

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202667Orig1s000**

**OTHER REVIEW(S)**

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

**PATIENT LABELING REVIEW**

Date: **December 21, 2011**

To: Renata Albrecht, MD, Director  
**Division of Transplant and Ophthalmology Products (DTOP)**

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

Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling Team  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling (Patient Package Insert and Instructions for Use)

Drug Name (established name): COSOPT PF (dorzolamide hydrochloride and timolol maleate)

Dosage Form and Route: Ophthalmic Solution 2.0% / 0.5%

Application Type/Number: NDA 202-667

Applicant: Merck, Sharp and Dohme Corporation

## 1 INTRODUCTION

On February 16, 2011, Merck, Sharp and Dohme Corporation submitted a New Drug Application (NDA 202-667) for COSOPT PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution) 2.0% / 0.5%, a carbonic anhydrase inhibitor with a beta-adrenergic receptor blocking agent indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone.

This review is written in response to a request by the Division of Transplant and Ophthalmology Products (DTOP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Cosopt PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution) 2.0% / 0.5%.

## 2 MATERIAL REVIEWED

- Draft COSOPT PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution) 2.0% / 0.5% Patient Package Insert (PPI) and Instructions for Use (IFU) received on February 16, 2011 and received by DMPP on December 19, 2011.
- Draft COSOPT PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution) 2.0% / 0.5% Prescribing Information (PI) received February 16, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on December 19, 2011.
- ZIOPTAN (tafluprost ophthalmic solution) 0.0015% comparator labeling.

## 3 REVIEW METHODS

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

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

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the prescribing information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

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/s/  
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SHAWNA L HUTCHINS  
12/21/2011

MELISSA I HULETT  
12/21/2011

MEMORANDUM

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

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DATE: December 14, 2011

TO: Rhea Lloyd, M.D.  
Medical Officer  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products

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

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

THROUGH: Tejashri Purohit-Sheth, M.D.  
Division Director (Acting)  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: NDA 202667

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

DRUG: Cosopt Preservative-Free Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate)

NME: No

THERAPEUTIC CLASSIFICATION: No

INDICATIONS: For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers

NDA : 202667

CONSULTATION REQUEST DATE: February 18, 2011

PDUFA DATE: December 16, 2011

**I. BACKGROUND:**

This CIS Addendum is submitted to addend the CIS for Cosopt Preservative-Free Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate) entered into DARRTS on July 16, 2011 in order to provide supplemental information regarding OSI recommendation.

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., (Merck), submitted a new drug application NDA 202-667: COSOPT® Preservative-Free Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate) on February 16, 2011. The proposed indication is the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers. Preservative-free (PF) COSOPT is a fixed dose combination of 2.0% dorzolamide hydrochloride and 0.5% timolol maleate (also referred to as PF dorzolamide/timolol or PF combination). It is identical to a previously marketed combination of dorzolamide hydrochloride/timolol maleate ophthalmic solution except for the lack of the preservative. To support the approval, the Applicant provided data from a single investigator, single-center, randomized, double-masked study in support of the application. The clinical portion of the application has been preliminarily reviewed by the Division, and no issues have been identified to date to suggest a problem with data integrity. The protocol to be inspected was Protocol 081 which is a multiple-dose, double-masked, parallel, active treatment controlled study of preservative-free 2.0% dorzolamide/0.5% timolol combination and 2.0% dorzolamide/0.5% timolol combination with preservative in patients with elevated IOP. This study was conducted at a single center by a single investigator, and it was completed in 1997.

A consult from DAIOP to DSI (now OSI) was received on February 18, 2011. The data generated from the above study was considered pivotal and inspection of the above site was requested to verify the quality of conduct of the study for this NDA. There is no change in the previous conclusion regarding data integrity for the clinical investigator. This addendum was

written at the request of the DTOP Division Director Dr. Renata Albrecht who requested a recommendation from OSI as to whether this study can be used to support NDA 202667 approval. Please see the original CIS for further background, including outlines of the protocols audited and a brief summary of study results.

