

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202667Orig1s000

MEDICAL REVIEW(S)

Deputy Division Director Review of NDA 202-667

(Amended Application after Complete Response Letter)

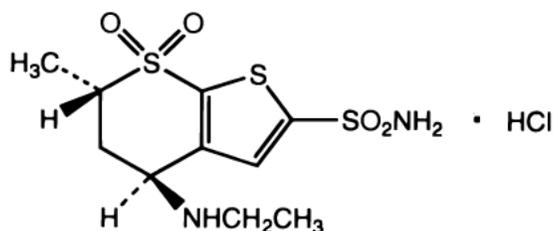
Date	January 31, 2012
From	Wiley A. Chambers, M.D.
NDA #	202-667
Applicant	Merck, Sharp & Dohme Corp.
Date of Original Submission	February 16, 2011
Date of Amendment	January 24, 2012
Type of Application	505(b)(1)
Name	Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone
Recommended:	Recommended for Approval

1. Introduction

Chemical Structures

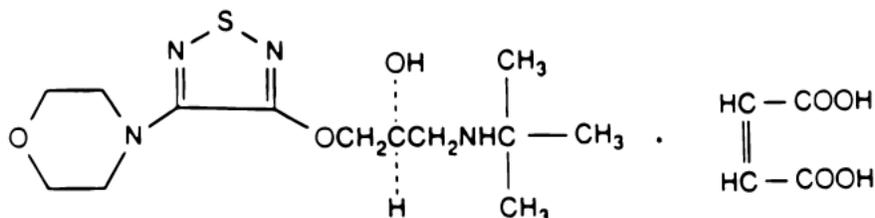
Dorzolamide hydrochloride

$C_{10}H_{16}N_2O_4S_3 \cdot HCl$



Timolol maleate

$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$



NDA 20-869, the benzalkonium chloride preserved version of Cosopt (dorzolamide hydrochloride and timolol maleate ophthalmic solution) was approved for marketing in the United States on April 7, 1998. Cosopt combines a beta blocker with a topical carbonic anhydrase inhibitor (CAI). Both active components in this fixed-dose combination are expected to lower IOP by decreasing aqueous humor production. As demonstrated in the original Cosopt application, the IOP lowering effect is greater with concomitant administration than it is with

combination therapy, but combination therapy is better than with either product used alone. This application is the same as NDA 20-869, except that there is no preservative in the currently proposed NDA and the product is to be marketed in single dose containers.

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% is marketed in other 22 other countries.

The application relies on the Agency's determination of the safety and efficacy in the following applications:

- NDA 18-086, Timoptic (timolol maleate ophthalmic solution) 0.5% approved August 17, 1978.
- NDA 20-408, Trusopt (dorzolamide hydrochloride ophthalmic solution) 2.0% approved December 9, 1994.
- NDA 20-869, Cosopt (dorzolamide hydrochloride - timolol maleate ophthalmic solution) approved April 7, 1998.

In a Pre-NDA meeting held on April 28, 2010, the Agency agreed that Protocol 081 together with cross reference to the studies submitted in support of NDA 20-869, Cosopt, would be sufficient to enable review of an NDA for the preservative-free dorzolamide/timolol formulation.

2. CMC

The drug substances, timolol maleate and dorzolamide hydrochloride, are described in approved NDAs, and this information is incorporated by reference. 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 ^(b)₍₄₎ pipettes is placed in an ^(b)₍₄₎ foil pack.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Composition of Preservative Free Dorzolamide Hydrochloride and Timolol Maleate 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 ¹	Ph. Eur., NF		
Sodium Hydroxide ²	Ph. Eur., NF	ph Adjustment	q.s pH 5.60
Mannitol	Ph. Eur., USP		^(b) ₍₄₎
Water for Injection	Ph. Eur., USP		

^(b)₍₄₎

Proposed Regulatory Specifications

Test	Method	Acceptance Criterion
Appearance	Visual	Clear, colorless to nearly colorless, slightly viscous solution which practically free from particles
Identity of dorzolamide	HPLC	Conforms to standard (b) (4)
Identity of dorzolamide	TLC	Conforms to standard (b) (4)
Identity of timolol	HPLC	Conforms to standard
Identity of timolol	TLC	Conforms to standard
Viscosity		(b) (4)
Deliverable volume	EP 2.9.28	≥ 0.2 mL
pH	EP 2.2.3	5.5-5.8
Osmolality	FP depression	242-323 mOsm
(b) (4) orzolamide assay	HPLC	90.0-110.0%
Timolol assay	HPLC	90.0-110.0%
(b) (4)		(b) (4)
(b) (4)		
Any unspecified impurity		
(b) (4) related total		
(b) (4) related degradants (b) (4)		
related degradants (b) (4)		
related degradants (b) (4)		
Any unspecified impurity		
(b) (4) related degradants total		
Sterility	USP <71>	Sterile
Endotoxins	USP <85>	≤ 5 EU/mL
Particulate matter	USP <789>	NMT 50 particles greater than 10 microns in diameter, NMT 5 particles greater than 25 microns in diameter and NMT 2 particles greater than 50 microns in diameter [per mL.

Reviewer's Comments: *The regulatory specification for unspecified impurities should have been no more than (b) (4) of the timolol concentration to be consistent other ophthalmic applications approved over the past 15 years. The regulatory specifications are otherwise acceptable. In a telephone conversation on December 16, 2011, Merck agreed to amend the specifications to change unspecified degradants to unspecified impurities retaining the threshold level at (b) (4) because the preserved formulation of Cosopt does not have a (b) (4) specification.*

FACILITIES INSPECTIONS:

On June 27, 2011, an overall recommendation from the Office of Compliance was made. The recommendation was to withhold approval of the drug product. On December 16, 2011, the recommendation was changed to acceptable.

3. Nonclinical Pharmacology/Toxicology

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

- NDA 20,408, **TRUSOPT**, Dorzolamide hydrochloride (Approval date: December 9, 1994)
- NDA 18,086, **TIMOPTIC**, Timolol maleate (Approval date: August 17, 1978)
- 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.

4. Clinical Pharmacology/Biopharmaceutics

The applicant has requested a waiver of the requirement for the submission of in vivo bioavailability data. No clinical pharmacology studies of the COSOPT PF formulation were conducted, and no pharmacokinetic samples were obtained in the Phase 3 trial conducted in support of this NDA. The applicant's request for a waiver of the in vivo bioavailability requirement is being granted. The clinical pharmacology program conducted for the approval of the original Cosopt product is sufficient for the approval of the Cosopt PF product.

5. Sterility Assurance

In the Product Quality Microbiology Filing Review of NDA 202667 dated March 23, 2011, the applicant was sent an additional comment regarding the lack of bacterial endotoxins specification in this submission. In the amendment of September 9, 2011, the applicant agreed to add a specification for endotoxins of no more than (b) (4) No other deficiencies from a sterility assurance prospective were noted.

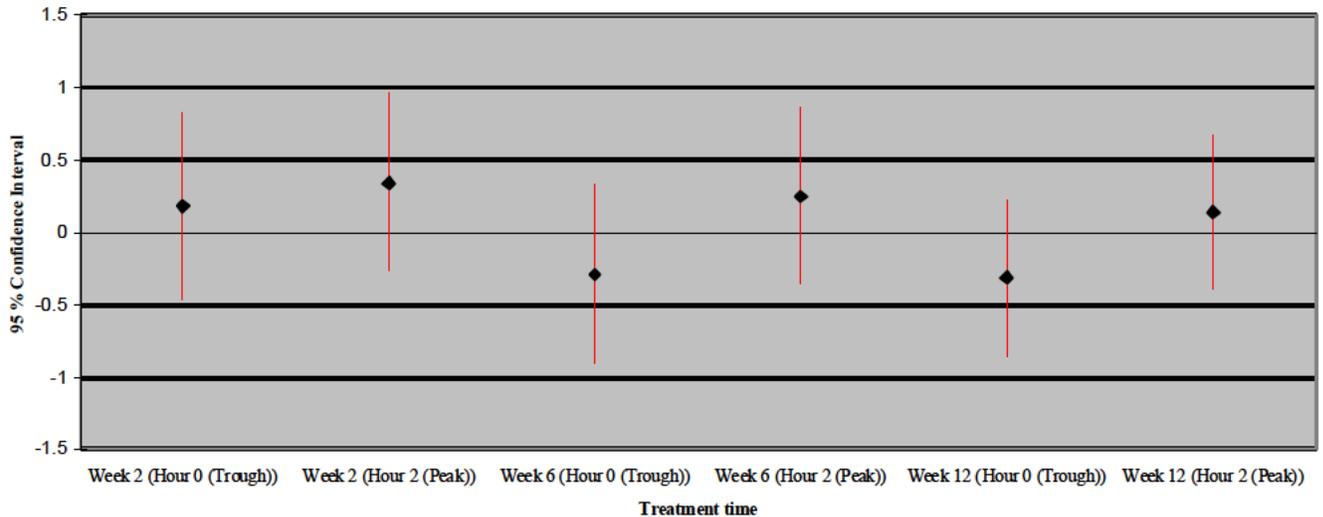
6. Clinical/Statistical - Efficacy

Study P-081 was submitted in support of the proposed indication, the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers. The mean intraocular pressure treatment group comparisons and the 95% confidence intervals around the mean differences at all time points are presented for the full patient population and several subsets of the full population. Equivalence was defined as having the 95% confidence interval around the true treatment group difference of the mean changes from Day -1 to Week 12 in trough (Hour 0) and peak (Hour 2) IOP being less than 1.5 mmHg at all time points and less than 1 mmHg at the majority of timepoints.

**Mean IOP Comparison of PF Dorzolamide/Timolol and Dorzolamide/Timolol
 at Morning Dose Peak and Trough - APT-LOCF Worse Eye**



**95% Confidence Intervals of the IOP Mean Difference Between
 PF Dorzolamide/Timolol and Dorzolamide/Timolol at Morning Dose Peak and Trough
 APT LOCF - Worse Eye**



The 95% confidence interval for the mean difference in IOP between the preservative free dorzolamide/timolol and preservative containing dorzolamide/timolol treatment groups is less than 1.0 mmHg for all peak and trough time points from Week 2 through Week 12 in multiple different populations. The graphs above are representative of the comparisons. There were no significant treatment group interactions with regard to age, iris color, gender or race for changes in IOP.

7. Safety

This application relies in part on three previously approved NDAs, Cosopt (NDA 20-869), Trusopt (NDA 20-408) and Timoptic (NDA 18-086) for demonstration of the safety of dorzolamide hydrochloride/ timolol maleate. In addition, as noted above, Study P081 was performed.

All 261 patients who entered Study 081 were included in the analysis of clinical safety.

	Cosopt PF	Cosopt
0 to 7 days	1	0
8 to 22 days	1	2
23 to 49 days	2	1
50 to 80 days	1	1
81 to 94 days	126	126

There were relatively few serious clinical adverse events.

Patient No.	Gender/Age	Relative Day of Onset	Adverse Experience	Outcome
0313	M / 64	43	Neoplasm, Thyroid, Benign	Recovered
0356	F / 84	42	Osteoarthritis	Recovered

Adverse events leading to discontinuation are noted below.

