

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202667Orig1s000**

**PHARMACOLOGY REVIEW(S)**



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

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 202667  
SERIAL NUMBER: 0000  
DATE RECEIVED BY CENTER: 02/16/11  
PRODUCT: COSOPT® Preservative-Free Ophthalmic Solution  
(dorzolamide 2.0% and timolol 0.5%)  
INTENDED CLINICAL POPULATION: Patients with open-angle glaucoma or ocular  
hypertension who are insufficiently responsive to  
beta-blockers  
SPONSOR: Merck Sharp & Dohme  
DOCUMENTS REVIEWED: Electronic submission  
REVIEW DIVISION: Division of Anti-Infective and Ophthalmology  
Products  
PHARM/TOX REVIEWER: Conrad H. Chen, Ph.D.  
PHARM/TOX SUPERVISOR: Wendelyn Schmidt, Ph.D.  
ACTING DIVISION DIRECTOR: Wiley Chambers, MD  
PROJECT MANAGER: Alison Rodgers

Date of review submission to Division File System (DFS):

## ***EXECUTIVE SUMMARY***

### **I. Recommendations**

- A. Recommendation on approvability  
Recommend approval.
- B. Recommendation for nonclinical studies  
None.
- C. Recommendations on labeling  
Recommend to use a similar labeling as the approved COSOPT®.

### **II. Summary of nonclinical findings**

- A. Brief overview of nonclinical findings  
Reference is made to the Non-Clinical Pharmacology and Toxicology Documentation of the following NDAs previously approved by the FDA:  
NDA 18,086, **TIMOPTIC®**, Timolol maleate (Approval date: August 17, 1978).  
NDA 20,408, **TRUSOPT®**, Dorzolamide hydrochloride (Approval date: December 9, 1994).  
NDA 20,869, **COSOPT®**, Dorzolamide Hydrochloride/Timolol Maleate combination (Approval date: April 7, 1998).
- B. Pharmacologic activity  
Dorzolamide hydrochloride, a carbonic anhydrase inhibitor, lowers intraocular pressure by decreasing the secretion of aqueous humor from the ciliary process. Timolol, a beta –adrenergic receptor blocking agent, elicits ocular hypotension by blocking beta-adrenoceptors in the ciliary process.
- C. Nonclinical safety issues relevant to clinical use  
The removal of preservative (0.0075% benzalkonium chloride) in the new formulation will not cause any safety issues.

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 202667

**Review number:** No.1

**Sequence number/date/type of submission:** SN0000/Feb.16, 2011/Electronic original submission

**Information to sponsor:** Yes (x) No ( )

**Sponsor and/or agent:** Merck Sharp & Dohme

**Manufacturer for drug substance:**

**Reviewer name:** Conrad H. Chen, Ph.D.

**Division name:** division of Anti-Infective and Ophthalmology Products

**Review completion date:** May 11, 2011

#### Drug:

Trade name: COSOPT® Preservative-Free Ophthalmic Solution (COSOPT® PF)

Generic name: Dorzolamide 20 mg and Timolol 5 mg (b) (4) solution

Code name:

Dorzolamide: L-671,152-001E, MK-0507

Timolol: L-000671152 (+) L-000714503, L-714,503-001T, MK-0950, SP 1918

Chemical name:

Dorzolamide: (4S-trans)-4-Ethylamino-5,6-dihydro-6-methyl-4H-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride

Timolol: (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

CAS registry number:

Dorzolamide: 130693-82-2

Timolol: 26921-17-5

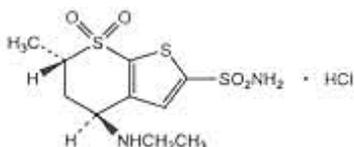
Molecular formula/molecular weight:

Dorzolamide: C<sub>10</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S<sub>3</sub>•HCl/360

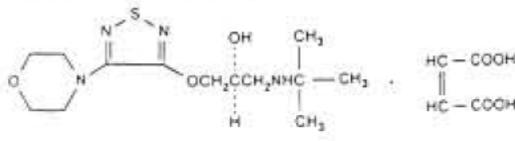
Timolol: C<sub>13</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>S • C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>/432.50

Structure:

Dorzolamide Hydrochloride:



Timolol Maleate:



