

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202667Orig1s000

CHEMISTRY REVIEW(S)

NDA 202-667

**COSOPT[®] PF (dorzolamide hydrochloride-timolol maleate
2%/0.5%)**

Merck, Sharp & Dohme Corporation

George Lunn, Ph.D.

**Division of New Drug Quality Assessment II/Branch V
Office of New Drug Quality Assessment**

Table of Contents

| | |
|---|-----------|
| Table of Contents | 2 |
| Chemistry Review Data Sheet..... | 3 |
| The Executive Summary | 7 |
| I. Recommendations | 7 |
| A. Recommendation and Conclusion on Approvability | 7 |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 7 |
| II. Summary of Chemistry Assessments..... | 7 |
| A. Description of the Drug Product(s) and Drug Substance(s) | 7 |
| B. Description of How the Drug Product is Intended to be Used..... | 9 |
| C. Basis for Approvability or Not-Approval Recommendation..... | 9 |
| III. Administrative..... | 9 |
| A. Reviewer's Signature..... | 9 |
| B. Endorsement Block..... | 9 |
| C. CC Block | 9 |
| Chemistry Assessment | 11 |
| I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data..... | 11 |
| S DRUG SUBSTANCE [Dorzolamide hydrochloride/timolol maleate] | 11 |
| P DRUG PRODUCT [COSOPT Preservative-Free Ophthalmic Solution] | 11 |
| A APPENDICES | 15 |
| R REGIONAL INFORMATION | 15 |
| II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 | 15 |
| A. Labeling & Package Insert | 15 |
| B. Environmental Assessment Or Claim Of Categorical Exclusion | 20 |
| III. List Of Deficiencies To Be Communicated..... | 20 |
| IV. EES Report..... | 20 |

Chemistry Review Data Sheet

1. NDA 202-667
2. REVIEW #: 3
3. REVIEW DATE: 25-JAN-2012
4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

CMC Review 2

Document Date

17-OCT-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment

Document Date

23-JAN-2012

7. NAME & ADDRESS OF APPLICANT:

| | |
|-----------------|------------------------------------|
| Name: | Merck Sharp & Dohme Corp. |
| Address: | P.O. Box 2000 RY33-204 |
| Representative: | Rahway, NJ 07065-0900 |
| Telephone: | 732 594 0599 (fax) 732 594 1030 |

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: COSOPT Preservative-Free Ophthalmic Solution
b) Non-Proprietary Name (USAN): dorzolamide hydrochloride and timolol maleate
preservative-free ophthalmic solution
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Treatment of intraocular pressure

11. DOSAGE FORM: Liquid

12. STRENGTH/POTENCY: 2.0% and 0.5%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

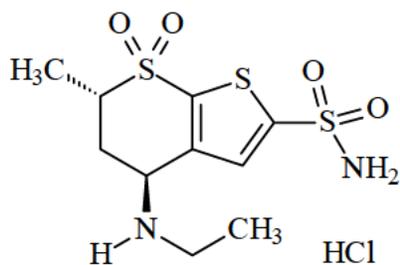
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

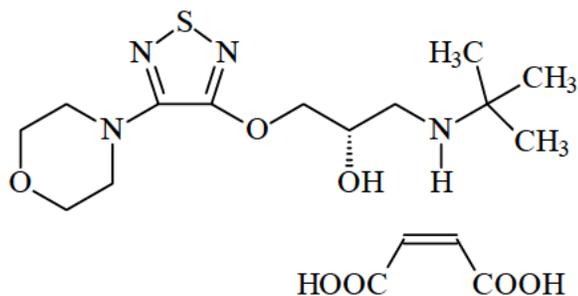
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet



Dorzolamide hydrochloride
 (4*S*,6*S*)-4-(Ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride
 $C_{10}H_{16}N_2O_4S_3$
 MW 324.44 (free base)



Timolol maleate
 (2*S*)-1-[(1,1-Dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (*Z*)-2-butenedioate (1:1) salt
 $C_{13}H_{24}N_4O_3S.C_4H_4O_4$
 MW 316.42 (free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|---------------------|
| (b) (4) | III | (b) (4) | (b) (4) | 4 | Adequate | | |
| | III | | | 1 | Adequate | 6/21/11 | Reviewed by G. Lunn |
| | III | | | | Adequate | 6/30/11 | Reviewed by G. Lunn |

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Chemistry Review Data Sheet

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|---|
| NDA | 20-869 | COSOPT Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate) [contains preservatives] |
| NDA | 20-408 | TRUSOPT (dorzolamide hydrochloride) ophthalmic solution |
| NDA | 18-086 | TIMOPTIC (timolol maleate) ophthalmic solution |
| IND | 52,080 | Dorzolamide hydrochloride and timolol maleate ophthalmic solution |

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|---|-------------|----------|
| Biometrics | NA | | |
| EES | Acceptable | 19-DEC-2011 | |
| Pharm/Tox | NA | | |
| Biopharm | Not required, no dissolution | | |
| LNC | NA | | |
| Methods Validation | Not required | | |
| OPDRA | NA | | |
| EA | Categorical exemption claimed, claim accepted | 15-MAR-2011 | G. Lunn |
| Microbiology | NA | | |

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 202-667

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

An Overall Recommendation of Acceptable was made by the Office of Compliance on 16-Dec-2011.

Therefore, from the CMC perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substances, timolol maleate and dorzolamide hydrochloride, are described in approved NDAs and this information is incorporated by reference. There are no outstanding CMC concerns. The drug substance specifications conform to the USP specifications but additional testing is carried out beyond that recommended by USP.

The drug product is a sterile, isotonic, pH-adjusted, aqueous solution that contains no preservative. The dorzolamide concentration is 20 mg/mL and the timolol concentration is 5 mg/mL. The solution is packaged in an LDPE unit dose pipette and a group of 5 pipettes is placed in an ^{(b) (4)} foil pack. The product was developed from the currently marketed Cosopt solution which contains benzalkonium chloride as a preservative and is supplied in a multi-use container.

The drug product will be manufactured, packaged, and tested for release by Laboratories Merck Sharp & Dohme – Chibret, Clermont-Ferrand, France and stability testing will be carried out by Merck Sharp & Dohme Ltd., Cramlington, UK. An Establishment Evaluation Request has been submitted and an overall recommendation of Acceptable has been made.

Executive Summary Section

The manufacturing process involves (b) (4)

The manufacturing process has been found to be acceptable from a Quality Micro perspective (see separate review).