Reason for Discontinuation	Treatment	Patient Number
Adverse event – dermatitis, itching	Cosopt PF	0178
Adverse event – blurred vision, stinging upon instillation	Cosopt PF	0219
Adverse event – burning upon instillation	Cosopt PF	0354
Adverse event – sinus congestion, sinus headache, itching, stinging upon instillation	Cosopt PF	0357
Adverse event – Nausea, loss of appetite	Cosopt	0264
Adverse event – Dermatitis, itching	Cosopt	0273
Adverse event – Burning upon instillation	Cosopt	0355

The most common adverse events are listed below:

Body System or Adverse Experience	Cosopt PF N=131		Cosopt N=130	
	n	(%)	n	(%)
Patients with one or more adverse experiences	35	(27)	44	(34)
Patients with no adverse experience	96	(73)	86	(66)
Body as a Whole / Site Unspecified	1	(1)	2	(2)
Asthenia/Fatigue	1	(1)	0	
Flu-like Illness	0		2	(2)
Digestive System	0		1	(1)
Anorexia	0		1	(1)
Nausea	0		1	(1)
Endocrine System	1	(1)	0	
Neoplasm, Thyroid, Benign	1	(1)	0	
Musculoskeletal System	1	(1)	0	
Osteoarthritis	1	(1)	0	
Nervous System and Psychiatric	4	(3)	2	(2)
Depression	1	(1)	0	
Dizziness	1	(1)	0	
Headache	2	(2)	2	(2)
Insomnia	1	(1)	0	
Respiratory System	2	(2)	2	(2)
Influenza	0		1	(1)
Pharyngitis	1	(1)	0	
Rhinorrhea	0		1	(1)
Sinus Disorder	1	(1)	0	
Skin & Skin Appendage	4	(3)	2	(2)
Dermatitis	2	(2)	1	(1)
Pruritus	2	(2)	1	(1)
Urticaria	1	(1)	1	(1)
Special Senses	28	(21)	38	(29)
Abrasion, Corneal	0		1	(1)
Blurred Vision	2	(2)	2	(2)
Burning/Stinging, Eye	21	(16)	28	(22)
Cataract	0		1	(1)
Defect, Visual Field	0		1	(1)
Discharge, Eye	0		1	(1)
Erosion, Corneal	3	(2)	3	(2)
Foreign Body Sensation	1	(1)	1	(1)
Hemianopia	1	(1)	0	
Hemorrhage, subconjunctival	0		1	(1)
Inflammation, eyelid	1	(1)	0	
Irritation, eyelid	1	(1)	0	
Itching, eye	1	(1)	1	(1)

Body System or Adverse Experience	Cosopt PF N=131		Cosopt N=130	
	n	(%)	n	(%)
Otitis	0		1	(1)
Perversion, Taste	4	(3)	7	(5)
Photophobia	0		1	(1)
Tearing	1	(1)	1	(1)
Urogenital System	0		1	(1)
Infection, Urinary Tract	0		1	(1)

Note: Although a patient may have had two or more adverse experiences, the patient is counted only once within a category and in the overall total. The same patient may appear in different categories. All body systems are listed in which at least 1 patient had an adverse experience.

The most frequently reported adverse events occurring in up to 30% of patients were taste perversion (bitter, sour, or unusual taste) or ocular burning and/or stinging. The following adverse reactions were reported in 5-15% of patients: conjunctival hyperemia, blurred vision, superficial punctate keratitis or eye itching.

8. Advisory Committee Meeting

No Advisory Committee Meeting was scheduled. There were no outstanding clinical issues which were believed to benefit from an advisory committee discussion.

9. Pediatrics

The safety and effectiveness of preservative-containing dorzolamide hydrochloride ophthalmic solution and preservative-containing timolol maleate ophthalmic solution have been established when administered individually in pediatric patients aged 2 years and older and this is reflected in the approved Cosopt label in the US. Based on these data and the demonstrated clinical equivalence of preservative-free formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate to the preservative-containing formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate, no additional pediatric studies were required in support of NDA 202-667.

10. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. An inspection of Dr. Laibovitz's site was not conducted at this time because according to the clinical investigator, all records had been reportedly discarded or destroyed upon his retirement. Dr. Laibovitz's site had been inspected around the time that this clinical study was conducted. The inspectional history of Dr. Laibovitz's shows that he was inspected on November 7, 1996, (Sponsor: (b) (4) for NDA (b) (4)), on May 9, 1989 (Sponsor: (b) (4)).

(b) (4) and on December 28, 1995 (Sponsor (b) (4)). All the above mentioned inspections except for NDA (b) (4) (NAI) revealed minor regulatory deviations and were classified VAI. While regulatory deviations were observed during inspections for NDA (b) (4) and NDA (b) (4), the CI's data for the inspected studies was considered generally reliable.

FINANCIAL DISCLOSURE

Merck has attempted to comply with the FDA regulation, Financial Disclosure by Clinical Investigators. Protocol 081 was a single investigator clinical study for which Robert A. Laibovitz, MD served as clinical investigator in 1997. Dr. Laibovitz has since retired. Dr. Laibovitz did not provide the requested financial disclosure information by the cut-off date and therefore could not be certified. In compliance with the regulatory requirement for the Sponsor to demonstrate "due diligence" (21 CFR 54.4), multiple requests for this information were made, when possible, to the investigator who did not respond within the required time frame. Dr. Laibovitz did not return the certification form with requested information. The form was sent by Merck & Co., on April 19, 2010, April 23, 2010 and May 18, 2010.

Dr. Laibovitz was the primary investigator at site 0001 for MK507A-081 in 1997. Dr. Laibovitz retroactively completed a Certification/ Disclosure form in which he indicated he could not recall his equity interests in Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), as the study was conducted fourteen years ago. Dr. Laibovitz did, however, confirm the absence of a proprietary or financial interest, and compensation for outcome of the study. Merck completed an internal financial search and it was confirmed no reportable significant payments of other sorts were made to the investigator by Merck.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name; Cosopt PF, acceptable in OSE Review 2010-510, dated May 13, 2011, and in a second pre-action OSE Review 2011 – 2609, dated October 14, 2011.

11. Labeling

The amendment dated 1/24/2012 contains revisions to the proposed labeling. The revised labeling is considered acceptable and is included below.

20 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

WILEY A CHAMBERS
01/31/2012

Medical Officer's Review of Complete Response
Proposed Labeling

NDA 202667
SDN-013

Submission Date: January 24, 2012
Receipt Date: January 24, 2012
Review Date: January 25, 2012

Applicant:

Merck & Co., Inc.
Sumneytown Pike
P. O. Box 4, BLA-20
West Point, PA 19486

Applicant's
Representative:

Manager, Worldwide Regulatory Affairs
805-531-9707

Drug:

COSOPT PF™ (dorzolamide hydrochloride-timolol
maleate ophthalmic solution), 2% / 0.5%

Pharmacologic
Category:

Carbonic anhydrase inhibitor – beta blocking agent

Submitted:

The applicant has submitted a complete response to the
Complete Response letter dated, December 16, 2011.

The submitted carton and container labeling is consistent
with the Agency's recommendations. It is identical to the
Applicant's proposed revised draft labeling submitted by
email on December 22, 2011.

The submitted package insert and patient package insert are
consistent with the Applicant's draft revisions which were
submitted by email on January 17, 2012 and discussed at
the teleconference on January 18, 2012.

Following is the applicant's proposed draft labeling for the
product.

Reviewer's deletions are noted by and insertions
by underline.

(b) (4)

19 pages of draft labeling has been withheld in full as
B(4) CCI/TS immediately following this page

Recommendations:

The submitted carton and container labeling is consistent with the Agency recommendations and is acceptable.

The submitted package insert, patient package insert are consistent with the revisions discussed at the teleconference with Merck on January 18, 2012. They are acceptable.

NDA 202667 for Cosopt PF (dorzolamide hydrochloride-timolol maleate ophthalmic solution) 2%/0.5% is recommended for approval with the labeling submitted on January 24, 2012, provided the remaining CMC issues from the December 16, 2011, Complete Response Letter have been resolved.

Rhea A. Lloyd, MD
Medical Officer

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/s/

RHEA A LLOYD
01/27/2012

WILLIAM M BOYD
01/27/2012

Deputy Division Director Addendum to Review of NDA 202-667

Date	December 16, 2011
From	Wiley A. Chambers, M.D.
NDA #	202-667
Applicant	Merck, Sharp & Dohme Corp.

This memo serves to clarify a comment on my Deputy Division Director Review. Page 3 notes that I have recommended that the regulatory specifications include a limit on the unspecified impurities that are not necessarily related to dorzolamide or timolol. These impurities may come from the bottle components, packaging or labeling. While I have recommended a regulatory specification for unspecified impurities to be no more than (b)(4); at the present time, Merck has only agreed to submit a modification to the specification changing the unspecified degradants to any unspecified impurity and retaining the threshold limit at (b)(4)

Wiley A. Chambers, MD
Deputy Division Director

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/s/

WILEY A CHAMBERS
12/16/2011

NDA 202667

COSOPT PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution)

Proposed indication: reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products ¹
Subject	Division Director Summary Review
NDA Number	NDA 202667
Related IND Related NDAs	IND 52080 for COSOPT NDA 20869 for COSOPT NDA 18086 for Timoptic (timolol maleate) NDA 20408 for Trusopt (dorzolamide HCl)
Applicant Name	Merck Sharp & Dohme Corp.
Date of Submission Date of Receipt	February 16, 2011 February 16, 2011
PDUFA Goal Date	December 16, 2011
Proprietary Name / Established (USAN) Name	COSOPT PF dorzolamide hydrochloride -timolol maleate ophthalmic solution, 2% / 0.5%
Formulation Dose	Topical ophthalmic solution, 2% / 0.5% one drop two times daily
Proposed Indication(s)	reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone
Action for NME	<i>Complete Response due to pending labeling</i>

¹ The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

NDA 202667

COSOPT PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution)

Proposed indication: reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Rhea Lloyd, Bill Boyd, Wiley Chambers 12/7/2011
CDTL Review	Bill Boyd 12/12/2011
Deputy Director	Wiley Chambers 12/12/2011, 12/16/2011
Statistical Review	Mushfiqur Rashid, Yan Wang 8/29/2011
Pharmacology/Toxicology Review	Conrad Chen, Wendelyn Schmidt 6/14/2011
Clinical Pharmacology Review	Ryan Owen, Philip Colangelo 5/31/2011
Product Quality Manufacturing Reviews ONDQA/DNDQAII	George Lunn, Balajee Shanbmugam 10/17/2011, 11/25/2011, 12/14/2011 Rapti Madurawe 12/16/2011
Product Quality Microbiology Reviews	Vinayak Pawar, Bryan Riley 6/24/2011, 8/10/2011
OC/Facilities Inspection	Acceptable (see CMC review 12/16/2011)
OSI/DGCPC	Kassa Ayalew, Susan Thompson, Jean Mulinde 6/16/2011, 12/15/2011
OSE/DMEPA Proprietary Name	Morgan Walker, Irene Chan, Carol Holquist 5/13/2011, 5/16/2011, 10/14/2011
OSE/DMEPA Labeling Review	Morgan Walker, Irene Chan, Carol Holquist 8/2/2011
OPDP/DPP (formerly DDMAC)	Christine Corser 9/30/2011
Pediatric Review Committee	This application does not trigger PREA
Project Manager	Alison Rodgers/ Judit Milstein