This was a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of this application.

## II. RESULTS (by Site):

### The site was not inspected:

Name of CI	Protocol # and # of Subjects:	Inspection Date	Final Classification
<b>Robert A. Laibovitz, MD</b> Eye Research Associates 3307 Northland Drive, Suite 470 Austin, TX 78731 Phone #: 512-345-7040	Study 081/ 261 subjects	Not applicable	Not applicable/ Unable to verify data

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

#### 1. Dr. Robert A. Laibovitz, MD

Eye Research Associates  
 3307 Northland Drive,  
 Suite 470  
 Austin, TX 78731  
 Phone #: 512-345-7040

##### a. What was inspected?

This inspection of Dr. Laibovitz's site was not conducted because according to the clinical investigator, all records had been reportedly discarded or destroyed upon his retirement.

**b. General observations/commentary:**

Inspection of the CI records for the study was not possible because the source data were discarded.

The CI is retired, and he is no longer conducting research. Dr. Laibovitz's site had been inspected in the past. The inspectional history of Dr. Laibovitz shows that he was inspected on November 7, 1996 (Sponsor: (b)(4)) on May 9, 1989 (Sponsor: (b)(4)) and on December 28, 1995 (Sponsor (b)(4)). All the above mentioned inspections except for NDA (b)(4) (NAI) revealed regulatory violations and were classified VAI. Examples of a regulatory violations observed during previous inspections include failure to adhere to protocol (NDA (b)(4)) and inadequate patient consent form (NDA (b)(4)). While regulatory violations were observed during inspections for NDA (b)(4) and NDA (b)(4), the CI's data for the inspected studies was considered generally reliable.

**c. Assessment of data integrity:**

An inspection of CI records was not possible because the CI's original Study 081 records and associated subjects' source records were not available. As a result, we are unable to verify the adequacy of conduct of the study at Dr. Laibovitz's site and thus are unable to make a recommendation on the overall reliability of safety and efficacy data for this study.

**IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

OSI's recommendations on data reliability are based on on-site inspections of study related documents at a small sample of sites, which may include clinical investigator, sponsor, and/or CRO sites responsible for study related procedures and/or oversight. An inspection of Dr. Laibovitz's original Study 081 records and associated subjects' source records for this study was not possible because records were destroyed by the clinical investigator upon his retirement. Therefore, no verification of Study 081 data provided by Dr. Laibovitz is possible, and we are unable to make an assessment regarding the reliability of the data (e.g., existence of subjects, adequacy of informed consent process, confirmation of subject eligibility or outcome, drug compliance or accountability, etc.) from this site based on inspection of on-site clinical trial records.

Given the inability to verify source clinical trial records at the clinical site of Dr. Laibovitz, a possible inspection of the sponsor/applicant to evaluate sponsor/monitor records related to Dr. Laibovitz's site was discussed in May 2011 with Dr. Wiley, then Division Director of DAIOP. The decision was made to not conduct an inspection of Merck based on the discussion with Dr. Wiley, as the clinical investigator reported that source records were destroyed and verification of the site's actual source documentation would still be

impossible.

**Recommendations:**

As noted above, OSI recommendations regarding data reliability are based on the results of on-site inspections conducted at clinical investigator, sponsor, and/or CRO sites. Unfortunately, the CI records were destroyed at Dr. Laibovitz's site, the sole study site that enrolled subjects in Study 081, and no inspection of clinical trial records could be conducted. Study data verification could not be accomplished with inspection of the sponsor Merck, since the source data were destroyed. Since OSI is unable to verify the adequacy of conduct of the study at Dr. Laibovitz's site, we are unable to make a specific recommendation on the overall reliability of the safety and efficacy data submitted by the sponsor in support of Study 081.