All inactive ingredients are compendial. The viscosity of the hydroxyethylcellulose is controlled by (b) (4)

Reasonable specifications for appearance, identity, viscosity, deliverable volume, pH, osmolality, assay, degradants, sterility, and particulates are provided. A justification of the specification is provided. In general the specifications are conventional for a product of this type. They are also the same as those for the approved Cosopt with preservative. The analytical methods are described in reasonable detail.

Satisfactory batch analysis data for four full-scale production batches manufactured at the commercial facility are provided.

The container-closure system consists of single-use pipettes manufactured from USP Grade LDPE. The pipettes are (b) (4)

The pipettes are labeled with paper labels using a pressure-sensitive adhesive, overwrapped with foil pouches, and placed in cartons. (b) (4) The (b) (4) and foil (b) (4) are covered by DMFs that have been reviewed and found adequate.

Leachables have been studied by stress testing and a leachables experiment has been carried out on an expired batch. Dye ingress testing using and microbial ingress testing has been carried out.

Satisfactory stability data are supplied for 3 primary stability batches made at the commercial scale (b) (4) at the proposed commercial site. For batches stored at 25°C/40% RH 24 months of data are supplied and for batches stored at 40°C/20% RH 6 months of data are supplied. The product is quite stable. There are no out of specification results and the only trend is an (b) (4) in the (b) (4) of dorzolamide. The first 3 commercial batches manufactured using (b) (4) (b) (4) foil will be placed on stability and at least one lot will be placed on stability each year. The first 3 commercial batches will also be tested for weight loss.

The proposed expiration dating period of 24 months and the storage statement "Store at 20-25°C (68-77°F), (b) (4)

Do not freeze. Store in the original pouch. After pouch is opened, store the single-use containers in the foil pouch to protect from light. Throw away any unused single-use containers 15 days after first opening the pouch." are acceptable and supported by the stability data.

Executive Summary Section

The Package Insert and container labels are acceptable from the CMC point of view.

The applicant claims a categorical exemption from the requirement to perform an Environmental Assessment and this claim is accepted.

B. Description of How the Drug Product is Intended to be Used

COSOPT PF (dorzolamide hydrochloride and timolol maleate) Ophthalmic Solution is a carbonic anhydrase inhibitor (dorzolamide) with a beta-adrenergic receptor blocking agent (timolol) 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. The recommended dose is one drop per eye twice a day.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes, and process controls. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. In the drug product specification the applicant has changed the term "Any Unspecified Degradate" to "Any Unspecified Impurity" as requested by FDA in the Complete response letter.

An Overall Recommendation of Acceptable was made by the Office of Compliance on 16-Dec-2011.

All labels have the required information and are acceptable from a CMC point of view.

Therefore, from the CMC perspective, this NDA is recommended for approval.

III. Administrative**A. Reviewer's Signature**

George Lunn, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

Branch Chief: Rapti Madurawe, Ph.D. {Signed Electronically in DFS}

C. CC Block

15 pages have been withheld in full as B(4) CCI/TS immediately following this page

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

/s/

GEORGE LUNN

01/27/2012

Overall recommendation of Acceptable has been made by Compliance and the specification has been modified as requested. This application is now recommended for approval from the CMC point of view.

RAPTI D MADURAWAWE

01/30/2012

To: File
From: Rapti D. Madurawe, ONDQA
Date: 16-Dec-2011
Re: NDA 202-667

Dr. George Lunn's, review dated 11/25/2011 did not recommend approval of NDA 202-667 due to the Withhold status of a facility provided for in the NDA.

On 16-Dec-2011, Office of Compliance issued an overall recommendation of ACCEPTABLE for the facilities provided for in the NDA. This deficiency is now resolved. The EES report is attached below.

Therefore, from the ONDQA-perspective, NDA 202-667 is now recommended for approval.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

| | | | |
|---------------------|--|---|---|
| Application: | NDA 202667/000 | Action Goal: | |
| Stamp Date: | 16-FEB-2011 | District Goal: | 17-OCT-2011 |
| Regulatory: | 16-DEC-2011 | | |
| Applicant: | MERCK SHARP DOHME 126 EAST LINCOLN AVE RY33 204 RAHWAY, NJ 07065 | Brand Name: | Cosopt PF |
| | | Estab. Name: | |
| | | Generic Name: | |
| Priority: | 5 | Product Number; Dosage Form; Ingredient; Strengths | |
| Org. Code: | 590 | | 001; SOLUTION; DORZOLAMIDE HYDROCHLORIDE; 2% 001; SOLUTION; TIMOLOL MALEATE; .5% |

Application Comment:

| | | | | |
|----------------------|---------|-----------------|---------|--------------|
| FDA Contacts: | A. CUFF | Project Manager | (HF-01) | 301-796-4061 |
| | L. NG | Team Leader | | 301-796-1426 |

| | | | | | |
|--------------------------------|------------|----------------|-------------|-----------|--------------|
| Overall Recommendation: | ACCEPTABLE | on 16-DEC-2011 | by M. STOCK | (HFD-320) | 301-796-4753 |
| | WITHHOLD | on 26-OCT-2011 | by D. SMITH | () | |
| | PENDING | on 19-SEP-2011 | by EES_PROD | | |
| | WITHHOLD | on 27-JUN-2011 | by EES_PROD | | |

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** FEI: 3003121602
LABORATOIRES MERCK SHARP AND DOHME-CHIBRET
USINE DE LA VALLEE Z.I. BLAVOZY
SAINT GERMAIN LAPRADE, AUVERGNE, FRANCE

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: DRUG SUBSTANCE MANUFACTURING, PACKAGING AND RELEASE TESTING (on 02-MAR-2011 by A. CUFF (HF-01) 301-796-4061)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