OND=Office of New Drugs

CDTL=Cross-Discipline Team Leader

ONDQA/DNDQAII = Office of New Drug Quality Assessment/Division of New Drug Quality Assessment II/ Branch V

OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI))

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

OPDP/DPP=Office of Prescription Drug Promotion/Division of Professional Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication

PMHT=Pediatric and Maternal Health Staff

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1. Summary and Recommendations

COSOPT PF is a combination product identical to the currently marketed COSOPT; the only difference is that the COSOPT PF (preservative-free) formulation does not contain 0.0075% benzalkonium chloride as a preservative. Although all primary review disciplines including clinical, statistics, clinical pharmacology, and pharmacology/toxicology recommend approval, until the morning of December 16, 2011 (the PDUFA goal date), the Office of Compliance continued to recommend “withhold” for the approval of this application due to facility problems at the Elkton VA facility and noted that CDER OC was reviewing a corporate warning letter for the Elkton VA and PA (not for this product) facilities. However, on December 16, 2011, FDA CDER EES was updated that per conversation with OC/DDDQ, the Baltimore district is downgrading the inspection to VAI and the district recommendation was upgraded to acceptable. (See review by Dr. Madurawe 12/16/2011)

In addition, there was a difference in the recommendations from chemistry and clinical regarding the unspecified impurities; clinical proposed a limit of (b) (4) whereas chemistry agreed and provided a summary justification with the company’s proposed (b) (4) limit. The latter is also the specific limit for the marketed COSOPT approved product. During further internal discussion, it was decided that Merck needed to correct the terminology when discussing drug product specifications. Specifically, they should revise the test currently identified as “Any Unspecified Degradate” to read “Any Unspecified Impurity.”

Preliminary review of the package insert, patient package insert and carton container labeling has been done. However, labeling discussions have not been finalized given the outstanding manufacturing deficiency. The proprietary name was found acceptable by DMEPA.

As noted above, because this product differs in only one aspect from the marketed COSOPT, there was no advisory committee needed, and the application did not trigger PREA.

1.1 Deficiencies

- Per 21 CFR 314.125 (a)(8) , the drug product’s proposed labeling does not comply with the requirements for labels and labeling in part 201. Specifically, we recommend that you submit draft labeling which is consistent with the package insert, patient package insert, carton and container labeling attached to this letter.
- In addition, there is ambiguity in the terminology of the drug product specifications. To correct this ambiguity, as part of the drug product specifications, please revise the test currently identified as “Any unspecified Degradate” to read “Any unspecified impurity.”

1.2 Post-Marketing Studies:

N/A.

NDA 202667

COSOPT PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution)

Proposed indication: reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone

1.3 Other Issues

N/A.

2. Background

Merck Sharp & Dohme Corp. (Merck) submitted NDA 202667 for COSOPT® PF (preservative-free) ophthalmic solution on February 16, 2011. The product is a combination of dorzolamide hydrochloride 2% and timolol maleate 0.5%, and the same as the currently marketed COSOPT® (NDA 20869 approved April 7, 1998) with the exception of the omission of the preservative, benzalkonium chloride. 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.

This NDA submission contains the results of one clinical trial conducted in 1997 which compared the COSOPT formulation (with preservative) to the COSOPT PF formulation and the NDA also contains cross-references to clinical trials used to support the approval of COSOPT PF.

In all Merck cited their earlier NDA submissions for COSOPT® (NDA 20,869, approved April 7, 1998), TRUSOPT® (NDA 20,408 approved December 9, 1994) and TIMOPTIC® (NDA 18,086 approved August 17, 1978). Merck is the NDA holder for COSOPT® and TRUSOPT®. The rights to the NDA for TIMOPTIC® are currently owned by Aton Pharma and a Letter of Authorization from Aton Pharma was submitted in module 1.4.4 of the CTD.

Merck's hypothesis is that benzalkonium chloride (BAK) has been shown to have potential for toxicity to a variety of tissues of the ocular surface, and may be associated with reduced tolerability of these formulations over time, especially in patients with co-morbid ocular surface disease such as chronic dry eye. In addition, a subset of patients experiences a delayed type hypersensitivity reaction (allergy) to BAK. Such preservative-associated complications may be amplified in glaucoma patients, many of whom are chronically utilizing multiple preservative containing agents on a daily basis, and in whom the ocular surface already has abnormalities such as induced goblet cell loss, increased subepithelial collagen deposition, and infiltration of substantia propria by inflammatory cells. Furthermore, due to concerns about potential preservative toxicity, the European Medicines Agency (EMA) has been examining the value and use of antimicrobial preservative products in the eye and on 08-Dec-2009, an ad-hoc expert group at the Agency issued a public statement that preservative-free ophthalmic preparations are a valuable alternative for patients receiving long-term treatment (EMEA/622721/2009). (Dr Pawar's review, 8/10/2011)

To support approval, Merck provided data from a single investigator, single-center, randomized, double-masked study, controlled trial of the preservative-free product compared to the preservative containing product. The study was done under Protocol 081 and completed in 1997 (fourteen years before NDA submission). Merck also relied on studies from its other NDAs for the individual component products and the combination COSOPT product.

NDA 202667

COSOPT PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution)

Proposed indication: reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone

During a pre-NDA meeting on April 28, 2010, the Division agreed with this plan. An inspection of the trial from 1997 was requested from OSI because this is the only clinical trial of the preservative-free formulation and inspection of the above site was needed to verify the quality of study conduct and data for this NDA. However, OSI determined that the investigator had destroyed study records upon his retirement; therefore, OSI could not verify study data and source documentation.

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. Timolol is a beta – adrenergic receptor blocking agent that blocks the beta-adrenoceptors in the ciliary process. Both lower pressure by reducing aqueous humor secretion. The approved COSOPT labeling states that the “combined effect of these two agents administered as COSOPT b.i.d. results in additional intraocular pressure reduction compared to either component administered alone, but the reduction is not as much as when dorzolamide t.i.d. and timolol b.i.d. are administered concomitantly (see *Clinical Studies*).”

The text of the *Clinical Studies* states:

Clinical studies of 3 to 15 months duration were conducted to compare the IOP-lowering effect over the course of the day of COSOPT b.i.d. (dosed morning and bedtime) to individually-and concomitantly-administered 0.5% timolol (b.i.d.) and 2.0% dorzolamide (b.i.d. and t.i.d.). The IOP-lowering effect of COSOPT b.i.d. was greater (1-3 mmHg) than that of monotherapy with either 2.0% dorzolamide t.i.d. or 0.5% timolol b.i.d. The IOP-lowering effect of COSOPT b.i.d. was approximately 1 mmHg less than that of concomitant therapy with 2.0% dorzolamide t.i.d. and 0.5% timolol b.i.d.

Open-label extensions of two studies were conducted for up to 12 months. During this period, the IOP-lowering effect of COSOPT b.i.d. was consistent during the 12 month follow-up period.

2.1 Available Products

There are currently multiple products available for the treatment of IOP including alpha-2 agonists, beta-adrenergic antagonists, carbonic anhydrase inhibitors, cholinergic agonists, prostaglandin analogues, sympathomimetics, osmotics, and a number of combination products, including COSOPT. A complete list is found in the Clinical Reviews.

3. CMC/Product Quality Microbiology

The details of the product quality CMC is found in Dr. Lunn’s reviews and sterility in Dr. Pawar’s review. Information requests from Dr Rapti Madurawe of ONDQA were sent April 19, June 20, and September 9, 2011 with 12, 4 and 3 requests, respectively.

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

3.1 Product Quality

Per Dr. Lunn’s review, 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 is identical to the currently marketed COSOPT with the exception that it contains no preservative, as shown in the table of composition, below. The dorzolamide concentration is 20 mg/mL and the timolol

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Proposed indication: reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone

concentration is 5 mg/mL (free base). The solution is packaged in an LDPE unit dose pipette and a group of 15 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.

Component	Function	Preservative free FE-1542	NDA 20-869 FE-1543
Dorzolamide hydrochloride, USP	Active	22.26 mg/mL*	22.26 mg/mL*
Timolol maleate, USP	Active	6.83 mg/mL*	6.83 mg/mL*
Sodium citrate, USP	(b) (4)	(b) (4)	(b) (4)
Hydroxyethylcellulose, NF	(b) (4)	(b) (4)	(b) (4)
Benzalkonium chloride	Preservative	-	0.075 mg/mL
Sodium hydroxide, NF	pH adjustment	qs pH 5.60	qs pH 5.60
Mannitol, USP	(b) (4)	(b) (4)	(b) (4)
Water for injection, USP	(b) (4)	(b) (4)	(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.

Dr. Lunn concluded that, this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. In addition, Dr. Lunn's addendum dated December 14, 2011 discussed the setting for unspecified impurities for COSOPT PF and he concurred with the (b) (4) limit proposed by the applicant, stating in part that this is in conformance with ICH Q3B, is the same limit for the currently marketed COSOPT and is acceptable.

Dr. Chambers also commented on the product specifications and recommends that unspecified impurities should be no more than (b) (4) of the timolol concentration, and agrees on other specifications.

During further internal discussion on December 16, 2011, it was decided that Merck needed to correct the terminology when discussing drug product specifications. Specifically, they should revise the test currently identified as "Any Unspecified Degradate" to read "Any Unspecified Impurity."

3.2 Product Quality Microbiology

The product quality reviewer, Dr Pawar notes that the product is provided in a unit dose LDPE pipette, and is sterilized by (b) (4). The manufacturing process consists of (b) (4)

labels containing a pressure-sensitive adhesive. The pipettes which are overwrapped in protective (b) (4) foil pouches. Each (b) (4) pouch contains 3 strips of 5 unit dose pipettes, these are packaged in a carton.

The integrity of the container closure, unit-dose LDPE, was verified by Dye Ingress and Microbial Ingress Testing. For each lot, 300 pipettes, 5 pipettes for positive controls and 5 pipettes for negative controls were run.

The data submitted support an expiry period of 24 months. Pipettes stored in the protective (b) (4) pouch should be used within 15 days after pouch are opened.

Regarding the issue of endotoxin in the finished product, FDA asked Merck about lack of bacterial endotoxin specifications on April 19, 2011 and Merck's response May 27, 2011 was that they did not believe such testing necessary, the product was topically administered and endotoxin limits were not specified in 80 other USP monographs for sterile ophthalmic solutions and suspensions. In response on June 22, 2011 FDA wrote:

“It is the policy of the ophthalmic review division that endotoxin should be controlled in topical ophthalmic products. Therefore, it recommended that applicants include an endotoxin specification for topical ophthalmic products targeted at an acceptance level of 0.5 EU/mL.” [Text from Dr Pawan's 8/10/2011 review]

Batches manufactured so far have endotoxins ranging from (b) (4). Merck responded in their September 9, 2011 submission with a limit of ≤ 5 EU/mL compared to the 0.5 EU/mL requested by FDA. Dr. Lunn notes that the limit of 5 EU/mL will be reassessed by the applicant after the manufacture of 25 lots or one year whichever comes first. The proposed limit is acceptable to the reviewers for this topical product.

