aids and defined.pdf in the meeting package, therefore we may have additional comments regarding the statistical review aids, and defined.pdf once they are submitted.

For the analysis datasets, please include a flag to indicate the values that were imputed using the LOCF method. We may request additional datasets and SAS programs during the NDA review process.

Meeting Comments: Merck will provide a statistical review aid when it is finalized.

IND 062690

Teleconference Minutes 08-13-10

Page 8

Question 14

To maintain confidentiality, financial disclosure information will be submitted for the following studies conducted by Santen Inc.: Study 74458, 15-003, 74460, 15-001, 15-002, 74457, 77550 and 77552. In addition, the financial disclosure information will also be provided for Protocol 001 conducted by Merck. The financial disclosure information for the Santen studies and the Merck study will be submitted as separate eCTD sequences for the preservative-free tafluprost NDA filing. The complete eCTD information for the NDA filing for preservative-free tafluprost including the separate eCTD sequences for the financial disclosure information will be submitted on the same day. Does the Agency agree with this proposal?

FDA Response: Acceptable.

Meeting Comments: There was no further discussion of this issue.

Labeling

Question 15

Does the Agency agree that the proposed draft labeling included in Section 4 of this Background Package could be supported by the clinical development program as described in Section 5?

FDA Response: Final labeling is a review issue and will be determined at the time of the NDA review.

Meeting Comments: There was no further discussion of this issue.

Regulatory Planning

Question 16

For planning purposes, Merck would like to request FDA feedback on whether the Division anticipates that an Advisory Committee meeting will be required during the review of the NDA for preservative-free tafluprost.

FDA Response: The Agency routinely conducts an Advisory Committee Meeting for all new molecular entities.

Meeting Comments: There was no further discussion of this issue.

IND 062690

Teleconference Minutes 08-13-10

Page 9

Constantine J. Markos, Pharm.D., R.Ph.
Regulatory Health Project Manager

Wiley A. Chambers, M.D.
Acting Division Director

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/s/

WILEY A CHAMBERS
09/30/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 62,690

MEETING MINUTES

Santen Incorporated
c/o Merck & Co., Incorporated
Attention: Peter J. Basseches, Ph.D.
Director, Worldwide Regulatory Affairs
Sumneytown Pike
P.O. Box 1000, UG2CD-48
North Wales, Pennsylvania 19454-1099

Dear Dr. Basseches:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-2452 (Tafluprost).

We also refer to the End of Phase 2 meeting between representatives of your firm and the FDA on August 24, 2009.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective
and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 24, 2009

MEETING TIME: 1:00 pm

APPLICATION (DRUG): IND 62,690
MK-2452 (Tafluprost)

SPONSOR: Santen Inc. c/o Merck & Co., Inc.

TYPE OF MEETING: Type-B, End of Phase 2

MEETING CHAIR: Wiley A. Chambers, M.D.

MEETING RECORDER: Michael Puglisi

FDA PARTICIPANTS: Division of Anti-Infective and Ophthalmology Products

Wiley Chambers/ Acting Director
Jennifer Harris/ Medical Officer
Lucious Lim/ Medical Officer
Martin Nevitt/ Medical Officer
Sonal Wadhwa/ Medical Officer
Yunfan Deng/ Statistical Reviewer
Yan Wang/ Statistical Team Leader
Linda Ng/ Premarketing Pharmaceutical Assessment Lead
Theresa Allio/ PharmTox Reviewer
Charles Bonapace/ ClinPharm Team Leader
Yongheng Zhang/ ClinPharm Reviewer
Fariba Izadi/ Project Manager
Michael Puglisi/ Project Manager

INDUSTRY PARTICIPANTS:

Representing Santen, Inc.

Peter Basseches/ Regulatory Affairs
Tamra Goodrow/ Regulatory Affairs
Tony Ho/ Clinical Neuroscience & Ophthalmology
David Michelson/ Clinical Neuroscience & Ophthalmology
Jeffrey Seeburger/ Clinical Neuroscience & Ophthalmology
Lisa Mahnke/ Clinical Pharmacology

Richard Entsuah/ Biostatistics

Robert Lupinacci/ Biostatistics

(b) (4)

MEETING OBJECTIVE: To discuss the Sponsor's Phase 3 development program for MK-2452 (Tafluprost) for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

SUMMARY OF DISCUSSION:

Agency responses to the questions outlined in the July 24, 2009, background package were provided to the Sponsor in a facsimile dated August 18, 2009 (see text in italics below). This meeting served to clarify those responses, as follows:

Questions for the Agency:

Clinical

Question 1: As noted above, MRL plans to use timolol maleate as the active comparator. In a previous conversation with MRL and previous Santen Type C meeting (2005), FDA indicated that timolol was acceptable for use as an active comparator in glaucoma trials. Could FDA please confirm that use of preservative-free timolol maleate is acceptable as the active comparator in this additional Phase III study intended to support US registration?

FDA Response: *The use of the approved preservative free timolol maleate is acceptable.*

Comment: There was no discussion of this matter during the meeting.