**Relevant INDs/NDAs/DMFs:**

NDA 20-408 for TRUSOPT® (dorzolamide hydrochloride 2%) Ophthalmic Solution, approval date: 12/9/1994

NDA 20869 for COSOPT® (dorzolamide hydrochloride 2%/ timolol maleate 0.5%) Ophthalmic Solution, containing 0.0075% benzalkonium chloride as preservative, approval date: 4/7/1998

NDA 18086 for TIMOPTIC® (timolol maleate 0.25% and 0.5%) Ophthalmic Solution, approval date: 8/17/1978

IND 52080 for COSOPT® Ophthalmic Solution

**Drug class:**

Dorzolamide: Carbonic anhydrase inhibitor

Timolol: Beta –adrenergic receptor blocking agent

**Intended clinical population:** COSOPT® PF is 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.

**Clinical formulation:**

Composition of Preservative-Free Dorzolamide Hydrochloride and Timolol Maleate 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)

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**Route of administration:** The dose is one drop of COSOPT® PF in the affected eye(s) two times daily.

**NON-CLINICAL STUDIES:**

Reference is made to the Non-Clinical Pharmacology and Toxicology Documentation of the following NDAs previously approved by the FDA:

NDA 18,086, **TIMOPTIC®**, Timolol maleate (Approval date: August 17, 1978).

NDA 20,408, **TRUSOPT®**, Dorzolamide hydrochloride (Approval date: December 9, 1994).

NDA 20,869, **COSOPT®**, Dorzolamide Hydrochloride/Timolol Maleate combination (Approval date: April 7, 1998).

## **2.6.2 PHARMACOLOGY**

Although no other non-clinical studies were conducted for COSOPT® PF, three preclinical in vivo studies, one in primate and two in rabbits, were conducted to determine if the removal of the preservative modified the pharmacological response to dorzolamide/timolol containing the preservative.

### **2.6.2.1 Brief summary**

It has been demonstrated that the ocular hypotensive effect of topically applied 2% dorzolamide/0.5% timolol maleate ophthalmic solution both in monkeys and rabbits with elevated intraocular pressure and in ocular normotensive rabbits is unaltered by the removal of its preservative.

### **2.6.2.2 Primary pharmacodynamics**

#### **1. Effect on Intraocular Pressure (IOP) of Ocular Hypertensive Monkeys**

Ocular hypertension was induced in the right eye of cynomolgus monkeys by photocoagulating the trabecular meshwork with an argon laser. This model mimics many of the features present in the glaucomatous human eye. This model was used to compare the ocular hypotensive effects of a pharmaceutical formulation of 2% dorzolamide/0.5% timolol with and without the preservative (0.0075% benzalkonium chloride).

The intraocular pressure of ocular hypertensive cynomolgus monkeys was significantly decreased at all time points from thirty minutes out to, and including, six hours following the instillation of the pharmaceutical formulation of dorzolamide/timolol containing 0.0075% benzalkonium chloride as preservative. The peak decline in intraocular pressure occurred at three hours post-dosing and was a reduction of 54% from the corresponding vehicle-treated value of 40.7 mm Hg. Intraocular pressure was significantly decreased from one hour up to and including six hours following the instillation of the pharmaceutical formulation of 2% dorzolamide/0.5% timolol without benzalkonium chloride as preservative. The greatest intraocular pressure lowering effects occurred at six hours post-dosing and was a reduction of 50% from the corresponding vehicle-treated value of 32.8 mm Hg.

Another study was undertaken in ocular hypertensive monkeys in which a 2% solution of dorzolamide and 0.5% timolol, both dissolved in 0.5% hydroxyethylcellulose, were coadministered to evaluate the effects on intraocular pressure. Dorzolamide was instilled ten minutes after timolol and intraocular pressure was recorded at the times stated following dosing with timolol. Significant declines in the intraocular pressure of ocular hypertensive monkeys were present at all time points from one hour to six hours with the peak decline being present at six hours post-dosing. This was a peak reduction of 52% from the corresponding vehicle-treated value of 33.4 mm Hg.

In summary, the peak percentage reductions in intraocular pressure relative to vehicle following the instillation of the pharmaceutical formulation containing 2% dorzolamide/0.5% timolol and benzalkonium chloride preservative, the preservative-free 2% dorzolamide/0.5% timolol formulation, and co-administered 2% dorzolamide and

0.5% timolol were 54%, 50% and 52%, respectively. Hence, it has been clearly demonstrated that the removal of 0.0075% benzalkonium chloride from the pharmaceutical formulation of dorzolamide/timolol did not modify activity in ocular hypertensive cynomolgus monkeys, a model viewed as most closely resembling the clinical situation.