Comment:

The application is recommended for approval from the product microbiology standpoint (review 8/10/2011). The Product Quality reviewer received notification on December 16, 2011 that the facilities were “acceptable” until that date the Office of Compliance recommended “withhold.” There is a difference of recommendation for unspecified impurities and the resolution is that Merck should correct their terminology to Any Unspecified Impurity instead of Any Unspecified Degradate. I agree with the recommendations from ONDQA for the unspecified impurity limit of (b) (4) based on their justification.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review by Dr. Chen notes that the agency previously approved the following Merck products: timolol, dorzolamide, and COSOPT.

Merck relied on studies from the above three approved NDAs and conducted three preclinical in vivo studies, one in primate and two in rabbits comparing the preservative-containing and preservative-free product. These showed that removal of the preservative (0.0075% benzalkonium chloride) did not alter the ocular hypotensive effect of the product in ocular hypertensive monkeys and rabbits, as well as ocular normotensive rabbits. Dr Chen concludes that removal of the preservative will not cause any safety issues.

Comment:

The NDA is recommended for approval from a Pharmacology/Toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

As summarized in Dr. Owen's review, the Sponsor has requested a waiver of the requirement for the submission of in vivo bioavailability data on the grounds that there is no strong empirical evidence to expect that removal of the preservative would alter bioavailability. Accordingly, no clinical pharmacology studies of the COSOPT PF formulation were conducted, and no pharmacokinetic samples were obtained in the Phase 3 trial conducted in support of this NDA.

The Reviewer concurs with the Sponsor's request for a waiver of the in vivo bioavailability requirement. The clinical pharmacology program conducted for the approval of the original COSOPT product is sufficient for the approval of the COSOPT PF product.

Comment:

The NDA is acceptable from the Clinical Pharmacology perspective.

6. Clinical Microbiology/Immunology

N/A

7. Clinical/Statistical-Efficacy

As summarized in the clinical and statistical reviews, one study examined the preservative-free COSOPT formulation in a double-masked, controlled clinical trial conducted by one investigator in Austin, Texas under protocol 081. The study was conducted from March 1997 through December 1997, and enrolled 261 patients. Patients over the age of 21 years with open-angle glaucoma or elevated IOP were enrolled who, following a 3-week run-in on 0.5% timolol twice daily had IOP 22 mmHg or greater. COSOPT PF was given to 131 patients and COSOPT (preservative containing) to 130 patients.

NDA 202667

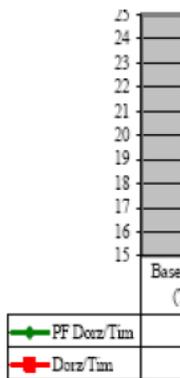
COSOPT PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution)

Proposed indication: reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone

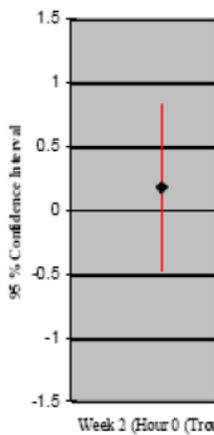
The Division requested that analysis include evaluation of IOP (by Goldmann applanation) prior to morning dose (trough) and 2 hours later (peak) at the following time points: baseline, weeks 2, 6 and 12 to evaluate efficacy, and that both ANCOVA (adjusting for baseline) and ANOVA (unadjusted for baseline) results should be presented. In these analyses two endpoints, change from baseline in IOP and raw IOP, would be presented at each timepoint.

The following figures show the ITT population results; all but 7 patients had IOP values available through week 12.

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PF



The statistical and clinical reviews have additional figures which show results consistent with the ITT population.

The Medical Officer concluded that:

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COSOPT PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution)

Proposed indication: reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone

The difference between the IOP lowering effect of preservative free dorzolamide 2% / timolol 0.5% ophthalmic solution and dorzolamide 2% / timolol 0.5% ophthalmic solution with preservative at peak and trough around the morning dose were neither clinically relevant nor statistically significant in the All Patients Treated-LOCF or the Per Protocol populations.

The 95% confidence interval for the mean difference in IOP between the preservative free dorzolamide/timolol and preservative containing dorzolamide/timolol treatment groups is less than 1.0 mmHg for all peak and trough time points from Week 2 through Week 12 in the All Patients Treated-LOCF or the Per Protocol populations.

The additional analyses of raw IOP and change from baseline IOP using both ANOVA (unadjusted for baseline IOP) and ANCOVA (adjusted for baseline IOP) methods for both the All Patients Treated-Last Observation Carried Forward (APT LOCF) and Per Protocol-Observed Cases (PP-OC) approaches provided results similar to the primary and secondary efficacy analyses.

As requested by the Division, Merck provided an overview of studies conducted with the preservative-containing COSOPT, these are summarized in tabular form below, and these trials provided further support for the application.

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Protocol Number	R
043	
044	
047	
058	
063	

Protocol Number	R
064	
081	

[Ref. 5.3.5.1: P081]

Source: Dr Rashid's review 8/29/2011

7.1 Noninferiority Margin:

The sponsor's criterion for establishing equivalency was defined as follows: confidence must be 95% or better that the true difference between the 2 treatments in mean IOP changes from Baseline (Day -1) to Week 12 (at morning trough-just prior to morning dose) falls within the Interval (-1.5, 1.5) mm Hg. This comparison was considered to be a criterion for equivalency.

The non-inferiority margin of 1.5 mmHg was discussed during the April 28, 2010 meeting. In addition, as noted in the results of these trials, patients whose baseline values were 22 mmHg or greater showed maximum reduction of IOP to 18 mmHg after treatment, greater than seen with placebo.²

The statistical reviewer, Dr. Rashid, concluded that in an active-treatment-controlled, parallel, double-masked study in 261 patients with elevated intraocular pressure 22 mmHg in one or both eyes, COSOPT Preservative-Free treatment is non-inferior to COSOPT Preservative-Containing in lowering IOP (using non-inferiority margin of 1.5 mmHg). The safety profile of COSOPT Preservative-Free was similar to COSOPT Preservative-Containing. (Dr Rashid's review, 8/29/2011).

Comment:

The clinical reviewers and statistical reviewers recommend the application has data demonstrating the efficacy of COSOPT PF.

8. Safety

The safety evaluation is summarized in the reviews by Dr. Lloyd, Dr. Boyd, and Dr. Chambers and by Dr. Rashid.

Safety data were available for 261 patients, 131 on COSOPT PF.

Visual acuity, external ocular examination, slit-lamp evaluation, Goldmann applanation IOP (measured on Day 1), ophthalmoscopy, and visual field evaluation, as well as monitoring of adverse experiences were safety parameters in this study. Day 1 assessments of IOP were only used for safety comparisons. Other safety parameters included measures visual acuity, external ocular and slit lamp evaluations, ophthalmoscopy, visual field evaluations, and changes in the cup to disk ratio. Incidence rates for ocular signs and symptoms and for clinical adverse experiences were compared using Fisher's exact tests (two-sided). Significantly more females were on COSOPT than the COSOPT PF (67% vs 51%).

² Rikkert vsn der Valk et al, Intraocular pressure-lowering effects of all commonly used glaucoma drugs- A meta-analysis of randomized clinical trials. *Ophthalmology* 2005; 112:1177-1185.

<http://medicaidprovider.hhs.mt.gov/pdf/lumiganstudy.pdf>

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COSOPT PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution)

Proposed indication: reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone

Seven patients (2.7%) discontinued the study early; 4 (3.1%) patients in the PF dorzolamide/timolol treatment group and 3 (2.3%) patients in the PC dorzolamide/timolol treatment group. All 7 patients discontinued the study due to a clinical adverse experience. Of the 4 patients who discontinued while receiving PF dorzolamide/timolol treatment, 2 discontinued during Week 2, and 2 discontinued during Week 6. Three patients discontinued while receiving PC dorzolamide/timolol, 2 patients discontinued during Week 2, and 1 discontinued during Week 6. There were no deaths in the study.

Visual field data showed that most patients had no change in visual field (table from Dr. Lloyd's review)

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Improved
No Change
Worsened
Unsure

- a Visual field examination
- b For the patient 1 considered "improved"
- c No significant difference
- d AN 0200
- e AN 0223, AN 0207
- f AN 0354
- g AN 0207
- e AN 0148, AN 0207

8.1 Common Adverse Reactions

Adverse events were reported in 27% of COSOPT PF patients and 34% of COSOPT patients. The most common were burning/irritation and alternation in taste. The most common ocular sign was punctate epithelial erosions seen in 17% COSOPT PF and 24% COSOPT patients.

The combination product COSOPT was first approved in 1998 in Mexico and the COSOPT PF product was first approved in Canada in 2004. Post-marketing data show that more than half the reports involve the eye: eye irritation, eye pain, ocular hyperemia, blurred vision and eye pruritus. Other adverse events were reported for general disorders and administration site conditions, nervous system, and skin. These events included pain, asthenia, drug ineffective, and medication error, stinging and burning. Nervous system disorders included dysgeusia, headache, dizziness, burning sensation. Skin reactions included pruritus, rash, dermatitis and alopecia.

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COSOPT PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution)

Proposed indication: reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone

Comment:

The clinical and statistical reviewers recommend approval.

9. Advisory Committee Meeting

The application was not discussed before a public advisory committee.

10. Pediatrics

The applicant submitted a preservative-free formulation of the marketed product COSOPT. The application does not have a new active ingredient, a new indication, a new dosage regimen, a new route of administration; therefore, it does not trigger PREA. The company was informed they are exempt from PREA requirements in the 74-day letter issued April 21, 2011.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection –

Establishment evaluation system (EES) document included in the 11/25/2011 review by Dr. Lunn had information on manufacturing sites, and the following recommendations. As stated in Dr. Lunn’s review, per email 8/25/2011 from April Inyard of OC, the Elkton, VA site is under consideration for a warning letter. The information in EES was updated on December 16, 2011 (the PDUFA goal date) to Acceptable.

Site	Date	Recommendation
Merck Sharp Dohme, Rahway, NJ	Oct 2011	Withhold
	December 16, 2011	Acceptable
Laboratories Merck, Sharp and Dohme Chibret, Mirabel Plant, Cedex, France, CFN – FCFR252 Manufacture, packaging and testing for release of COSOPT PF. This plant is currently approved for COSOPT with preservative manufacture (ERN 1000173162)	Oct 2011	Acceptable
Laboratories Merck, Sharp and Dohme Chibret, Saint Germain Laprade, Auvergne, France, (FEI 3003121602) – timolol maleate manufacture	Sept 2011	Acceptable
Merck and Co, Inc. Wilson, NC – dorzolamide stability testing, timolol stability testing	March 2011	Acceptable
Merck and Co, Inc. Elkton, VA – dorzolamide HCl manufacture	Oct 2011	Withhold
	December 16, 2011	Acceptable

Merck Sharp Dohme Cramlington, UK – COSOPT PF stability testing	March 2011	Acceptable
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11.2 Office of Scientific Investigation (OSI) Audits

The OSI review by Dr Ayalew states that

“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.