Question 2: Based on the summary of results from the studies described above (and as described in this meeting background package), does the Agency concur that the 0.0015% dose is the appropriate dose for clinical use, and that no further dose-exploration is required?

FDA Response: *Based on the information provided in the meeting package, the 0.0015% dose appears appropriate for future phase 3 trials based on its relative safety and IOP lowering.*

Comment: There was no discussion of this matter during the meeting.

Question 3: Does FDA concur that the results from the bridging study between preservative-free and preservative-containing formulations of tafluprost are adequate to support bridging to available clinical studies that employed the preservative-containing formulation of tafluprost?

FDA Response: *No. The duration of the bridging trial is inadequate. Applanation tonometry (IOP) should be measured at both peak and trough timepoints during the day at baseline, week (1 or 2), week 6, and week 12.*

Meeting Comments: The Sponsor proposed a 3-month study of preservative-free tafluprost compared to timolol to demonstrate equivalence of preservative-free tafluprost to tafluprost with

preservative without generating additional bridging data. FDA concurred that the proposed study in combination with study(ies) which demonstrated the efficacy of tafluprost with preservative may be sufficient to support review of a preservative-free tafluprost. It would not support equivalence between preserved tafluprost and non-preserved tafluprost.

Question 4: Assuming successful demonstration of non-inferiority to timolol maleate in the new study MRL is planning to conduct, MRL believes that the combined data from the three pivotal studies (the proposed MRL study plus the two Phase III studies conducted by Santen) will be sufficient to support the approval of tafluprost PF and PC formulations. Does the Agency concur?

FDA Response: See response to Question 3. Approval is a review issue; data from the planned studies of at least 12 weeks duration would support the filing of a NDA for the formulations tested for at least 12 weeks.

Comment: There was no discussion of this matter during the meeting.

Question 5: [REDACTED] (b) (4)

FDA Response: [REDACTED] (b) (4)

Meeting Comments: [REDACTED] (b) (4)

Question 6: [REDACTED] (b) (4)

Question 7: Does the Agency concur that the clinical pharmacology studies conducted to date are sufficient to support registration of tafluprost?

FDA Response: *Concur.*

Comment: There was no discussion of this matter during the meeting.

Question 8: Based on the evidence described above, we do not feel it would be necessary to perform endothelial cell density and morphology. Does the Agency concur?

FDA Response: *Concur.*

Comment: There was no discussion of this matter during the meeting.

Question 9: Based on the results of previous clinical laboratory evaluation, we do not expect to observe clinically important laboratory trends in the proposed study and do not feel it would be necessary to perform these investigations in the proposed Phase III study. Does the Agency concur?

FDA Response: *Yes.*

Comment: There was no discussion of this matter during the meeting.

Question 10: a) Does the Agency concur that it is not necessary to perform ECG in the proposed Phase III study?

FDA Response: *Yes.*

Comment: There was no discussion of this matter during the meeting.

b) Does the Agency concur that conduct of a thorough QT study is not warranted to support topical administration of tafluprost?

FDA Response: *Yes.*

Comment: There was no discussion of this matter during the meeting.

Question 11: Overall, iris, eyelid, and eyelash changes have been well studied and documented in the previous tafluprost development program and for the drug class. We would expect that the results of the proposed 12-week study would support those already established in the previous development program and in field, and so we do not feel that it would be necessary to photographically document and analyze these changes. Any clinically important events would still be captured through adverse event reporting. Does the Agency concur with this strategy?

FDA Response:

(b) (4)

[Redacted]

[Redacted]

(b) (4)

Question 12: MRL proposes to use the analytic strategy described above to evaluate the primary efficacy hypothesis. Does the Agency concur with the proposed analytic strategy?

FDA Response: *No. We recommend that the IOP change from baseline at each time point be analyzed separately. The proposed modeling approach may be used for the purpose of sensitivity analysis. The statistical analysis plan should clearly describe the model and the underlying assumptions; and please also provide all relevant references cited in the analysis plan.*

Additional Statistical Comments:

1. *Please delineate the primary hypotheses in statistical terms (including the population parameters, non-inferiority margin, and endpoint assessment time-points). Based on the proposed testing procedure, the Type I error rate is not controlled if one intends to claim non-inferiority of the test drug over the control at the majority of the 9 time points using 1.0 mmHg margin.*
2. *We recommend you use the ITT analysis set as the primary analysis set. The PP analysis should also be included to support the robustness of the treatment effect.*
3. *Please describe your plan for handling missing data for the primary analysis.*
4. *To claim superiority, the test drug would need to be superior to the control at all 9 time points tested in replicated trials.*
5. *Please provide the justification for the proposed sample size, describing clearly the rationale and assumption for choosing 324 patients and its resulting type II error.*

Meeting Comments: The Agency reiterated its position that it does not accept the Sponsor's proposed constrained longitudinal data analysis method as the primary statistical approach, although it may be used as a sensitivity analysis. The Agency does not believe the longitudinal based model is appropriate since there is the potential to see differential efficacy across the different timepoints. The Agency stated that its preference was to use the ITT as the primary

population but indicated that either population could be primary, as long as both populations are analyzed. It was recommended that the Sponsor use Baseline Observation Carried Forward to handle missing data in the final analysis.