| <u>Milestone Name</u> | <u>Milestone Date</u> | <u>Request Type</u> | <u>Planned Completion</u> | <u>Decision</u> | <u>Creator</u> |
|---|-----------------------|---------------------|---------------------------|------------------------------------|---------------------|
| <u>Comment</u> | | | | <u>Reason</u> | |
| SUBMITTED TO OC | 14-MAR-2011 | | | | CUFFA |
| SUBMITTED TO DO | 14-MAR-2011 | Product Specific | | | TOULOUSEM |
| ASSIGNED INSPECTION TO IB | 18-MAR-2011 | GMP Inspection | | | PHILPYE |
| INSPECTION SCHEDULED | 09-MAY-2011 | | 26-MAY-2011 | | IRIVERA |
| INSPECTION PERFORMED | 27-MAY-2011 | | 27-MAY-2011 | | DEMITRIA.ARGIROPOUI |
| <p>This initial inspection of an active pharmaceutical ingredient manufacturer was initiated pursuant to FACTS Assignment #6571658, part of the DFI International Operations Group (IOG) FY11 Work plan. This inspectional assignment requested coverage of NDA 202667/000 (Dorzolamide HCl/Timolol Maleate API). This inspection was conducted in accordance with CP 7356.002F Active Pharmaceutical Ingredient Process Inspection, CP 7356.002 Drug Process Inspection, CP 7346.832 Pre-Approval Inspections and ICH Q7A.</p> <p>The previous inspection was conducted in 12/2006 and was classified VAI and an FDA-483 List of Inspectional Observations for one observation concerning laboratory control records for testing of API intermediates & finished bulk drug products on analyst worksheets did not include a statement of test results and how they compared with established acceptance criteria.</p> <p>The current inspection included a review of the firm's Quality, Facilities & Equipment, Production and Laboratory Systems and revealed the following objectionable conditions in reference to the manufacture of Dorzolamide HCl/Timolol Maleate API for NDA 202667/000: Global Technical Operations Report No.: RFPROM12 (dated 4/30/09). ?Validation Report of Timolol Maleate.. "Additional TFB batch (b) (4) concluded the process was validated even though deficiencies occurred; inadequate written procedures to ensure manufacturing and laboratory deviations are investigated, root causes are identified and corrective action is implemented; Firm failed to provide data to monitor (b) (4) in the drug product (Timolol Maleate); The HPLC and GC chromatograms for Timolol Maleate API provided during the inspection, did not include raw data information such as: injection date and time, sample name, operator name, method name, last changed, analyst method, last changed, sequence line, vial number, injection number, injected volume and sequ</p> | | | | | |
| DO RECOMMENDATION | 17-OCT-2011 | | | ACCEPTABLE INSPECTION | STOCKM |
| OC RECOMMENDATION | 17-OCT-2011 | | | ACCEPTABLE DISTRICT RECOMMENDATION | STOCKM |

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9610718 FEI: 1000173162
 LABORATORIES MERCK SHARP AND DOHME CHIBRET
 ROUTE DE MARSAT
 CLERMONT-FERRAND CEDEX, , FRANCE

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURING, PACKAGING AND RELEASE TESTING (on 14-MAR-2011 by A. CUFF (HF-01) 301-796-4061)

Profile: LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS, OAI Status: NONE

| <u>Milestone Name</u> | <u>Milestone Date</u> | <u>Request Type</u> | <u>Planned Completion</u> | <u>Decision</u> | <u>Creator</u> |
|---------------------------|-----------------------|---------------------|---------------------------|---------------------------------------|----------------|
| <u>Comment</u> | | | | <u>Reason</u> | |
| SUBMITTED TO OC | 14-MAR-2011 | | | | CUFFA |
| SUBMITTED TO DO | 15-MAR-2011 | Product Specific | | | TOULOUSEM |
| ASSIGNED INSPECTION TO IB | 18-MAR-2011 | Product Specific | | | PHILPYE |
| DO RECOMMENDATION | 19-SEP-2011 | | | ACCEPTABLE INSPECTION | STOCKM |
| OC RECOMMENDATION | 29-SEP-2011 | | | ACCEPTABLE DISTRICT RECOMMENDATION | SMITHDE |

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** **FEI:** 3002807653
 MERCK SHARP DOHME
 SHOTTEN LANE
 CRAMLINGTON, , UNITED KINGDOM

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT STABILITY TESTING (on 02-MAR-2011 by A. CUFF (HF-01) 301-796-4061)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

| <u>Milestone Name</u> | <u>Milestone Date</u> | <u>Request Type</u> | <u>Planned Completion</u> | <u>Decision</u> | <u>Creator</u> |
|-----------------------|-----------------------|---------------------|---------------------------|--------------------------------|----------------|
| <u>Comment</u> | | | | <u>Reason</u> | |
| SUBMITTED TO OC | 14-MAR-2011 | | | | CUFFA |
| OC RECOMMENDATION | 14-MAR-2011 | | | ACCEPTABLE BASED ON PROFILE | TOULOUSEM |

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

/s/

RAPTI D MADURAWA
12/16/2011

From: George Lunn

Through: Balajee Shanmugam, CMC lead

To: Rapti Madurawe, Branch Chief

Date: December 14, 2011

Re: Unspecified Impurities Limit in the Drug Product Specification for NDA 202-667 for COSOPT® Preservative-Free Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate)

As originally proposed the unspecified impurities limit was NMT (b) (4) measured using either the dorzolamide HPLC method or the timolol HPLC method.

In an Information Request of 7/20/11 ONDQA asked for this to be lowered to NMT (b) (4) In the Amendment of 8/4/11 the applicant declined stating that the limit was NMT (b) (4) in the approved NDA for the original (preserved) COSOPT and that NMT (b) (4) conformed to Q3B.

Leachables were studied by stress testing at 50°C for 3 days. By HPLC, (b) (4) peaks that were (b) (4) (b) (4) were detected. The (b) (4) largest peaks were (b) (4) In the Amendment of 8/30/11 the applicant supplied the results of a leachables experiment performed on an expired batch (after 24 months at 25°C/40% RH). No new leachable peaks were observed. It should perhaps be noted that (b) (4) corresponds to the concentration in the ophthalmic solution. The unspecified impurity limit is quoted as a percent of the active measured using that HPLC method. For this product the active with the lowest concentration is timolol at (b) (4) and setting the impurity spec to NMT (b) (4) would allow an impurity level of (b) (4) Thus the observed leachables by the stress test studies (worse case scenario) are (b) (4) of the impurity level that would be permitted by a NMT (b) (4) spec. Given that the unspecified impurities limit has been NMT (b) (4) in the preserved COSOPT used for many years without reported adverse events, and the levels of leachables observed during one-time stress tests are negligible it is the opinion of ONDQA that the unspecified impurities limit of NMT (b) (4) (in conformance with ICH Q3B) is acceptable .

All CMC deficiencies and information requests communicated to the applicant during the review cycle have been adequately addressed.

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

/s/

GEORGE LUNN

12/14/2011

Unspecified impurities limit is acceptable. All CMC deficiencies have been addressed.

RAPTI D MADURAWAWE

12/14/2011

NDA 202-667

**COSOPT[®] Preservative-Free Ophthalmic Solution
(dorzolamide hydrochloride and timolol maleate)**

Merck, Sharp & Dohme Corporation

George Lunn, Ph.D.