Table 2.6.2: 1

## Intraocular Pressure (IOP) of Ocular Hypertensive Cynomolgus Monkeys

Time Treatment (hr)	IOP Decrease (mm Hg)		
	2% Dorzolamide/0.5% Timolol		Concomitant Administration
	Preservative Containing	Preservative Free	
0.5	-5.2 ± 1.3 <sup>a</sup>	-3.1 ± 1.9	-1.6 ± 1.7
1	-13.7 ± 1.3 <sup>a, b</sup>	-6.7 ± 2.3 <sup>a</sup>	-8.5 ± 1.7 <sup>a</sup>
2	-19.8 ± 1.4 <sup>a, b</sup>	-12.0 ± 2.2 <sup>a</sup>	-13.6 ± 1.9 <sup>a</sup>
3	-22.1 ± 1.3 <sup>a, b</sup>	-13.4 ± 2.1 <sup>a</sup>	-15.5 ± 2.3 <sup>a</sup>
4	-21.1 ± 1.4 <sup>a</sup>	-15.7 ± 1.9 <sup>a</sup>	-17.1 ± 2.0 <sup>a</sup>
5	-21.0 ± 1.5 <sup>a</sup>	-15.9 ± 2.0 <sup>a</sup>	-16.8 ± 2.2 <sup>a</sup>
6	-20.2 ± 1.6 <sup>a</sup>	-16.3 ± 2.1 <sup>a</sup>	-17.3 ± 2.1 <sup>a</sup>

All values represent mean ± S.E.M.  
N = 16-32 animals  
<sup>a</sup>: Significantly different from vehicle-treated values for p<0.05 using Paired "t" test.  
<sup>b</sup>: Significantly different from preservative-free value for p<0.05 using Student's "t" test.

## 2. Effect on the Intraocular Pressure (IOP) of Ocular Normotensive Conscious Rabbits

The species most widely used in the search for ocular hypotensive agents is the albino rabbit. After the instillation of a pharmaceutical formulation containing 2% dorzolamide/0.5% timolol with 0.0075% benzalkonium chloride as preservative, and a preservative-free formulation of 2% dorzolamide/0.5% timolol, the reductions in the intraocular pressure of ocular normotensive albino rabbits were very similar at 30 minutes (4.2 vs. 4.5 mm Hg), one (6.0 vs. 5.1 mm Hg), two (4.2 vs. 4.7 mm Hg), three (2.5 vs. 2.6 mm Hg) and four hours (1.6 vs. 2.0 mm Hg).

Table 2.6.2: 2

Intraocular Pressure (IOP) of Ocular Normotensive Albino Rabbits

Time Treatment (hr)	IOP Decrease (mm Hg)	
	2% Dorzolamide/0.5% Timolol	
	Preservative Present <sup>a</sup>	Preservative Free <sup>a</sup>
0.5	-4.2 ± 2.1	-4.5 ± 1.8
1	-6.0 ± 2.1	-5.1 ± 2.1
2	-4.2 ± 1.7	-4.7 ± 2.7
3	-2.5 ± 1.9	-2.6 ± 2.5
4	-1.6 ± 2.6	-2.0 ± 3.0

All values represent mean ± S.D.  
<sup>a</sup>: N = 12 animals

### 3. Effect on the Alpha-Chymotrypsin-Induced Elevation of Intraocular Pressure (IOP) in Rabbits

Ocular hypertension was induced in the right eye of albino rabbits by the intraocular injection of alpha-chymotrypsin. Following the instillation of pharmaceutical formulations containing 2% dorzolamide/0.5% timolol with or without benzalkonium chloride preservative, the declines in intraocular pressure were very similar and were not statistically different from each other at any time point from 30 minutes out to and including five hours, which was the last measured time point. Dorzolamide/timolol with preservative elicited a maximum intraocular pressure lowering effect of 7.6 mm Hg. The corresponding reduction in intraocular pressure for preservative-free dorzolamide/timolol was 7.4 mm Hg.