In the absence of inspectional data for Study 081, we suggest that the review division consider the following information relevant to assessment of Dr. Laibovitz's general study conduct. We note that OSI has not received specific negative information on Dr. Laibovitz's conduct of this study, and there have been no relevant complaints submitted to OSI. Previous OSI inspections of his site for other studies (detailed above in part b.) did not identify serious regulatory violations. Although OSI is unable to make any specific recommendation on data reliability for Study 081 due to the inability to verify the data through on-site inspections, based on the above assessment of previous inspectional history, there are no specific concerns that are raised regarding Dr. Laibovitz's general compliance with Good Clinical Practice. In light of this, OSI recommends that the review division assess the data for Study 081 just as would be done for an NDA if no clinical investigator/sponsor/CRO inspections had been requested.

*{See appended electronic signature page}*

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

CONCURRENCE:

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Susan Thompson, M.D.  
Acting Team Leader  
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Office of Scientific Investigations

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Tejashri Purohit-Sheth, M.D.  
Acting Division Director  
Division of Good Clinical Practice Compliance  
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/s/  
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KASSA AYALEW  
12/14/2011

SUSAN D THOMPSON  
12/14/2011

TEJASHRI S PUROHIT-SHETH  
12/15/2011

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

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

## Memorandum

**Date:** September 30, 2011

**To:** Alison Rodgers, Regulatory Project Manager  
Division of Transplant and Ophthalmology Products

**From:** Christine Corser, Pharm.D., Regulatory Review Officer  
Division of Professional Promotion (DPP)

**Subject:** NDA 202667  
Cosopt PF (dorzolamide hydrochloride and timolol maleate)  
Ophthalmic Solution

---

As requested in your consult dated March 23, 2011, DPP has reviewed the draft labeling for Cosopt PF (dorzolamide hydrochloride and timolol maleate) Ophthalmic Solution.

DPP's comments are based on the substantially complete version of the labeling titled, "Label draft #1 091911.doc," which was sent via email from Alison Rodgers on September 19, 2011.

DPP's comments are provided in the attached, clean version of the labeling.

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

Thank you for the opportunity to provide comments.

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/s/  
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CHRISTINE G CORSER  
09/30/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

Date: August 2, 2011

Application Type/Number: NDA 202667

To: Renata Albrecht, MD, Director  
Division of Transplant and Ophthalmology (DTOP)

Through: Irene Z. Chan, Pharm.D., BCPS, Team Leader  
Carol Holquist, R.Ph., Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Morgan Walker, Pharm.D., M.B.A., Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Cosopt PF (Dorzolamide HCl and Timolol Maleate) Ophthalmic Solution, 2%/0.5%

Applicant: Merck Sharp & Dohme Corp.

OSE RCM #: 2011-511

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## 1 INTRODUCTION

This review responds to a request from the Division of Transplant and Ophthalmology Products (DTOP) for a medication error assessment of the labels and labeling submitted by Merck Sharp & Dohme Corporation on February 18, 2011.

### 1.1 PRODUCT INFORMATION

Cosopt PF is a combination of Dorzolamide Hydrochloride/Timolol Maleate Ophthalmic Solution. Cosopt PF differs from the currently marketed Cosopt because it lacks a preservative (benzalkonium chloride 0.0075%,). Dorzolamide hydrochloride 2% is an ophthalmic carbonic anhydrase inhibiting drug. Timolol maleate 0.5% is a beta-blocking drug. Both drugs work to lower intraocular pressure in the eye in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers. The dose and frequency for Cosopt PF is 1 drop into the affected eye(s) twice daily. Cosopt PF will be supplied in a foil pouch containing 15 low-density polyethylene (LDPE) single use containers, with 0.2 mL per container. Cosopt is packaged in bottle containing 10 mL of the drug.

## 2 METHODS AND MATERIALS

### 2.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Cosopt is currently marketed; therefore, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on 6/19/2011, to identify medication errors involving Cosopt, dorzolamide or timolol.

The MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues” were used as search criteria for *Reactions*. The search criteria used for *Products* were active ingredients “dorzolamide” and “timolol”, trade name “Cosopt”, and verbatim substance search “dorz%”, “tim%”, and “cos%”. Date limitations were April 7, 1998 (Cosopt approval date) to present.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review were excluded from further analysis.

### 2.2 LABEL AND LABELING

Using failure mode and effects analysis (FMEA), the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the labels and labeling of products. This review evaluates the labels and labeling submitted on February 18, 2011 (see Appendices A-F). In addition, DMEPA reviewed approved labels and labeling for the currently marketed Cosopt (see Appendices G). These were reviewed so that comparisons could be made across the product line.

### 3 RESULTS

The following section describes our findings and analysis of the FDA Adverse Event Reporting System (AERS) search and review of the labels and labeling. We note that the packaging configuration contains more than the recommended dose and the usual dosage statement on the carton labeling and container label states [REDACTED] (b) (4). Our concerns with the combination of the packaging configuration and the accompanying statement are discussed in Section 4.

#### 3.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE:

The AERS search conducted on May 19, 2011 to identify errors with Cosopt, yielded 127 cases (see Appendix H). None of the 127 cases involved the product Cosopt. However, there were a total of 24 cases in which there were potential medication errors and wrong drug dispensed due to similar packaging involving the following medications:

- Timolol Maleate Ophthalmic Solution, USP 0.5%
- Levobunolol Hydrochloride Ophthalmic Solution, USP 0.5%
- Betaxolol Hydrochloride 0.5%
- Timolol Gel Forming Solution Ophthalmic Gel 0.25% and 0.5%
- Timoptic XE 0.25% and 0.5%
- Tobramycin
- Tropicamide
- Trusopt 2%
- Prednisolone 1%
- Betoptic
- Betimol

All of the above mentioned product labels were reviewed and compared to Cosopt PF labels and found not to pose any risk of confusion with Cosopt PF. Therefore, all 127 cases were considered not relevant to this review.

#### 3.2 LABEL AND LABELING:

A comparison between Cosopt and Cosopt PF labels did not identify a risk for selection error, since the Cosopt PF labels and labeling are adequately differentiated from Cosopt labels and labeling. However, a review of the Cosopt PF labels and labeling identified the following deficiency:

- Inadequate prominence of important information on the pouch labels and carton labeling

We provide labeling recommendations in section 4 to address this deficiency.

### 4 DISCUSSION

The Office of New Drug Quality Assessment (ONDQA) has informed DMEPA that the container for this drug product contains a deliverable volume of 200 microliters.

(b) (4) Since the recommended dose is one drop in affected eye(s), the container has (b) (4) the amount needed for administration.

This may encourage patients to inappropriately hoard ‘extra’ doses or not properly discard the remainder after each use.

Additionally, the user may be encouraged to use more in one eye than is needed (consistent with the ‘more is better’ doctrine). Although there may not be any safety issues related to overdose from a clinical standpoint, the practice of saving the remaining contents of the container for future doses may cause bacterial contamination of the eye since this is a preservative-free product. Thus, the importance of discarding the unused portion needs to be clearly communicated.

One way to minimize this risk is to use the least amount of overfill beyond the volume needed for one drop. However, we recognize that this may not be feasible given the stage of the application process. We therefore recommend managing the risk of overdose through our labeling and label recommendations in Section 5.2.

## **5 CONCLUSION AND RECOMMENDATIONS**

Our evaluation of the proposed retail and professional sample carton labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1 Comments to the Division to be discussed. Section 4.2 (*Comments to the Applicant*) contains our recommendations for the container labels, carton and pouch labeling. We request these recommendations be communicated to the Applicant prior to approval of this NDA.

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

### **5.1 COMMENTS TO THE DIVISION**

#### **A. GENERAL COMMENTS**

DMEPA was informed by CMC that the current labels and labeling do not reflect the correct established name. We defer to CMC for determination of the appropriate established name that will be included on all labels and labeling for this product.