**Division of New Drug Quality Assessment II/Branch V
Office of New Drug Quality Assessment**

Table of Contents

| | |
|---|-----------|
| Table of Contents | 2 |
| Chemistry Review Data Sheet..... | 3 |
| The Executive Summary | 7 |
| I. Recommendations | 7 |
| A. Recommendation and Conclusion on Approvability | 7 |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 7 |
| II. Summary of Chemistry Assessments..... | 7 |
| A. Description of the Drug Product(s) and Drug Substance(s) | 7 |
| The Package Insert and container labels are acceptable from the CMC point of view. | 9 |
| B. Description of How the Drug Product is Intended to be Used..... | 9 |
| C. Basis for Approvability or Not-Approval Recommendation..... | 9 |
| III. Administrative..... | 9 |
| A. Reviewer's Signature..... | 9 |
| B. Endorsement Block..... | 9 |
| C. CC Block | 9 |
| Chemistry Assessment | 11 |
| I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data..... | 11 |
| S DRUG SUBSTANCE [Dorzolamide hydrochloride/timolol maleate] | 11 |
| P DRUG PRODUCT [COSOPT Preservative-Free Ophthalmic Solution] | 17 |
| A APPENDICES | 47 |
| R REGIONAL INFORMATION | 47 |
| II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 | 48 |
| A. Labeling & Package Insert | 48 |
| B. Environmental Assessment Or Claim Of Categorical Exclusion | 54 |
| III. List Of Deficiencies To Be Communicated..... | 54 |
| IV. EES Report..... | 57 |

Chemistry Review Data Sheet

1. NDA 202-667
2. REVIEW #: 2
3. REVIEW DATE: 17-OCT-2011
4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

| | |
|-----------|-------------|
| Original | 16-FEB-2011 |
| Amendment | 27-MAY-2011 |
| Amendment | 04-AUG-2011 |
| Amendment | 30-AUG-2011 |
| Amendment | 09-SEP-2011 |
| Amendment | 23-SEP-2011 |

7. NAME & ADDRESS OF APPLICANT:

Name:

Merck Sharp & Dohme Corp.

Chemistry Review Data Sheet

Address: P.O. Box 2000
RY33-204

Representative: Rahway, NJ 07065-0900

Telephone: 732 594 0599
(fax) 732 594 1030

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: COSOPT Preservative-Free Ophthalmic Solution
- b) Non-Proprietary Name (USAN): dorzolamide hydrochloride and timolol maleate
preservative-free ophthalmic solution
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Treatment of intraocular pressure

11. DOSAGE FORM: Liquid

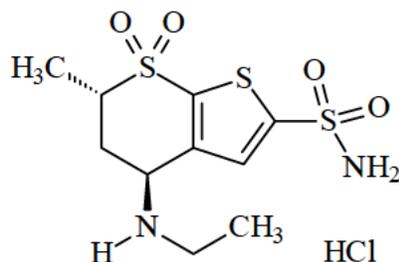
12. STRENGTH/POTENCY: 2.0% and 0.5%

13. ROUTE OF ADMINISTRATION: Topical

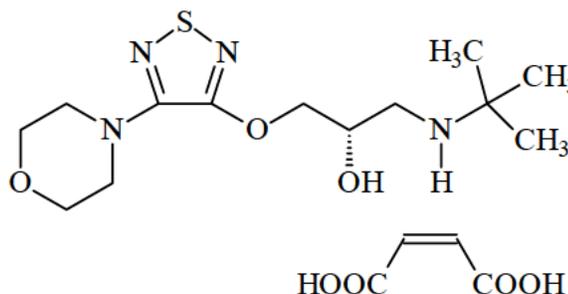
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Dorzolamide hydrochloride
 (4*S*,6*S*)-4-(Ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride
 $C_{10}H_{16}N_2O_4S_3$
 MW 324.44 (free base)



Timolol maleate
 (2*S*)-1-[(1,1-Dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (*Z*)-2-butenedioate (1:1) salt
 $C_{13}H_{24}N_4O_3S.C_4H_4O_4$
 MW 316.42 (free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|---------------------|
| (b) (4) | III | (b) (4) | (b) (4) | 4 | Adequate | | |
| | III | | | 1 | Adequate | 6/21/11 | Reviewed by G. Lunn |
| | III | | | | Adequate | 6/30/11 | Reviewed by G. Lunn |

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|---|
| NDA | 20-869 | COSOPT Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate) [contains preservatives] |
| NDA | 20-408 | TRUSOPT (dorzolamide hydrochloride) ophthalmic solution |
| NDA | 18-086 | TIMOPTIC (timolol maleate) ophthalmic solution |
| IND | 52,080 | Dorzolamide hydrochloride and timolol maleate ophthalmic solution |

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|---|-------------|----------|
| Biometrics | NA | | |
| EES | Withhold | 10/17/11 | |
| Pharm/Tox | NA | | |
| Biopharm | Not required, no dissolution | | |
| LNC | NA | | |
| Methods Validation | Not required | | |
| OPDRA | NA | | |
| EA | Categorical exemption claimed, claim accepted | 15-MAR-2011 | G. Lunn |
| Microbiology | NA | | |

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 202-667

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

A recommendation of Withhold from the Office of Compliance is in effect as of the date of this review.

Therefore, from the CMC perspective, this NDA is *not recommended for approval* until all pending issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substances, timolol maleate and dorzolamide hydrochloride, are described in approved NDAs and this information is incorporated by reference. There are no outstanding CMC concerns. The drug substance specifications conform to the USP specifications but additional testing is carried out beyond that recommended by USP.

The drug product is a sterile, isotonic, pH-adjusted, aqueous solution that contains no preservative. The dorzolamide concentration is 20 mg/mL and the timolol concentration is 5 mg/mL. The solution is packaged in an LDPE unit dose pipette and a group of 5 pipettes is placed in an (b) (4) foil pack. The product was developed from the currently marketed Cosopt solution which contains benzalkonium chloride as a preservative and is supplied in a multi-use container.

The drug product will be manufactured, packaged, and tested for release by Laboratories Merck Sharp & Dohme – Chibret, Clermont-Ferrand, France and stability testing will be carried out by Merck Sharp & Dohme Ltd., Cramlington, UK. An Establishment Evaluation Request has been submitted and an overall recommendation of Withhold has been made.

Executive Summary Section

The manufacturing process involves (b) (4)

The manufacturing process has been found to be acceptable from a Quality Micro perspective (see separate review).

All inactive ingredients are compendial. The viscosity of the hydroxyethylcellulose is controlled by (b) (4)

Reasonable specifications for appearance, identity, viscosity, deliverable volume, pH, osmolality, assay, degradants, sterility, and particulates are provided. A justification of the specification is provided. In general the specifications are conventional for a product of this type. They are also the same as those for the approved Cosopt with preservative. The analytical methods are described in reasonable detail.