Table 2.6.2: 3

Alpha-Chymotrypsin-Induced Elevation of Intraocular Pressure (IOP) in Rabbits

Time Treatment (hr)	IOP Decrease (mm Hg)	
	2% Dorzolamide/0.5% Timolol	
	Preservative Present <sup>a</sup>	Preservative Free <sup>a</sup>
0.5	-4.6 ± 3.8	-4.5 ± 1.7
1	-6.7 ± 3.2	-6.8 ± 3.0
2	-7.2 ± 2.3	-7.4 ± 1.9
3	-6.7 ± 2.2	-7.3 ± 3.6
4	-7.4 ± 2.8	-6.9 ± 2.5
5	-7.6 ± 2.8	-6.3 ± 4.0

All values represent mean ± S.D.  
<sup>a</sup>: N = 12 animals

**2.6.2.3 Secondary pharmacodynamics**

No new secondary pharmacodynamics study was conducted with COSOPT® PF.

**2.6.2.4 Safety pharmacology**

No new safety pharmacology study was conducted with COSOPT® PF.

**2.6.4 PHARMACOKINETICS/TOXICOKINETICS**

No new pharmacokinetics and toxicokinetics study was conducted with COSOPT® PF.

**2.6.6 TOXICOLOGY**

No new toxicology study was conducted with COSOPT® PF.

**OVERALL CONCLUSIONS AND RECOMMENDATIONS**

## Conclusions:

Dorzolamide hydrochloride and timolol maleate were first introduced for the treatment of ocular hypertension and/or glaucoma in 1995 and 1978, respectively, and both efficacy and ocular and systemic safety profiles of both have been well established. The marketed formulation of 2% dorzolamide/0.5% timolol maleate ophthalmic solution (COSOPT®) contains 0.0075% benzalkonium chloride as preservative.

In this NDA, the sponsor proposes to remove 0.0075% benzalkonium chloride from the formulation and develop COSOPT® Preservative-Free Ophthalmic Solution (COSOPT® PF) for the same indication as COSOPT®. Reference is made to the Non-Clinical Pharmacology and Toxicology Documentation of the following NDAs previously approved by the FDA:

NDA 18,086, **TIMOPTIC®**, Timolol maleate (Approval date: August 17, 1978).

NDA 20,408, **TRUSOPT®**, Dorzolamide hydrochloride (Approval date: December 9, 1994).

NDA 20,869, **COSOPT®**, Dorzolamide Hydrochloride/Timolol Maleate combination (Approval date: April 7, 1998).

Although no other non-clinical studies were conducted for COSOPT® PF, three preclinical pharmacodynamics studies were performed. It has been demonstrated that the ocular hypotensive effect of topically applied 2% dorzolamide/0.5% timolol maleate ophthalmic solution both in monkeys and rabbits with elevated intraocular pressure and in ocular normotensive rabbits was unaltered by the removal of its 0.0075% benzalkonium chloride as preservative. Nothing was observed in these studies to preclude the use of preservative-free dorzolamide/timolol ophthalmic solution at the same clinical dosage for the same indication for COSOPT®.

Unresolved toxicology issues (if any): None

## Recommendations:

The approval of NDA 202667 is recommended.

## Suggested labeling:

Use a similar labeling as the approved COSOPT®.

Signatures (optional):

Reviewer Signature \_\_\_\_\_

Conrad H. Chen, Ph.D

Supervisor Signature \_\_\_\_\_ Concurrence Yes  No

Wendelyn Schmidt, Ph.D.

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/s/  
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CONRAD H CHEN  
06/08/2011

WENDELYN J SCHMIDT  
06/14/2011

**PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST**

NDA Number: 202-667

Applicant: Merck Sharp & Dohme Stamp Date: 2-16-11

Drug Name: COSOPT®

Preservative-Free Ophthalmic Solution

IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? Yes [ x ] No [ ]

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?	x		
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review begin?	x		
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?	x		
4	Are ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?	x		
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?	x		
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?	x		
7	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?	x		
8	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	x		
9	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		
10	Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	x		
11	From a pharmacology perspective, is this NDA fileable?	x		

Note:

Reviewing Pharmacologist:

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Conrad Chen, Ph.D.

3-17-11

Date:

Team Leader:

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Wedelyn Schmidt, Ph.D.

Date

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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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CONRAD H CHEN  
03/18/2011

WENDELYN J SCHMIDT  
03/21/2011