“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.

“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.”

Dr. Lloyd notes that Merck has access to copies of case report forms, drug accountability records and labels, and concludes that it was decided that a clinical investigator site inspection would not be performed.

11.3 Debarment Certification

Merck certified that as required by paragraph 306(k)(1) of 21 U.S.C. 335a(k)(1), they certify that they did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

11.4 Financial Disclosure

Merck provides the following summary regarding the Principal investigator:

Dr. Robert A. Laibovitz was the primary investigator at site 0001 for MK507A-081 in 1997. Dr. Laibovitz retroactively completed a Certification/Disclosure form in which he indicated he could not recall his equity interests in Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), as the study was conducted fourteen years ago. Dr. Laibovitz did, however confirm the absence of a proprietary or financial interest, and compensation for outcome of the study. An internal financial search was completed and it was confirmed no reportable significant payments of other sorts were made to the investigator by Merck.

11.5 Other Regulatory Issues

None identified.

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA, OPDP/DPP and OBP.

- **Package insert (PI):** The PI is written in PLR format. Preliminary format and content comments were reviewed by Leanna Kelly and Maureen-Dillon Parker. DMEPA and OPDP provided labeling recommendations that have been addressed. Labeling has been sent to Merck.
- **Patient package insert (PPI):** The PPI is submitted for this product. The marketed COSOPT (preservative-containing) product has an approved patient package insert. The PPI will be consulted to Office of Medical Policy, per recent procedure change.
- **Carton and Container Labels:** The labels have been reviewed by ONDQA and DMEPA. Requested edits have been communication to Merck.
- **Proprietary Name:** DMEPA concluded that the proposed proprietary name COSOPT PF was not vulnerable to name confusion and was not found to be promotional in their review of May 13, 2011. A letter stating that the name is acceptable was issued by Dr. Holquist of DMEPA on May 16, 2011, and the pre-action review summarizing these recommendations was finalized October 14, 2011.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The NDA is recommended for *Complete Response*, due to outstanding labeling. A correction in terminology for “unspecified impurities,” in lieu of “unspecified degradants” is also requested.

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COSOPT PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution)

Proposed indication: reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone

13.2 Risk Benefit Assessment

The product cannot be approved until the above issues are addressed.

13.3 Recommendation for other Postmarketing Requirements and Commitments

N/A

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/s/

RENATA ALBRECHT
12/16/2011

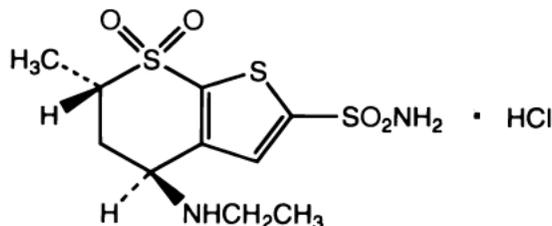
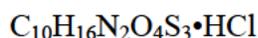
Deputy Division Director Amended Review of NDA 202-667

Date	December 16, 2011
From	Wiley A. Chambers, M.D.
NDA #	202-667
Applicant	Merck, Sharp & Dohme Corp.
Date of Submission	February 16, 2011
Type of Application	505(b)(1)
Name	Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone
Recommended:	Not recommended for Approval

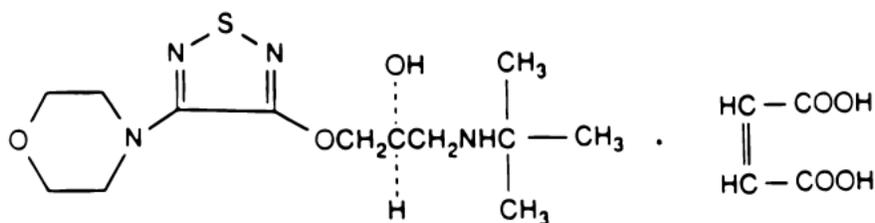
1. Introduction

Chemical Structures

Dorzolamide hydrochloride



Timolol maleate



NDA 20-869, the benzalkonium chloride preserved version of Cosopt (dorzolamide hydrochloride and timolol maleate ophthalmic solution) was approved for marketing in the United States on April 7, 1998. Cosopt combines a beta blocker with a topical carbonic anhydrase inhibitor (CAI). Both active components in this fixed-dose combination are expected to lower IOP by decreasing aqueous humor production. As demonstrated in the original Cosopt application, the IOP lowering effect is greater with

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

concomitant administration than it is with combination therapy, but combination therapy is better than with either product used alone. This application is the same as NDA 20-869, except that there is no preservative in the currently proposed NDA and the product is to be marketed in single dose containers.

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% is marketed in other 22 other countries.

The application relies on the Agency's determination of the safety and efficacy in the following applications:

- NDA 18-086, Timoptic (timolol maleate ophthalmic solution) 0.5% approved August 17, 1978.
- NDA 20-408, Trusopt (dorzolamide hydrochloride ophthalmic solution) 2.0% approved December 9, 1994.
- NDA 20-869, Cosopt (dorzolamide hydrochloride - timolol maleate ophthalmic solution) approved April 7, 1998.

In a Pre-NDA meeting held on April 28, 2010, the Agency agreed that Protocol 081 together with cross reference to the studies submitted in support of NDA 20-869, Cosopt, would be sufficient to enable review of an NDA for the preservative-free dorzolamide/timolol formulation.

2. CMC

The drug substances, timolol maleate and dorzolamide hydrochloride, are described in approved NDAs, and this information is incorporated by reference. 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 (b) pipettes is placed in an (b)(4) foil pack.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Composition of Preservative Free Dorzolamide Hydrochloride and Timolol Maleate 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 ¹	Ph. Eur., NF		
Sodium Hydroxide ²	Ph. Eur., NF	ph Adjustment	q.s pH 5.60
Mannitol	Ph. Eur., USP		(b)(4)
Water for Injection	Ph. Eur., USP		(b)(4)

Proposed Regulatory Specifications

Test	Method	Acceptance Criterion
Appearance	Visual	Clear, colorless to nearly colorless, slightly viscous solution which practically free from particles
Identity of dorzolamide	HPLC	Conforms to standard (b) (4)
Identity of dorzolamide	TLC	Conforms to standard (b) (4)
Identity of timolol	HPLC	Conforms to standard
Identity of timolol	TLC	Conforms to standard
Viscosity		(b) (4)
Deliverable volume	EP 2.9.28	≥ 0.2 mL
pH	EP 2.2.3	5.5-5.8
Osmolality	FP depression	242-323 mOsm
Dorzolamide assay	HPLC	90.0-110.0%
Timolol assay	HPLC	90.0-110.0%
(b) (4)		(b) (4)
(b) (4)		(b) (4)
(b) (4) related any unspecified		(b) (4)
(b) (4) related total		(b) (4)
(b) (4) related degradants	(b) (4)	(b) (4)
(b) (4) related degradants		(b) (4)
(b) (4) related degradants		(b) (4)
(b) (4) related degradants any unspecified		(b) (4)
(b) (4) related degradants total		(b) (4)
Sterility	USP <71>	Sterile
Endotoxins	USP <85>	≤ 5 EU/mL
Particulate matter	USP <789>	NMT 50 particles greater than 10 microns in diameter, NMT 5 particles greater than 25 microns in diameter and NMT 2 particles greater than 50 microns in diameter [per mL.

Reviewer's Comments: *The regulatory specifications should include a limit on the unspecified impurities that are not necessarily related to dorzolamide or timolol. These impurities may come from the bottle components, packaging or labeling. The regulatory specification for unspecified impurities should be no more than (b) (4) of the timolol concentration. The regulatory specifications are otherwise acceptable. In a telephone conversation on December 16, 2011, Merck agreed to amend the specifications.*

FACILITIES INSPECTIONS:

On 6/27/11, an overall recommendation from the Office of Compliance was made. The recommendation was to withhold approval of the drug product. In an e-mail of 8/25/11, April Inyard, OC, indicated that Merck site at Elkton, VA is under consideration for a warning letter. On December 16, 2011, the recommendation was changed to acceptable.

3. Nonclinical Pharmacology/Toxicology

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

- NDA 20,408, **TRUSOPT**, Dorzolamide hydrochloride (Approval date: December 9, 1994)
- NDA 18,086, **TIMOPTIC**, Timolol maleate (Approval date: August 17, 1978)
- 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.

4. Clinical Pharmacology/Biopharmaceutics

The applicant has requested a waiver of the requirement for the submission of in vivo bioavailability data. No clinical pharmacology studies of the COSOPT PF formulation were conducted, and no pharmacokinetic samples were obtained in the Phase 3 trial conducted in support of this NDA. The applicant's request for a waiver of the in vivo bioavailability requirement is being granted. The clinical pharmacology program conducted for the approval of the original Cosopt product is sufficient for the approval of the Cosopt PF product.

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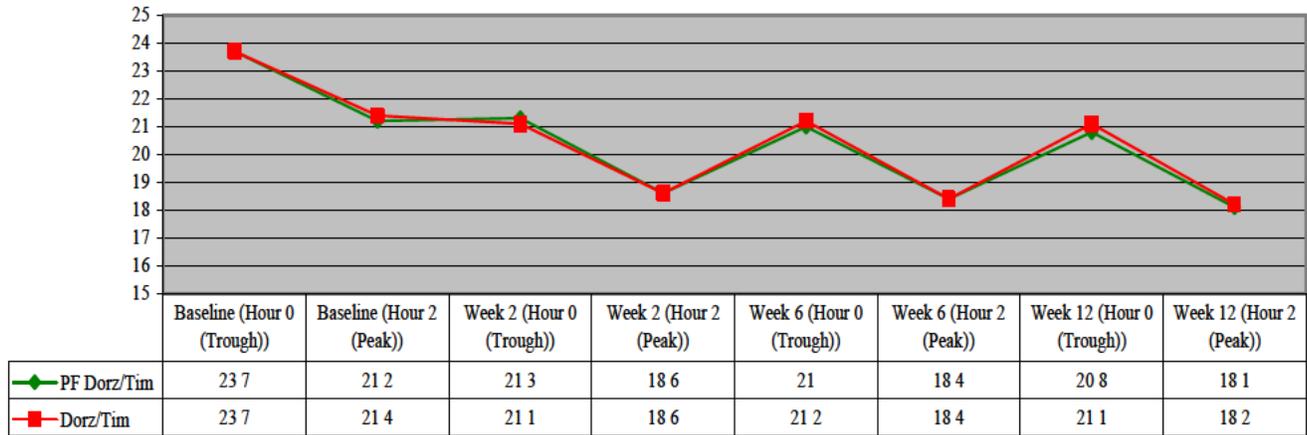
In the Product Quality Microbiology Filing Review of NDA 202667 dated March 23, 2011, the applicant was sent an additional comment regarding the lack of bacterial endotoxins specification in this submission. In the amendment of September 9, 2011, the applicant agreed to add a specification for endotoxins of no more than (b) (4). No other deficiencies from a sterility assurance prospective were noted.