Satisfactory batch analysis data for four full-scale production batches manufactured at the commercial facility are provided.

The container-closure system consists of single-use pipettes manufactured from USP Grade LDPE. (b) (4)

The pipettes are labeled with paper labels using a pressure-sensitive adhesive, overwrapped with foil pouches, and placed in cartons. (b) (4). The (b) (4) and foil (b) (4) are covered by DMFs that have been reviewed and found adequate.

Leachables have been studied by stress testing and a leachables experiment has been carried out on an expired batch. Dye ingress testing using and microbial ingress testing has been carried out.

Satisfactory stability data are supplied for 3 primary stability batches made at the commercial scale (b) (4) at the proposed commercial site. For batches stored at 25°C/40% RH 24 months of data are supplied and for batches stored at 40°C/20% RH 6 months of data are supplied. The product is quite stable. There are no out of specification results and the only trend is an (b) (4) in the (b) (4) of dorzolamide. The first 3 commercial batches manufactured using (b) (4) (b) (4) foil will be placed on stability and at least one lot will be placed on stability each year. The first 3 commercial batches will also be tested for weight loss.

The proposed expiration dating period of 24 months and the storage statement "Store at 20-25°C (68-77°F), (b) (4) (see USP Controlled Room Temperature]. Do not freeze. Store in the original pouch. After pouch is opened, store the single-use containers in the foil pouch to protect from light. Throw away any unused single-use containers 15 days after first opening the pouch." are acceptable and supported by the stability data.

Executive Summary Section

The Package Insert and container labels are acceptable from the CMC point of view.

The applicant claims a categorical exemption from the requirement to perform an Environmental Assessment and this claim is accepted.

B. Description of How the Drug Product is Intended to be Used

COSOPT PF (dorzolamide hydrochloride and timolol maleate) Ophthalmic Solution is a carbonic anhydrase inhibitor (dorzolamide) with a beta-adrenergic receptor blocking agent (timolol) 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. The recommended dose is one drop per eye twice a day.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes, and process controls. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

A recommendation of Withhold from the Office of Compliance is in effect as of the date of this review.

All labels have the required information. CMC recommendations for the package insert, bottle, blister and carton labels have been provided for review team discussion.

From the CMC perspective, this NDA is *not recommended for approval* until all pending issues are resolved.

III. Administrative**A. Reviewer's Signature**

George Lunn, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

Branch Chief: Rapti Madurawe, Ph.D. {Signed Electronically in DFS}

C. CC Block

51 pages has been withheld in full as B(4) CCI/TS immediately following this page

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

/s/

GEORGE LUNN

11/25/2011

Updated review containing EES report. product still not recommended for approval.

BALAJEE SHANMUGAM

11/25/2011

NDA 202-667

**COSOPT[®] Preservative-Free Ophthalmic Solution
(dorzolamide hydrochloride and timolol maleate)**

Merck, Sharp & Dohme Corporation

George Lunn, Ph.D.

**Division of New Drug Quality Assessment II/Branch V
Office of New Drug Quality Assessment**

Table of Contents

| | |
|---|-----------|
| Table of Contents | 2 |
| Chemistry Review Data Sheet..... | 3 |
| The Executive Summary | 7 |
| I. Recommendations | 7 |
| A. Recommendation and Conclusion on Approvability | 7 |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 7 |
| II. Summary of Chemistry Assessments..... | 7 |
| A. Description of the Drug Product(s) and Drug Substance(s) | 7 |
| The Package Insert and container labels are acceptable from the CMC point of view. | 9 |
| B. Description of How the Drug Product is Intended to be Used..... | 9 |
| C. Basis for Approvability or Not-Approval Recommendation..... | 9 |
| III. Administrative..... | 9 |
| A. Reviewer's Signature..... | 9 |
| B. Endorsement Block..... | 9 |
| C. CC Block | 9 |
| Chemistry Assessment | 11 |
| I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data..... | 11 |
| S DRUG SUBSTANCE [Dorzolamide hydrochloride/timolol maleate] | 11 |
| P DRUG PRODUCT [COSOPT Preservative-Free Ophthalmic Solution] | 17 |
| A APPENDICES | 47 |
| R REGIONAL INFORMATION | 47 |
| II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 | 48 |
| A. Labeling & Package Insert | 48 |
| B. Environmental Assessment Or Claim Of Categorical Exclusion | 54 |
| III. List Of Deficiencies To Be Communicated..... | 54 |

Chemistry Review Data Sheet

1. NDA 202-667
2. REVIEW #: 1
3. REVIEW DATE: 17-OCT-2011
4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

16-FEB-2011

Amendment

27-MAY-2011

Amendment

04-AUG-2011

Amendment

30-AUG-2011

Amendment

09-SEP-2011

Amendment

23-SEP-2011

7. NAME & ADDRESS OF APPLICANT:

Name:

Merck Sharp & Dohme Corp.

Chemistry Review Data Sheet

Address: P.O. Box 2000
RY33-204

Representative: Rahway, NJ 07065-0900

Telephone: 732 594 0599
(fax) 732 594 1030

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: COSOPT Preservative-Free Ophthalmic Solution
- b) Non-Proprietary Name (USAN): dorzolamide hydrochloride and timolol maleate preservative-free ophthalmic solution
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Treatment of intraocular pressure

11. DOSAGE FORM: Liquid

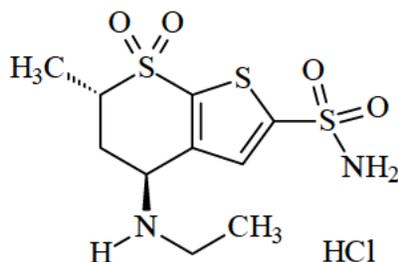
12. STRENGTH/POTENCY: 2.0% and 0.5%

13. ROUTE OF ADMINISTRATION: Topical

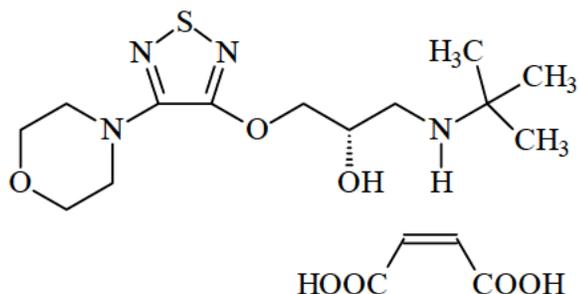
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Dorzolamide hydrochloride
 (4*S*,6*S*)-4-(Ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride
 $C_{10}H_{16}N_2O_4S_3$
 MW 324.44 (free base)