#### **B. INSERT LABELING**

In sections 3 and 11 of the insert labeling, the strength is expressed in terms of (b) (4) instead of “%” like the carton labeling and container labels. The insert should present the strength consistent with the container labels and carton labeling

## 5.2 COMMENTS TO THE APPLICANT:

### A. POUCH LABELS AND CARTON LABELING (retail and professional samples)

1. Revise the statement [REDACTED] (b) (4) to read “0.2 mL in each single-use container” in order to improve clarity.
2. Bold the statement “Throw away any unused single-use containers 15 days after first opening the pouch” in order to increase prominence.
3. Bold the statement “Attention:....immediately after use.” in order to increase prominence of this statement.

### B. POUCH LABELING (retail and professional samples)

As currently presented, the pouch labels (retail and professional samples) look crowded. Move the “Contains....” section to the back panel of the pouch to decrease crowding.

### C. CARTON LABELING (retail and professional samples)

The “Attention...” statement on the back panel is important information that should be moved to the principle display panel (PDP). In order to accommodate for this information without crowding the PDP, move the “Contains...Water for Injection” statement to the top of the back panel.

### D. CONTAINER LABELS (retail and professional samples)

As currently presented, the labels look crowded. Remove the [REDACTED] (b) (4) statement to decrease crowding.

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## Appendix H: All AERS reports (ISR#s)

3141835	3999620	4551168	5340684	6545997
3143043	4037011	4571708	5352179	6550585
3316634	4052204	4582216	5356434	6565936
3406432	4090727	4612479	5403335	6600636
3442465	4156235	4617611	5465682	6646221
3515169	4166975	4629247	5465725	6651667
3569189	4176161	4653367	5507805	6666713
3651685	4179937	4677967	5723030	6750399
3673136	4187365	4678680	5805170	6792589
3724347	4195110	4678713	5904810	6868840
3724363	4225184	4692998	5924668	6874458
3724370	4251511	4700935	5928770	6914591
3724373	4268545	4701244	5969064	6917622
3724374	4288909	4705171	6023377	6946768
3734722	4299832	4737870	6101427	7023639
3734726	4324585	4738358	6120589	7049542
3760225	4336638	4797438	6298853	7050646
3791669	4396873	4848389	6309163	7052032
3817844	4452104	4849922	6330235	7116833
3898850	4458100	4943088	6332893	7131129
3898853	4467130	5055206	6333171	7150577
3920159	4511834	5118061	6355630	7179725
3935459	4512886	5133629	6425122	7245228
3938138	4536688	5143387	6501669	7276421
3967251	4549477	5205373	6531946	7285025
3992077				7425717

The AERS search conducted on May 19, 2011 to identify errors with Cosopt, yielded 127 cases. None of the 127 cases yielded involved the product Cosopt. Thus, all 127 cases were considered not relevant to this review for the following reasons:

- Report of an adverse drug reaction (n=45)
- Report of adverse drug reaction to oral Timolol (n=1)
- Report of an accidental exposure in a child with Timolol (n=6)
- Report of accidental ingestion (1 report with Dorzolamide and 1 report with Timolol) (n=2)
- Unintentional overdose (3 reports with Dorzolamide and 2 reports with Timolol) (n=5)
- Improper dose errors, including intentional overdoses where labels and labeling were not cited as cause (n=8)
- Potential medication error due to similar packaging (n=12)
- Product quality complaint that is beyond the scope of this review (n=10)
- Wrong drug dispensed due to similar packaging (n=12)
- Wrong route of administration (n=5)
- Either Dorzolamide or Timolol was reported as a concomitant medication only and no error occurred (n=13)
- Duplicate therapy (n=1)
- Expired drug use (n=1)
- Drug-disease interaction (n=1)
- Dispensing error (n=5)