6. Clinical/Statistical - Efficacy

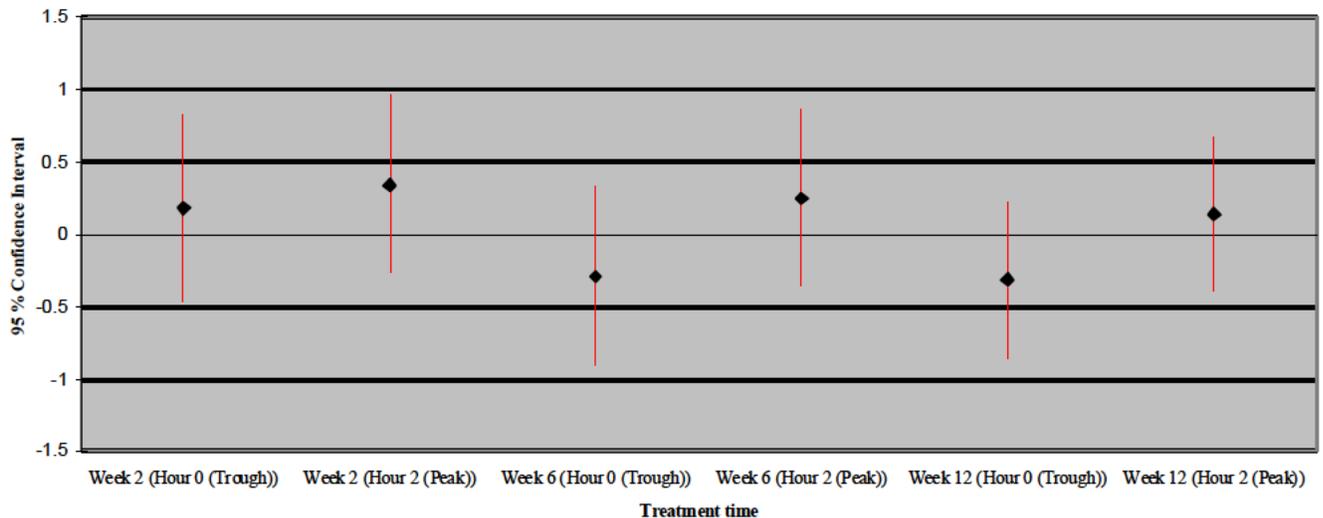
Study P-081 was submitted in support of the proposed indication, the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers. The mean intraocular pressure treatment group comparisons and the 95% confidence intervals around the mean differences at all time points are presented for the full patient population and several subsets of the full population. Equivalence was defined as having the 95% confidence interval around the true treatment group difference of the mean changes from Day -1 to

Week 12 in trough (Hour 0) and peak (Hour 2) IOP being less than 1.5 mmHg at all time points and less than 1 mmHg at the majority of timepoints.

Mean IOP Comparison of PF Dorzolamide/Timolol and Dorzolamide/Timolol at Morning Dose Peak and Trough - APT-LOCF Worse Eye



95% Confidence Intervals of the IOP Mean Difference Between PF Dorzolamide/Timolol and Dorzolamide/Timolol at Morning Dose Peak and Trough APT LOCF - Worse Eye



The 95% confidence interval for the mean difference in IOP between the preservative free dorzolamide/timolol and preservative containing dorzolamide/timolol treatment groups is less than 1.0 mmHg for all peak and trough time points from Week 2 through Week 12 in multiple different

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

populations. The graphs above are representative of the comparisons. There were no significant treatment group interactions with regard to age, iris color, gender or race for changes in IOP.

7. Safety

This application relies in part on three previously approved NDAs, Cosopt (NDA 20-869), Trusopt (NDA 20-408) and Timoptic (NDA 18-086) for demonstration of the safety of dorzolamide hydrochloride/ timolol maleate. In addition, as noted above, Study P081 was performed.

All 261 patients who entered Study 081 were included in the analysis of clinical safety.

	Cosopt PF	Cosopt
0 to 7 days	1	0
8 to 22 days	1	2
23 to 49 days	2	1
50 to 80 days	1	1
81 to 94 days	126	126

There were relatively few serious clinical adverse events.

Patient No.	Gender/Age	Relative Day of Onset	Adverse Experience	Outcome
0313	M / 64	43	Neoplasm, Thyroid, Benign	Recovered
0356	F / 84	42	Osteoarthritis	Recovered

Adverse events leading to discontinuation are noted below.

Reason for Discontinuation	Treatment	Patient Number
Adverse event – dermatitis, itching	Cosopt PF	0178
Adverse event – blurred vision, stinging upon instillation	Cosopt PF	0219
Adverse event – burning upon instillation	Cosopt PF	0354
Adverse event – sinus congestion, sinus headache, itching, stinging upon instillation	Cosopt PF	0357
Adverse event – Nausea, loss of appetite	Cosopt	0264
Adverse event – Dermatitis, itching	Cosopt	0273
Adverse event – Burning upon instillation	Cosopt	0355

The most common adverse events are listed below:

Body System or Adverse Experience	Cosopt PF N=131		Cosopt N=130	
	n	(%)	n	(%)
Patients with one or more adverse experiences	35	(27)	44	(34)
Patients with no adverse experience	96	(73)	86	(66)
Body as a Whole / Site Unspecified	1	(1)	2	(2)
Asthenia/Fatigue	1	(1)	0	
Flu-like Illness	0		2	(2)
Digestive System	0		1	(1)
Anorexia	0		1	(1)
Nausea	0		1	(1)
Endocrine System	1	(1)	0	
Neoplasm, Thyroid, Benign	1	(1)	0	
Musculoskeletal System	1	(1)	0	
Osteoarthritis	1	(1)	0	
Nervous System and Psychiatric	4	(3)	2	(2)
Depression	1	(1)	0	
Dizziness	1	(1)	0	
Headache	2	(2)	2	(2)
Insomnia	1	(1)	0	
Respiratory System	2	(2)	2	(2)
Influenza	0		1	(1)
Pharyngitis	1	(1)	0	
Rhinorrhea	0		1	(1)
Sinus Disorder	1	(1)	0	
Skin & Skin Appendage	4	(3)	2	(2)
Dermatitis	2	(2)	1	(1)
Pruritus	2	(2)	1	(1)
Urticaria	1	(1)	1	(1)
Special Senses	28	(21)	38	(29)
Abrasion, Corneal	0		1	(1)
Blurred Vision	2	(2)	2	(2)
Burning/Stinging, Eye	21	(16)	28	(22)
Cataract	0		1	(1)
Defect, Visual Field	0		1	(1)
Discharge, Eye	0		1	(1)
Erosion, Corneal	3	(2)	3	(2)
Foreign Body Sensation	1	(1)	1	(1)
Hemianopia	1	(1)	0	
Hemorrhage, subconjunctival	0		1	(1)
Inflammation, eyelid	1	(1)	0	

Body System or Adverse Experience	Cosopt PF N=131		Cosopt N=130	
	n	(%)	n	(%)
Irritation, eyelid	1	(1)	0	
Itching, eye	1	(1)	1	(1)
Otitis	0		1	(1)
Perversion, Taste	4	(3)	7	(5)
Photophobia	0		1	(1)
Tearing	1	(1)	1	(1)
Urogenital System	0		1	(1)
Infection, Urinary Tract	0		1	(1)

Note: Although a patient may have had two or more adverse experiences, the patient is counted only once within a category and in the overall total. The same patient may appear in different categories. All body systems are listed in which at least 1 patient had an adverse experience.

The most frequently reported adverse events occurring in up to 30% of patients were taste perversion (bitter, sour, or unusual taste) or ocular burning and/or stinging. The following adverse reactions were reported in 5-15% of patients: conjunctival hyperemia, blurred vision, superficial punctate keratitis or eye itching.

8. Advisory Committee Meeting

No Advisory Committee Meeting was scheduled. There were no outstanding clinical issues which were believed to benefit from an advisory committee discussion.

9. Pediatrics

The safety and effectiveness of preservative-containing dorzolamide hydrochloride ophthalmic solution and preservative-containing timolol maleate ophthalmic solution have been established when administered individually in pediatric patients aged 2 years and older and this is reflected in the approved Cosopt label in the US. Based on these data and the demonstrated clinical equivalence of preservative-free formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate to the preservative-containing formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate, no additional pediatric studies were required in support of NDA 202-667.

10. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. An inspection of Dr. Laibovitz's site was not conducted at this time because according to the clinical investigator, all records had been

reportedly discarded or destroyed upon his retirement. Dr. Laibovitz's site had been inspected around the time that this clinical study was conducted. 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 minor regulatory deviations and were classified VAI. While regulatory deviations were observed during inspections for NDA (b) (4) and NDA (b) (4), the CI's data for the inspected studies was considered generally reliable.

FINANCIAL DISCLOSURE

Merck has attempted to comply with the FDA regulation, Financial Disclosure by Clinical Investigators. Protocol 081 was a single investigator clinical study for which Robert A. Laibovitz, MD served as clinical investigator in 1997. Dr. Laibovitz has since retired. Dr. Laibovitz did not provide the requested financial disclosure information by the cut-off date and therefore could not be certified. In compliance with the regulatory requirement for the Sponsor to demonstrate "due diligence" (21 CFR 54.4), multiple requests for this information were made, when possible, to the investigator who did not respond within the required time frame. Dr. Laibovitz did not return the certification form with requested information. The form was sent by Merck & Co., on April 19, 2010, April 23, 2010 and May 18, 2010.

Dr. Laibovitz was the primary investigator at site 0001 for MK507A-081 in 1997. Dr. Laibovitz retroactively completed a Certification/ Disclosure form in which he indicated he could not recall his equity interests in Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), as the study was conducted fourteen years ago. Dr. Laibovitz did, however, confirm the absence of a proprietary or financial interest, and compensation for outcome of the study. Merck completed an internal financial search and it was confirmed no reportable significant payments of other sorts were made to the investigator by Merck.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name; Cosopt PF, acceptable in OSE Review 2010-510, dated May 13, 2011, and in a second pre-action OSE Review 2011 – 2609, dated October 14, 2011.

11. Labeling

The original Medical Officer's review dated 12/7/2011 contains revisions to the applicant's proposed package insert submitted via email on September 30, 2011, and proposed carton and container labeling submitted via email on October 19, 2011.

Proposed labeling changes have been recommended to Merck, but Merck has not submitted revised labeling. Up until today, there were outstanding facility issues (i.e. facilities not in compliance with good manufacturing practice regulations). Unfortunately, resolution of the inspectional deficiency did not occur until today. Merck stated in a telecon today that they would not be able to amend the application with revised labeling until sometime in the future.

12. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 202514, Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% is not currently recommended for approval 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.