Timolol maleate
 (2*S*)-1-[(1,1-Dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (*Z*)-2-butenedioate (1:1) salt
 $C_{13}H_{24}N_4O_3S.C_4H_4O_4$
 MW 316.42 (free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|---------------------|
| (b) (4) | III | (b) (4) | (b) (4) | 4 | Adequate | | |
| | III | | | 1 | Adequate | 6/21/11 | Reviewed by G. Lunn |
| | III | | | | Adequate | 6/30/11 | Reviewed by G. Lunn |

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|---|
| NDA | 20-869 | COSOPT Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate) [contains preservatives] |
| NDA | 20-408 | TRUSOPT (dorzolamide hydrochloride) ophthalmic solution |
| NDA | 18-086 | TIMOPTIC (timolol maleate) ophthalmic solution |
| IND | 52,080 | Dorzolamide hydrochloride and timolol maleate ophthalmic solution |

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|---|-------------|----------|
| Biometrics | NA | | |
| EES | Withhold | 10/17/11 | |
| Pharm/Tox | NA | | |
| Biopharm | Not required, no dissolution | | |
| LNC | NA | | |
| Methods Validation | Not required | | |
| OPDRA | NA | | |
| EA | Categorical exemption claimed, claim accepted | 15-MAR-2011 | G. Lunn |
| Microbiology | NA | | |

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 202-667

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

A recommendation of Withhold from the Office of Compliance is in effect as of the date of this review.

Therefore, from the CMC perspective, this NDA is *not recommended for approval* until all pending issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substances, timolol maleate and dorzolamide hydrochloride, are described in approved NDAs and this information is incorporated by reference. There are no outstanding CMC concerns. The drug substance specifications conform to the USP specifications but additional testing is carried out beyond that recommended by USP.

The drug product is a sterile, isotonic, pH-adjusted, aqueous solution that contains no preservative. The dorzolamide concentration is 20 mg/mL and the timolol concentration is 5 mg/mL. The solution is packaged in an LDPE unit dose pipette and a group of 5 pipettes is placed in an aluminum foil pack. The product was developed from the currently marketed Cosopt solution which contains benzalkonium chloride as a preservative and is supplied in a multi-use container.

The drug product will be manufactured, packaged, and tested for release by Laboratories Merck Sharp & Dohme – Chibret, Clermont-Ferrand, France and stability testing will be carried out by Merck Sharp & Dohme Ltd., Cramlington, UK. An Establishment Evaluation Request has been submitted and an overall recommendation of Withhold has been made.

Executive Summary Section

The manufacturing process involves (b) (4)

The manufacturing process has been found to be acceptable from a Quality Micro perspective (see separate review).

All inactive ingredients are compendial. The viscosity of the hydroxyethylcellulose is controlled by (b) (4)

Reasonable specifications for appearance, identity, viscosity, deliverable volume, pH, osmolality, assay, degradants, sterility, and particulates are provided. A justification of the specification is provided. In general the specifications are conventional for a product of this type. They are also the same as those for the approved Cosopt with preservative. The analytical methods are described in reasonable detail.

Satisfactory batch analysis data for four full-scale production batches manufactured at the commercial facility are provided.

The container-closure system consists of single-use pipettes manufactured from USP Grade LDPE. (b) (4)

The pipettes are labeled with paper labels using a pressure-sensitive adhesive, overwrapped with foil pouches, and placed in cartons. (b) (4) The (b) (4) and foil (b) (4) are covered by DMFs that have been reviewed and found adequate.

Leachables have been studied by stress testing and a leachables experiment has been carried out on an expired batch. Dye ingress testing using and microbial ingress testing has been carried out.

Satisfactory stability data are supplied for 3 primary stability batches made at the commercial scale (b) (4) at the proposed commercial site. For batches stored at 25°C/40% RH 24 months of data are supplied and for batches stored at 40°C/20% RH 6 months of data are supplied. The product is quite stable. There are no out of specification results and the only trend is an (b) (4) in the (b) (4) of dorzolamide. The first 3 commercial batches manufactured using (b) (4) foil will be placed on stability and at least one lot will be placed on stability each year. The first 3 commercial batches will also be tested for weight loss.

The proposed expiration dating period of 24 months and the storage statement "Store at 20-25°C (68-77°F), (b) (4) (see USP Controlled Room Temperature]. Do not freeze. Store in the original pouch. After pouch is opened, store the single-use containers in the foil pouch to protect from light. Throw away any unused single-use containers 15 days after first opening the pouch." are acceptable and supported by the stability data.

Executive Summary Section

The Package Insert and container labels are acceptable from the CMC point of view.

The applicant claims a categorical exemption from the requirement to perform an Environmental Assessment and this claim is accepted.

B. Description of How the Drug Product is Intended to be Used

COSOPT PF (dorzolamide hydrochloride and timolol maleate) Ophthalmic Solution is a carbonic anhydrase inhibitor (dorzolamide) with a beta-adrenergic receptor blocking agent (timolol) 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. The recommended dose is one drop per eye twice a day.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes, and process controls. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

A recommendation of Withhold from the Office of Compliance is in effect as of the date of this review.

All labels have the required information. CMC recommendations for the package insert, bottle, blister and carton labels have been provided for review team discussion.

From the CMC perspective, this NDA is *not recommended for approval* until all pending issues are resolved.

III. Administrative**A. Reviewer's Signature**

George Lunn, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

Branch Chief: Rapti Madurawe, Ph.D. {Signed Electronically in DFS}

C. CC Block

47 pages has been withheld in full as B(4) CCI/TS immediately following this page

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

/s/

GEORGE LUNN

10/17/2011

All issues have been resolved in a satisfactory manner except that Compliance continues to make a recommendation of Withhold. Therefore this application is not recommended for approval from a CMC point of view.