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/s/  
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MORGAN A WALKER  
08/02/2011

IRENE Z CHAN  
08/02/2011

CAROL A HOLQUIST  
08/02/2011

MEMORANDUM

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

---

DATE: June 14, 2011

TO: Rhea Lloyd, M.D.  
Medical Officer  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products

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

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

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

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: NDA 202667

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

DRUG: Cosopt Preservative-Free Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate)

NME: No

THERAPEUTIC CLASSIFICATION: No

INDICATIONS: For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers

NDA : 202667

CONSULTATION REQUEST DATE: February 18, 2011

PDUFA DATE: December 16, 2011

## **I. BACKGROUND:**

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., (Merck), submitted a new drug application NDA 202-667: COSOPT® Preservative-Free Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate) on February 16, 2011. The proposed indication is the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers.

Preservative-free (PF) COSOPT is a fixed dose combination of 2.0% dorzolamide hydrochloride and 0.5% timolol maleate (also referred to as PF dorzolamide/timolol or PF combination). It is identical to a previously marketed combination of dorzolamide hydrochloride/timolol maleate ophthalmic solution except for the lack of the preservative.

To support the approval, the Applicant provided data from a single investigator, single-center, randomized, double-masked study in support of the application. The clinical portion of the application has been preliminarily reviewed by the Division, and no issues have been identified to date to suggest a problem with data integrity.

The protocol to be inspected was Protocol 081 which is a multiple-dose, double-masked, parallel, active treatment controlled study of preservative-free 2.0% dorzolamide/0.5% timolol combination and 2.0% dorzolamide/0.5% timolol combination with preservative in patients with elevated IOP. This study was conducted at a single center by a single investigator, and it was completed in 1997.

A consult from DAIOP to DSI (now OSI) was received on February 18, 2011. The data generated from the above study was considered pivotal and inspection of the above site was requested to verify the quality of conduct of the study for this NDA.

This was a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of this application.

## II. RESULTS (by Site):

### The site was not inspected:

Name of CI	Protocol # and # of Subjects:	Inspection Date	Final Classification
<b>Robert A. Laibovitz, MD</b> Eye Research Associates 3307 Northland Drive, Suite 470 Austin, TX 78731 Phone #: 512-345-7040	Study 081/ 261 subjects	Not applicable	Not applicable/ Unable to verify data

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

#### 1. **Dr. Robert A. Laibovitz, MD**

Eye Research Associates  
 3307 Northland Drive,  
 Suite 470  
 Austin, TX 78731  
 Phone #: 512-345-7040

##### a. **What was inspected?**

This inspection of Dr. Laibovitz's site was not conducted because according to the clinical investigator, all records had been reportedly discarded or destroyed upon his retirement.

##### b. **General observations/commentary:**

Inspection of the CI records for the study was not possible because the source data were discarded.

The CI is retired, and he is not longer conducting research. Dr. Laibovitz's site had been inspected in the past. The inspectional history of Dr. Laibovitz's shows that he was inspected on November 7, 1996 (Sponsor: (b) (4)) on May 9, 1989 (Sponsor: (b) (4)) and on December 28, 1995 (Sponsor (b) (4)). All the above mentioned inspections except for NDA (b) (4) (NAI) revealed regulatory violations and were classified VAI. Examples of a regulatory violations observed during previous inspections include failure to adhere to protocol (NDA (b) (4)) and inadequate patient consent form (NDA (b) (4)). While regulatory violations were observed during inspections for NDA (b) (4) and NDA (b) (4), the CI's data for the inspected studies was considered generally reliable.

**c. Assessment of data integrity:**

An inspection of CI records was not possible because the CI's original Study 081 records and associated subjects' source records were not available. As a result, we are unable to verify the adequacy of conduct of the study at Dr. Laibovitz's site and we are unable to make a recommendation on the overall reliability of safety and efficacy data for this study.