The drug product specifications should include a control for unspecified impurities and revised labeling as described in the Medical Officer's Review should be submitted prior to approval.

Wiley A. Chambers, MD
Deputy Division Director

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

/s/

WILEY A CHAMBERS
12/16/2011

Deputy Division Director Review of NDA 202-667

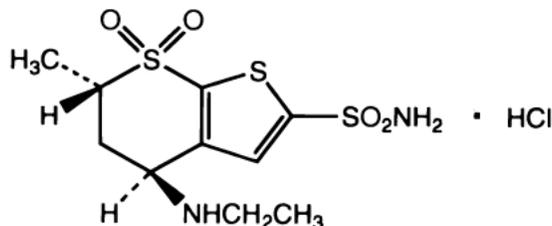
Date	December 12, 2011
From	Wiley A. Chambers, M.D.
NDA #	202-667
Applicant	Merck, Sharp & Dohme Corp.
Date of Submission	February 16, 2011
Type of Application	505(b)(1)
Name	Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone
Recommended:	Not recommended for Approval

1. Introduction

Chemical Structures

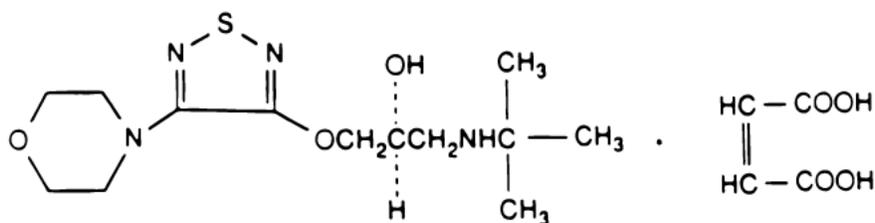
Dorzolamide hydrochloride

$C_{10}H_{16}N_2O_4S_3 \cdot HCl$



Timolol maleate

$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$



NDA 20-869, the benzalkonium chloride preserved version of Cosopt (dorzolamide hydrochloride and timolol maleate ophthalmic solution) was approved for marketing in the United States on April 7, 1998. Cosopt combines a beta blocker with a topical carbonic anhydrase inhibitor (CAI). Both active components in this fixed-dose combination are expected to lower IOP by decreasing aqueous humor production. As demonstrated in the original Cosopt application, the IOP lowering effect is greater with

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

concomitant administration than it is with combination therapy, but combination therapy is better than with either product used alone. This application is the same as NDA 20-869, except that there is no preservative in the currently proposed NDA and the product is to be marketed in single dose containers.

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% is marketed in other 22 other countries.

The application relies on the Agency's determination of the safety and efficacy in the following applications:

- NDA 18-086, Timoptic (timolol maleate ophthalmic solution) 0.5% approved August 17, 1978.
- NDA 20-408, Trusopt (dorzolamide hydrochloride ophthalmic solution) 2.0% approved December 9, 1994.
- NDA 20-869, Cosopt (dorzolamide hydrochloride - timolol maleate ophthalmic solution) approved April 7, 1998.

In a Pre-NDA meeting held on April 28, 2010, the Agency agreed that Protocol 081 together with cross reference to the studies submitted in support of NDA 20-869, Cosopt, would be sufficient to enable review of an NDA for the preservative-free dorzolamide/timolol formulation.

2. CMC

The drug substances, timolol maleate and dorzolamide hydrochloride, are described in approved NDAs, and this information is incorporated by reference. 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 (b) pipettes is placed in an (b)(4) foil pack.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Composition of Preservative Free Dorzolamide Hydrochloride and Timolol Maleate 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 ¹	Ph. Eur., NF		
Sodium Hydroxide ²	Ph. Eur., NF	ph Adjustment	q.s pH 5.60
Mannitol	Ph. Eur., USP		(b)(4)
Water for Injection	Ph. Eur., USP		(b)(4)

Proposed Regulatory Specifications

Test	Method	Acceptance Criterion
Appearance	Visual	Clear, colorless to nearly colorless, slightly viscous solution which practically free from particles
Identity of dorzolamide	HPLC	Conforms to standard (b) (4)
Identity of dorzolamide	TLC	Conforms to standard (b) (4)
Identity of timolol	HPLC	Conforms to standard
Identity of timolol	TLC	Conforms to standard
Viscosity		(b) (4)
Deliverable volume	EP 2.9.28	≥ 0.2 mL
pH	EP 2.2.3	5.5-5.8
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Reviewer's Comments: *The regulatory specifications should include a limit on the unspecified impurities that are not necessarily related to dorzolamide or timolol. These impurities may come from the bottle components, packaging or labeling. The regulatory specification for unspecified impurities should be no more than (b) (4) of the timolol concentration. The regulatory specifications are otherwise acceptable.*

FACILITIES INSPECTIONS:

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Wiley A. Chambers, M.D.

NDA 202514

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

Establishment: **CFN:** 1112271 **FEI:** 1112271
 MERCK AND CO INC
 2778 SOUTH EAST SIDE HWY
 ELKTON, VA 22827

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)
 DISTRICT IS SEEKING REGULATORY ACTION DUE TO DEFICIENCIES CITED IN THE APRIL/MAY 2011 INSPECTION. INSPECTIONAL DEFICIENCIES RELATE TO STERILE API MANUFACTURING PROCESS. (on 25-JUL-2011 by B. HIGGINS (HFR-CE2545) 804-747-0124)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** POTENTIAL OAI

<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
SUBMITTED TO DO	27-JUN-2011	10-Day Letter			STOCKM
INSPECTION WAS PERFORMED AFTER PROFILE-BASED DECISION WAS ENTERED FOR THIS APPLICATION.					
DO RECOMMENDATION	13-SEP-2011			WITHHOLD	BSEEMAN
PENDING CORPORATE WARNING LETTER. RECOMMENDATION SUBMITTED BY PHI-DO TO CDER 9/11.				PEND REG ACTION - WARNING LTR	
OC RECOMMENDATION	26-OCT-2011			WITHHOLD	SMITHDE
CDER OC REVIEWING CORPORATE WARNING LETTER (TWO SITES: VA AND PA).				DISTRICT RECOMMENDATION	

It appears that this site duplicates the activities proposed at Laboratoires Merck Sharp and Dohme-Chibret in Saint Germain Laprade, Auvergne, France. The applicant may consider withdrawing the Elkton, VA site and only using the site in Auvergne, France.

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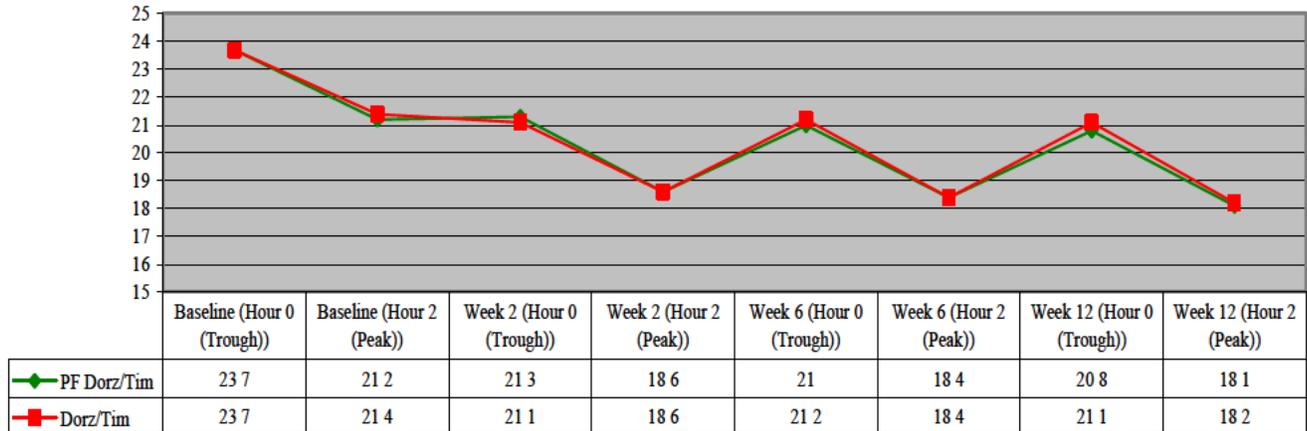
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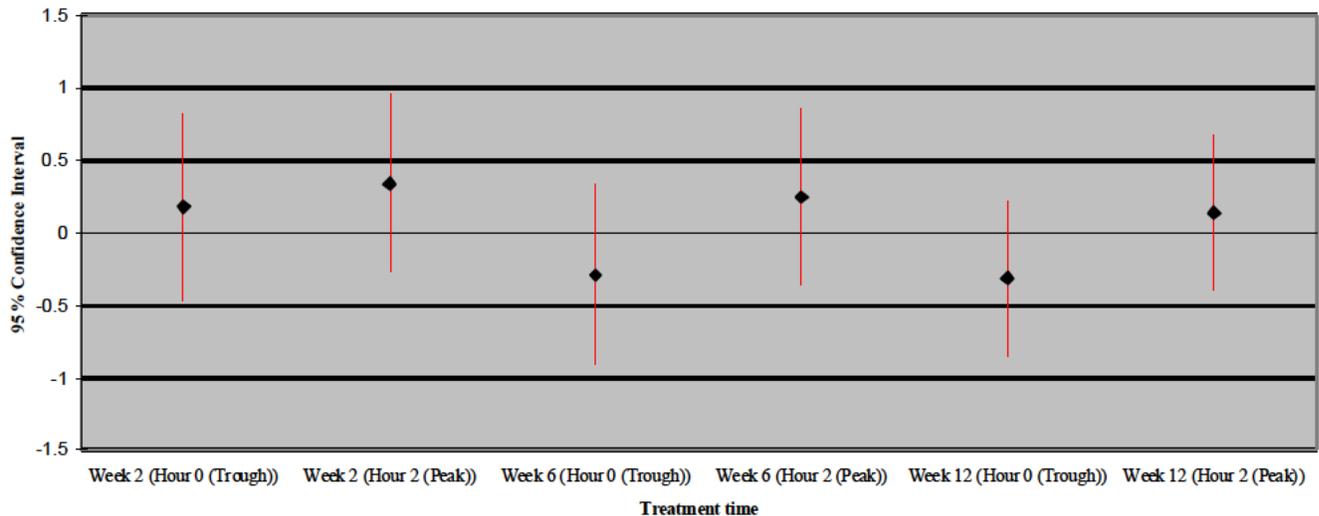
NDA 202514

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

**Mean IOP Comparison of PF Dorzolamide/Timolol and Dorzolamide/Timolol
 at Morning Dose Peak and Trough - APT-LOCF Worse Eye**



**95% Confidence Intervals of the IOP Mean Difference Between
 PF Dorzolamide/Timolol and Dorzolamide/Timolol at Morning Dose Peak and Trough
 APT LOCF - Worse Eye**



The 95% confidence interval for the mean difference in IOP between the preservative free dorzolamide/timolol and preservative containing dorzolamide/timolol treatment groups is less than 1.0 mmHg for all peak and trough time points from Week 2 through Week 12 in multiple different populations. The graphs above are representative of the comparisons. There were no significant treatment group interactions with regard to age, iris color, gender or race for changes in IOP.