RAPTI D MADURAWAWE

10/17/2011

Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division: Division of Anti-Infective and Ophthalmology Products
NDA: 202-667
Applicant: Merck Sharp & Dohme Co
Stamp Date: February 16, 2011
PDUFA Date: December 17, 2011
Trademark: Cosopt PF
Established Name: Dorzolamide HCl and timolol maleate ophthalmic solution, 2.0% and 0.5%
Dosage Form: Ophthalmic Solution
Route of Administration: Topical
Indication: Reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

PAL: Linda Ng, Ph.D.

| | | |
|-----------------------------------|-------------------------------------|-------------------------------------|
| | YES | NO |
| ONDQA Fileability: | <input checked="" type="checkbox"/> | <input type="checkbox"/> |
| Comments for 74-Day Letter | <input type="checkbox"/> | <input checked="" type="checkbox"/> |

Summary and Critical Issues:

Summary

Cosopt PF (dorzolamide HCl and timolol maleate ophthalmic solution) 2.0% and 0.5% is a 5S NDA, dated February 16, 2011, by eCTD format, and accepted for standard review. Cosopt, NDA 20,869, an approved product, by the same applicant, contains a preservative and sold in a multi-dose container. Trusopt, NDA 20,408, by the same applicant, is approved for dorzolamide HCl preserved in a multi-dose container configuration. Timoptic, NDA 18,086, is approved for timolol maleate in a multi-dose container currently listed in the Orange Book under Aton Pharma Inc. Timoptic was originally approved for Merck.

The product in this NDA is a preservative-free unit dose in one strength and size for the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers. The related IND number is (b) (4)

A microbiology consult was submitted by the OND PM, Alison Rodgers and Dr. Vinnie Pawar was assigned. The trade name consult was sent directly from the applicant to OSE. The EES evaluation was performed by ONDQA PM Althea Cuff who confirmed site information with the applicant and finalized the request with the CMC reviewer George Lunn.

Dorzolamide HCl is sourced from the same manufacturer as Trusopt. Timolol maleate is from the same manufacturer as Timoptic. References are made to the respective NDAs for

manufacturing, controls and stability information. The acceptance specification of the two drug substances are submitted to this NDA. USP monographs exist for dorzolamide HCl drug substance, timolol maleate drug substance and timolol maleate in ophthalmic product. No monograph exists for the combination drug product.

The drug product, at pH of 5.5 to 5.8, contains mannitol (b) (4) sodium citrate (b) (4) (b) (4) hydroxyethylcellulose (b) (4) sodium hydroxide for pH adjustment and water for injection. 0.2 mL is filled in low density polyethylene (b) (4) unit dose pipette. Each (b) (4) foil pouch contains 3 strips of 5 unit dose pipettes. The drug product is manufactured at Laboratories Merck Sharp & Dohme – Chibret facility.

Dye and microbial ingress tests are performed on the drug product. A leachable study was performed using the market product with representative printed labels with adhesives and packaged in printed aluminium foil pouch. Photostability and freeze thaw studies are also performed.

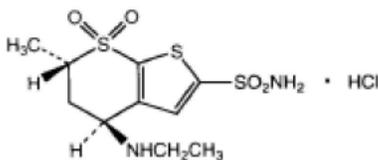
A comparability protocol for drug product site change was submitted.

The pipette (b) (4) is (b) (4) in DMF (b) (4) and (b) (4) foil material (b) (4) are described in DMFs (b) (4) and (b) (4). The drug product is (b) (4) at 0.2 ml. The trade and professional samples are the same. The number of pipettes per pouch differs. The trade product is stored with 15 and 60 pipettes and the professional sample stored with 15 and 30 pipettes.

The commercial batch size is claimed to be (b) (4). Maximum processing/hold time is (b) (4). The stability data included three batches at 25°C/40% relative humidity with 24 months stability data, and 6 months accelerated at 40°C/20% RH. An expiry of 24 months is claimed.

Structural Formula:

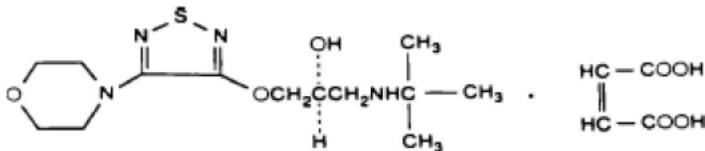
Dorzolamide Hydrochloride -



Molecular weight: 360.91

Molecular formula: C₁₀H₁₆N₂O₄S₃ HCl

Timolol Maleate -



Molecular weight: 432.5

Molecular formula: C₁₃H₂₄N₄O₃S C₄H₄O₄

Since this is a solution product, nanotechnology does not apply.

Critical issues for review

- All tests should be evaluated for meaningful conditions and criteria for both drug substance and drug product. In the drug substance and the drug product specifications, the Any individual unspecified impurity should be evaluated and (b) (4) For ophthalmic products at that strength, the criterion is usually set at NMT (b) (4) Microbial limits may need to be included. In the drug product, no endotoxin test is proposed. Micro will have to comment.
- A leachable study was submitted with leachable observed but none indicated in the drug product specification. It is expected leachable evaluation carried out as a one time study through expiry using appropriate screening methods. Reviewer should evaluate adequacy of the study and evaluate if an leachable should be included in the specification.
- The stability commitment 3.2.P.8.2 in the stability protocol is inadequate. Neither a statement that the Reviewing Division be informed with batch failure nor commit to inform the Agency within time specified according to the CFR.
- Comparability protocol for manufacturing site change is submitted. Reviewer should evaluate for acceptability.
- The water loss information appears to be missing. A one-time study through expiry is adequate; the product specification does not need to include water loss if the study is performed. The applicant has included the minimum fill in the specification. That test should be performed through stability if the one-time study is not performed. The foil pouch once opened may not be able to protect the individual unit from water loss. Reviewer should consider and follow up appropriately.

- **Comments for 74-Day Letter**

None recommended at this time.

D. Review, Comments and Recommendation:

Acceptable for filing. Dr. George Lunn has been assigned to review this NDA.

 Linda Ng, Ph.D.
 CMC Lead

 Date

 Stephen Miller, Ph.D.
 Acting Branch Chief

 Date

Cc: OND PM ARodgers
 ONDQA PM ACuff

Appendix 1. Composition of the Drug Product

Composition of Dorzolamide Hydrochloride (+) Timolol Maleate Preservative Free Ophthalmic Solution

| Ingredients | Reference | Role | Amount per mL |
|--|---------------|---------------|------------------------|
| Dorzolamide base (as Dorzolamide Hydrochloride) | Ph. Eur., USP | Active | 20.00 mg (22.26 mg) |
| Timolol base (as Timolol Maleate) | Ph. Eur., USP | Active | 5.00 mg (6.83 mg) |
| Sodium Citrate | Ph. Eur., USP | | (b) (4) |
| Hydroxyethylcellulose [†] | Ph. Eur., NF | | |
| Sodium Hydroxide [†] | Ph. Eur., NF | pH Adjustment | qs pH 5.60 |
| Mannitol | Ph. Eur., USP | | (b) (4) |
| Water for Injection | Ph. Eur., USP | | (b) (4) |