#### **IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

An inspection of the Dr. Laibovitz's original Study 081 records and associated subjects' source records for this study was not possible because records were destroyed by the clinical investigator upon his retirement. Therefore, no verification of Study 081 data provided by Dr. Laibovitz is possible, and we are unable to make an assessment regarding the reliability of the data (e.g., existence of subjects, adequacy of informed consent process, confirmation of subject eligibility or outcome, drug compliance or accountability, etc.) from this site.

Upon the review division's request, an inspection of the sponsor/applicant could be issued to evaluate sponsor/monitor records related to Dr. Laibovitz's site; however, as the clinical investigator reported that source records have been destroyed, verification of the site's actual source documentation would still be impossible.

*{See appended electronic signature page}*

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

CONCURRENCE:

*{See appended electronic signature page}*

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KASSA AYALEW  
06/16/2011

JEAN M MULINDE  
06/16/2011

SUSAN D THOMPSON  
06/16/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information	
NDA # 202667 BLA#	NDA Supplement #:S- BLA STN #
Efficacy Supplement Type SE-	
Proprietary Name: Cosopt PF Established/Proper Name: dorzolamide hydrochloride and timolol maleate Dosage Form: Ophthalmic Solution Strengths: 2% dorzolamide and 0.5% timolol	
Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):	
Date of Application: 2-16-11 Date of Receipt: 2-16-11 Date clock started after UN:	
PDUFA Goal Date: 12-16-11	Action Goal Date (if different): 12-9-11
Filing Date: 4-2-11	Date of Filing Meeting: 3-22-11
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5	
Proposed indication(s)/Proposed change(s): Treatment for lowering elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 52080				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p>X Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p>X Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</p>																		

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

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

1

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

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

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

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

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

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

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

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

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

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

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 4-28-10  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 3-22-11

**BLA/NDA/Supp #:** 202667

**PROPRIETARY NAME:** Cosopt PF

**ESTABLISHED/PROPER NAME:** dorzolamide hydrochloride and timolol maleate

**DOSAGE FORM/STRENGTH:** Ophthalmic Solution/ 2% dorzolamide hydrochloride and 0.5% timolol maleate

**APPLICANT:** Merck Sharp & Dohme Corp.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment for lowering elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

**BACKGROUND:** Merck, Sharp & Dohme Corp. submitted NDA 202667 for Cosopt Preservative Free (PF) on February 16, 2011. The product is identical to the previously marketed combination of dorzolamide hydrochloride/timolol maleate ophthalmic solution except for the lack of preservative. A Pre-NDA meeting was held on April 28, 2010.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Rodgers	Y
	CPMS/TL:	Maureen Dillon-Parker	N
Cross-Discipline Team Leader (CDTL)	William Boyd		Y
Clinical	Reviewer:	Rhea Lloyd	Y
	TL:	William Boyd	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Ryan Owen	Y
	TL:	Kim Bergman	Y
Biostatistics	Reviewer:	Mushfiger Rashid	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Conrad Chen	Y
	TL:	Wendy Schmidt	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	George Lunn	Y
	TL:	Stephen Miller	N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Vinnie Pawar	N
	TL:	David Hussong	M
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Edwin Melendez	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Charlene Baksh	Y
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Brantley Dorch, RPM, OSE		

**FILING MEETING DISCUSSION:**

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

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

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

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

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

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALISON K RODGERS  
03/23/2011

# REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA 202667

**Name of Drug:** Cosopt PF (dorzolamide hydrochloride and timolol maleate)

**Applicant:** Merck Sharp & Dohme Corp.

## Labeling Reviewed

**Submission Date:** February 16, 2011

**Receipt Date:** February 16, 2011

## Background and Summary Description

The application provides for a New Drug Application (NDA) for Cosopt Preservative-Free Ophthalmic Solution. Preservative-free (PF) Cosopt is a fixed dose combination of 2.0% dorzolamide hydrochloride and 0.5% timolol maleate. It is identical to a previously marketed combination of dorzolamide hydrochloride/timolol maleate ophthalmic solution except for the lack of the preservative.

## Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an “X.”

In addition, the following labeling issues were identified:

The subheading, Teratogenic effects, and the Pregnancy Category should be included under subsection 8.1 Pregnancy, [REDACTED] (b) (4)

## Recommendations

All labeling issues identified on the following pages with an “X” and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by May 25, 2011. The resubmitted labeling will be used for further labeling discussions.

Leanna Kelly	March 14, 2011
Consumer Safety Officer	Date
Maureen Dillon-Parker	March 21, 2011
Chief, Project Management Staff	Date

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading - if no contraindications are known, it must state "None")
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)

- **Revision Date** (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
  
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
  
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
  
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
  
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010.”
- **Indications and Usage**
  - If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
- **Contraindications**
  - This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
  - All contraindications listed in the FPI must also be listed in HL.
  - List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
  - For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.
- **Adverse Reactions**
  - Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
  - For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.
- **Patient Counseling Information Statement**
  - Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”
- **Revision Date**
  - A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**
  - A horizontal line must separate the TOC and FPI.
  - The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
  - Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - Must include a brief, concise summary of critical information and cross-reference to detailed

discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/  
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LEANNA M KELLY  
03/21/2011

## **DSI CONSULT: Request for Clinical Inspections**

**Date:** February 23, 2010

**To:** Tejashri Purohit-Sheth, M.D., Branch Chief, GCP 2  
Jean M. Mulinde, M.D., Acting Team Leader, GCP 2  
Kassa Ayalew, M.D. Medical Officer  
Division of Scientific Investigation  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Rhea A. Lloyd, MD, Medical Officer, 301-796-0753  
Division of Anti-Infective and Ophthalmology Products

**From:** Alison Rodgers, Regulatory Health Project Manager, 301-796-0797  
Division of Anti-Infective and Ophthalmology Products

**Subject:** **Request for Clinical Site Inspections**

### **I. General Information**

Application #: NDA-202667

Applicant/ Applicant contact information:

Chitkala Kalidas, Ph.D  
Director, Worldwide Regulatory Affairs  
Merck Sharp & Dohme Corp.  
chitkala\_kalidas@merck.com  
tel 732-594-0599

Drug Proprietary Name: Cosopt Preservative-Free Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate)

NME: No

Review Priority: No

Study Population includes < 17 years of age: No

Is this for Pediatric Exclusivity: No

Proposed Indication:

For the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers.

PDUFA: December 16, 2011

Action Goal Date: December 9, 2011  
Inspection Summary Goal Date: September 15, 2011

**II. Protocol/Site Identification**

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects Randomized</b>	<b>Indication</b>
Robert A. Laibovitz, MD Eye Research Associates 3307 Northland Drive, Suite 470 Austin, TX 78731	081	261	reduction of IOP in patients with open angle glaucoma or ocular hypertension who were insufficiently responsive to beta blockers

An inspection is requested for the above site since it is the only trial that is submitted in support of the NDA.

**III. Site Selection/Rationale**

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

Protocol 081 is a single investigator, single-center, randomized, double-masked trial of adequate duration which uses appropriate FDA recommended endpoints for the evaluation of intraocular pressure. **Note: This trial was completed in 1997.**

An inspection is requested for the above site, if feasible, since Dr. Laibovitz is the only investigator in this single center trial that is submitted in support of the NDA.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

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

**International Inspections:** Not applicable

Reasons for inspections (please check all that apply):

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

**Goal Date for Completion:**

If routine inspections are completed the Inspection Summary Results should be provided by September 15, 2011. **We intend to issue an action letter on this application December 9, 2011.**

Should you require any additional information, please contact Alison Rodgers at 301-796-0797 or Rhea Lloyd, MD at 301-796-0753.

**Additional Information:**

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALISON K RODGERS  
03/14/2011