The Agency stated that it would be acceptable to use a definition of non-inferiority; preservative free (PF) tafluprost (0.0015%) will be considered non-inferior to PF timolol maleate (0.5%) if the upper bound of the two-sided 95% confidence interval (CI) of the between-treatment difference in mean IOP change from baseline (PF tafluprost minus PF timolol maleate) is no higher than 1.5 mmHg at all 9 timepoints during the study (0800 hrs, 1000 hrs and 1600 hrs at Weeks 2, 6 and 12).

Nonclinical

Question 13: Does the Agency concur that the preclinical toxicology studies conducted to date are sufficient to support registration of tafluprost?

FDA Response: *The studies conducted to date would support an NDA filing. The question regarding sufficiency to support registration would be evaluated during the application review.*

Comment: There was no discussion of this matter during the meeting.

Question 14: Merck believes the carcinogenicity studies conducted are sufficient to support registration of tafluprost. Does the Agency concur?

FDA Response: *See response to question 13.*

Comment: There was no discussion of this matter during the meeting.

Action Items:

The Agency agreed to issue minutes of this meeting within 30 days.

Minutes Prepared by: *{See appended electronic signature page}*
Michael Puglisi
Project Manager

Concurrence by: *{See appended electronic signature page}*
Wiley A. Chambers, M.D.
Acting Division Director

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-62690	GI-1	SANTEN INC	AFP-168
IND-62690	GI-1	SANTEN INC	AFP-168

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

/s/

WILEY A CHAMBERS
09/23/2009



IND 62,690

Santen Incorporated
Attention: Nancy Yee
Manager, Regulatory Affairs
555 Gateway Drive
Napa, California 94558

Dear Ms. Yee:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AFP-168 (tafluprost ophthalmic solution).

We also refer to the meeting between representatives of your firm and the FDA on October 12, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective and Ophthalmology
Products, HFD-520
Office of Antimicrobials
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 12, 2005

MEETING TIME: 11:00 am

APPLICATION (DRUG): IND 62,690
AFP-168 (tafluprost ophthalmic solution)

SPONSOR: Santen Incorporated
TYPE OF MEETING: Type-C, Clinical Guidance

MEETING CHAIR: Wiley A. Chambers, M.D.
MEETING RECORDER: Michael Puglisi

FDA PARTICIPANTS:

Janice Soreth/ Division Director
Wiley Chambers/ Deputy Division Director
William Boyd/ Clinical Team Leader
Jennifer Harris/ Medical Officer
Lucious Lim/ Medical Officer
Rhea Lloyd/ Medical Officer
Martin Nevitt/ Medical Officer
Michael Puglisi/ Project Manager
Raphael Rodriguez/ Project Manager
Alison Rodgers/ Project Manager
Lori Gorski/ Project Manager

INDUSTRY PARTICIPANTS:

Nancy Yee/ Manager, Regulatory Affairs
Jeff Wells/ Vice President, Research & Development
Mark Mannebach/ Vice President, Regulatory Affairs
Mihoko Harr/ Manager, Worldwide Clinical Affairs
Masayo Hashimoto/ Project Management

MEETING OBJECTIVE: To discuss the Sponsor's clinical plans for a possible NDA submission of AFP-168 (tafluprost ophthalmic solution) for reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

SUMMARY OF DISCUSSION:

Agency responses to the Sponsor's meeting questions were provided to them in a fax dated October 6, 2005. This meeting served to clarify those responses, as follows:

Questions for the Agency:

1. Safety Profile

Once Santen's current Phase III studies are completed, human exposure to tafluprost 0.0015% will include topical ophthalmic use in up to 1,188 subjects, with up to 891 being exposed for twelve months. Does the Division concur that this level of exposure is adequate to allow an assessment of the safety of tafluprost 0.0015% for an NDA?

Agency Response: *Concur.*

2. Efficacy Profile

The designs of ongoing Phase III clinical studies and the design of an additional proposed Phase III study are provided in Attachment 1. Understanding the limitation that Phase III data are not yet available, does the Division concur that the proposed clinical program will be adequate to assess the efficacy of tafluprost 0.0015%?

Agency Response: *Concur. Although it is acceptable to use timolol maleate 0.5% as the active control in the proposed phase 3 study, the division recommends that the sponsor use latanoprost, brimatoprost, or travoprost as the active control in this additional study.*

The sponsor should be aware that Study 74458, conducted in the EU, does not have a primary efficacy variable acceptable in the U.S.

3. Cross-Reference of Data



Minutes Prepared by: Michael Puglisi
Project Manager

Concurrence by: Wiley A. Chambers, M.D.
Deputy Division Director

Janice M. Soreth, M.D.
Division Director

**This is a representation of an electronic record that was signed electronically and
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/s/

Janice Soreth
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