4 pages has been withheld in full as B(4) CCI/TS
 immediatley following this page

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

/s/

LINDA L NG
03/27/2011

STEPHEN P MILLER
04/08/2011

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-667 ONDQA)**

NDA Number: 202-667

Established/Proper Name:
Cosopt (dorzolamide
hydrochloride and timolol
maleate ophthalmic solution)
2.0% and 0.5%

Applicant: Merck Sharp
& Dohme Co

Letter Date: February 16, 2011

Stamp Date: February 16,
2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On initial overview of the NDA application for filing:

| A. GENERAL | | | | |
|------------|--|-----|----|-------------|
| | Parameter | Yes | No | Comment |
| 1. | Is the CMC section organized adequately? | x | | eCTD |
| 2. | Is the CMC section indexed and paginated (including all PDF files) adequately? | x | | |
| 3. | Are all the pages in the CMC section legible? | x | | |
| 4. | Has all information requested during the IND phase, and at the pre-NDA meetings been included? | x | | Seems to be |

| B. FACILITIES* | | | | |
|----------------|---|-----|----|----------------------------|
| | Parameter | Yes | No | Comment |
| 5. | Is a single, comprehensive list of all involved facilities available in one location in the application? | x | | Submitted in section 1.1.2 |
| 6. | For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API. | | | N/A |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-667 ONDQA)**

| | | | | |
|----|--|---|--|---|
| 7. | <p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | x | | <p align="center">Communication between ONDQA PM and applicant to obtain fax number and email address on all sites.</p> |
| 8. | <p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | x | | <p align="center">Communication between ONDQA PM and applicant to obtain fax number and email address on all sites.</p> |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-667 ONDQA)**

| | | | | |
|-----|---|---|--|--------------------|
| 9. | Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | X | | |
| 10. | Is a statement provided that all facilities are ready for GMP inspection at the time of submission? | X | | Submitted in 1.1.2 |

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

| C. ENVIRONMENTAL ASSESMENT | | | | |
|----------------------------|--|-----|----|-----------------|
| | Parameter | Yes | No | Comment |
| 11. | Has an environmental assessment report or categorical exclusion been provided? | X | | Section 1.12.14 |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-667 ONDQA)**

| D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API) | | | | |
|--|---|------------|-----------|---|
| | Parameter | Yes | No | Comment |
| 12. | Does the section contain a description of the DS manufacturing process? | x | | Both drug substances information are referred to the applicant's other NDAs. |
| 13. | Does the section contain identification and controls of critical steps and intermediates of the DS? | | x | Dorzolamide hydrochloride in NDA 20-408 for TRUSOPT Timolol maleate in NDA 18-086 for TIMOPTIC |
| 14. | Does the section contain information regarding the characterization of the DS? | | x | |
| 15. | Does the section contain controls for the DS? | x | | |
| 16. | Has stability data and analysis been provided for the drug substance? | | x | |
| 17. | Does the application contain Quality by Design (QbD) information regarding the DS? | | x | Not in this NDA |
| 18. | Does the application contain Process Analytical Technology (PAT) information regarding the DS? | | x | Not in this NDA |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-667 ONDQA)**

| E. DRUG PRODUCT (DP) | | | | |
|-----------------------------|---|------------|-----------|---|
| | Parameter | Yes | No | Comment |
| 19. | Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging? | x | | Cosopt ophthalmic solution manufactured at Laboratories Merck Sharp & Dohme – Chibret (Mirabel) |
| 20. | Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable? | x | | |
| 21. | Is there a batch production record and a proposed master batch record? | x | | Executed batch records for compounding and filling submitted. Section.3.2.R. |
| 22. | Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product? | x | | |
| 23. | Have any biowaivers been requested? | | x | Not needed for an Ophthalmic solution |
| 24. | Does the section contain description of to-be-marketed container/closure system and presentations)? | x | | |
| 25. | Does the section contain controls of the final drug product? | x | | |
| 26. | Has stability data and analysis been provided to support the requested expiration date? | x | | 3 batches of commercial strength at Laboratory Merck Sharp & Dohme, Cibret facility, for 24 months at 25°C/40%RH and accelerated temperature at 40°C/20%RH were submitted. Requested 24 months expiry |
| 27. | Does the application contain Quality by Design (QbD) information regarding the DP? | | x | |
| 28. | Does the application contain Process Analytical Technology (PAT) information regarding the DP? | | | Not obvious |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-667 ONDQA)**

| F. METHODS VALIDATION (MV) | | | | |
|-----------------------------------|--|------------|-----------|---------------------------|
| | Parameter | Yes | No | Comment |
| 29. | Is there a methods validation package? | x | | Included. Section 3.2.R.2 |

| G. MICROBIOLOGY | | | | |
|------------------------|--|------------|-----------|---|
| | Parameter | Yes | No | Comment |
| 30. | If appropriate, is a separate microbiological section included assuring sterility of the drug product? | x | | Incorporated in various part of the NDA including Section 3.2.P.3.5 |

| H. MASTER FILES (DMF/MAF) | | | | |
|----------------------------------|---|------------|-----------|----------------|
| | Parameter | Yes | No | Comment |
| 31. | Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete? | x | | |

| DMF # (b) (4) | TYPE | HOLDER (b) (4) | ITEM REFERENCED (b) (4) | LOA DATE | COMMENTS |
|------------------|------|-------------------|----------------------------|----------|----------|
| | III | | | 12/02/10 | |
| | III | | | 12/20/10 | |
| | III | | | 12/03/10 | |
| | | | | | |
| | | | | | |

| I. LABELING | | | | |
|--------------------|---|------------|-----------|---|
| | Parameter | Yes | No | Comment |
| 32. | Has the draft package insert been provided? | x | | |
| 33. | Have the immediate container and carton labels been provided? | x | | Mock up for pouch, carton, sample and trade |

| J. FILING CONCLUSION | | | | |
|-----------------------------|--|------------|-----------|----------------|
| | Parameter | Yes | No | Comment |
| 34. | IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? | x | | |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-667 ONDQA)**

| | | | | |
|-----|--|--|---|-----|
| 35. | If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant. | | | N/A |
| 36. | Are there any potential review issues to be forwarded to the Applicant for the 74-day letter? | | x | |

{See appended electronic signature page}

Linda Ng, Ph.D.
CMC Lead
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Stephen Miller, Ph.D.
Acting Branch Chief
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

cc: OND PM ARodgers
ONDQA PM ACuff
CMC Reviewer GLunn

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

/s/

LINDA L NG
03/18/2011

STEPHEN P MILLER
03/21/2011