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Anorexia	0		1	(1)
Nausea	0		1	(1)
Endocrine System	1	(1)	0	
Neoplasm, Thyroid, Benign	1	(1)	0	
Musculoskeletal System	1	(1)	0	
Osteoarthritis	1	(1)	0	
Nervous System and Psychiatric	4	(3)	2	(2)
Depression	1	(1)	0	
Dizziness	1	(1)	0	
Headache	2	(2)	2	(2)
Insomnia	1	(1)	0	
Respiratory System	2	(2)	2	(2)
Influenza	0		1	(1)
Pharyngitis	1	(1)	0	
Rhinorrhea	0		1	(1)
Sinus Disorder	1	(1)	0	
Skin & Skin Appendage	4	(3)	2	(2)
Dermatitis	2	(2)	1	(1)
Pruritus	2	(2)	1	(1)
Urticaria	1	(1)	1	(1)
Special Senses	28	(21)	38	(29)
Abrasion, Corneal	0		1	(1)
Blurred Vision	2	(2)	2	(2)
Burning/Stinging, Eye	21	(16)	28	(22)
Cataract	0		1	(1)
Defect, Visual Field	0		1	(1)
Discharge, Eye	0		1	(1)
Erosion, Corneal	3	(2)	3	(2)
Foreign Body Sensation	1	(1)	1	(1)
Hemianopia	1	(1)	0	
Hemorrhage, subconjunctival	0		1	(1)
Inflammation, eyelid	1	(1)	0	

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

Body System or Adverse Experience	Cosopt PF N=131		Cosopt N=130	
	n	(%)	n	(%)
Irritation, eyelid	1	(1)	0	
Itching, eye	1	(1)	1	(1)
Otitis	0		1	(1)
Perversion, Taste	4	(3)	7	(5)
Photophobia	0		1	(1)
Tearing	1	(1)	1	(1)
Urogenital System	0		1	(1)
Infection, Urinary Tract	0		1	(1)

Note: Although a patient may have had two or more adverse experiences, the patient is counted only once within a category and in the overall total. The same patient may appear in different categories. All body systems are listed in which at least 1 patient had an adverse experience.

The most frequently reported adverse events occurring in up to 30% of patients were taste perversion (bitter, sour, or unusual taste) or ocular burning and/or stinging. The following adverse reactions were reported in 5-15% of patients: conjunctival hyperemia, blurred vision, superficial punctate keratitis or eye itching.

8. Advisory Committee Meeting

No Advisory Committee Meeting was scheduled. There were no outstanding clinical issues which were believed to benefit from an advisory committee discussion.

9. Pediatrics

The safety and effectiveness of preservative-containing dorzolamide hydrochloride ophthalmic solution and preservative-containing timolol maleate ophthalmic solution have been established when administered individually in pediatric patients aged 2 years and older and this is reflected in the approved Cosopt label in the US. Based on these data and the demonstrated clinical equivalence of preservative-free formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate to the preservative-containing formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate, no additional pediatric studies were required in support of NDA 202-667.

10. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. An inspection of Dr. Laibovitz's site was not conducted at this time because according to the clinical investigator, all records had been

reportedly discarded or destroyed upon his retirement. Dr. Laibovitz's site had been inspected around the time that this clinical study was conducted. 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 minor regulatory deviations and were classified VAI. While regulatory deviations were observed during inspections for NDA (b)(4) and NDA (b)(4), the CI's data for the inspected studies was considered generally reliable.

FINANCIAL DISCLOSURE

Merck has attempted to comply with the FDA regulation, Financial Disclosure by Clinical Investigators. Protocol 081 was a single investigator clinical study for which Robert A. Laibovitz, MD served as clinical investigator in 1997. Dr. Laibovitz has since retired. Dr. Laibovitz did not provide the requested financial disclosure information by the cut-off date and therefore could not be certified. In compliance with the regulatory requirement for the Sponsor to demonstrate "due diligence" (21 CFR 54.4), multiple requests for this information were made, when possible, to the investigator who did not respond within the required time frame. Dr. Laibovitz did not return the certification form with requested information. The form was sent by Merck & Co., on April 19, 2010, April 23, 2010 and May 18, 2010.

Dr. Laibovitz was the primary investigator at site 0001 for MK507A-081 in 1997. Dr. Laibovitz retroactively completed a Certification/ Disclosure form in which he indicated he could not recall his equity interests in Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), as the study was conducted fourteen years ago. Dr. Laibovitz did, however, confirm the absence of a proprietary or financial interest, and compensation for outcome of the study. Merck completed an internal financial search and it was confirmed no reportable significant payments of other sorts were made to the investigator by Merck.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name; Cosopt PF, acceptable in OSE Review 2010-510, dated May 13, 2011, and in a second pre-action OSE Review 2011 – 2609, dated October 14, 2011.

11. Labeling

The original Medical Officer's review dated 12/7/2011 contains revisions to the applicant's proposed package insert submitted via email on September 30, 2011, and proposed carton and container labeling submitted via email on October 19, 2011.

Final labeling negotiation is deferred until outstanding Chemistry Manufacturing issues (i.e. facilities not in compliance with good manufacturing practice regulations) are resolved.

12. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 202514, Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% is not currently recommended for approval 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.

All manufacturing facilities for the drug substance are not in compliance with current good manufacturing practice. Satisfactory resolution of this deficiency or withdrawal of the site that is not in cGMP compliance should be required before this application may be approved.

The drug product specifications should include a control for unspecified impurities which should be no more than (b) (4) of the amount of timolol in the drug product.

Wiley A. Chambers, MD
Deputy Division Director

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

/s/

WILEY A CHAMBERS
12/12/2011

Cross-Discipline Team Leader Review of NDA 202-667

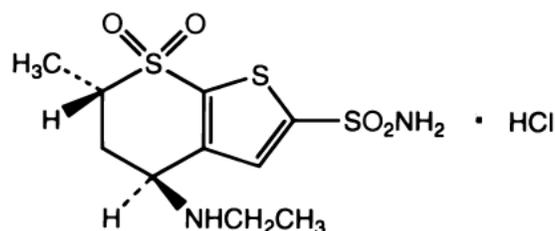
Date	December 1, 2011
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	202667
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	February 16, 2011
PDUFA Goal Date	December 16, 2011
Type of Application	505(b)(1)
Name	Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone
Recommended:	Not recommended for Approval

1. Introduction

Chemical Structures

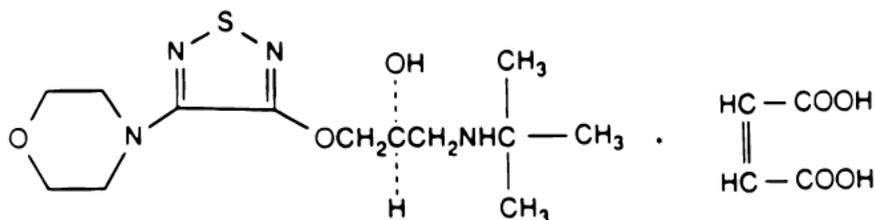
Dorzolamide hydrochloride

$C_{10}H_{16}N_2O_4S_3 \cdot HCl$



Timolol maleate

$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$



NDA 20-869 for Cosopt (dorzolamide hydrochloride and timolol maleate ophthalmic solution) was first approved for marketing in the US on April 7, 1998. Cosopt combines a beta blocker, a common first-line glaucoma therapy with a topical carbonic anhydrase inhibitor (CAI), a common add-on

therapy for lowering IOP and is preserved with benzalkonium chloride. Both active components in this fixed-dose combination of 2.0% dorzolamide hydrochloride and 0.5% timolol maleate lower IOP by decreasing aqueous humor production. Dorzolamide hydrochloride inhibits carbonic anhydrase isoenzyme II (CA-II) in the ciliary process of the eye. Timolol maleate inhibits aqueous humor inflow presumably by blocking catecholamine stimulation at the ciliary body. When both are used together, either as concomitant therapy or as a fixed combination, the IOP lowering effect is greater than with either product used alone.

In this NDA 202-667, Cosopt PF is the fixed combination of 2% dorzolamide hydrochloride and 0.5% timolol maleate ophthalmic solution formulated without the preservative benzalkonium chloride. Cosopt PF is otherwise identical to Cosopt, the currently marketed formulation of preservative containing dorzolamide hydrochloride - timolol maleate ophthalmic solution.

2. Background

There are many products of different pharmacologic classes including beta blocking agents, cholinergic medications, carbonic anhydrase inhibitors and prostaglandin analogues marketed for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Drug Products with Approved NDAs

Pharmacologic Class/Applicant	Tradename	Established Name
Alpha-2 agonists		
Alcon	Iopidine	Apraclonidine
Allergan, Inc.	Alphagan/ Alphagan P	brimonidine tartrate
Beta-adrenergic antagonists		
Alcon	Betoptic/ Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharmaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	brinzolamide

Pharmacologic Class/Applicant	Tradename	Established Name
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan	travoprost
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/pilocarpine hydrochloride
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% is marketed in other 22 other countries.

The application relies on the Agency's determination of the safety and efficacy in the following applications:

- NDA 18-086, Timoptic (timolol maleate ophthalmic solution) 0.5% approved August 17, 1978.
- NDA 20-408, Trusopt (dorzolamide hydrochloride ophthalmic solution) 2.0% approved December 9, 1994.
- NDA 20-869, Cosopt (dorzolamide hydrochloride - timolol maleate ophthalmic solution) approved April 7, 1998.

In a Pre-NDA meeting held on April 28, 2010, the Agency agreed that Protocol 081 together with cross reference to the studies submitted in support of NDA 20-869 Cosopt would be sufficient to enable review of an NDA for the preservative-free dorzolamide/timolol formulation. Requirements for the establishment of clinical equivalence between the two formulations were given. Additionally, the Agency requested that both ANCOVA (adjusting for baseline) and ANOVA (unadjusted for baseline) results be presented. Presentation of these analyses for two endpoints, change from baseline in IOP and raw IOP, at every efficacy visit (Weeks 2, 6, and 12) and time point (peak and trough) were requested.

3. CMC

From the two CMC Reviews finalized 10/17/2011 and 11/25//2011:

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.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

**Composition of Preservative Free
 Dorzolamide Hydrochloride and Timolol Maleate 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)	(b) (4)
Hydroxyethylcellulose ¹	Ph. Eur., NF		
Sodium Hydroxide ²	Ph. Eur., NF	ph Adjustment	qs pH 5.60
Mannitol	Ph. Eur., USP	(b) (4)	(b) (4)
Water for Injection	Ph. Eur., USP	(b) (4)	(b) (4)

In the amendment of 9/9/11 the applicant agreed, at the request of FDA, to add a specification for endotoxins.

PROPOSED REGULATORY SPECIFICATIONS:

Test		Method	Acceptance Criterion
Appearance		Visual	Clear, colorless to nearly colorless, slightly viscous solution which is practically free from particles
Identity of dorzolamide		HPLC	Conforms to standard (b) (4)
Identity of dorzolamide		TLC	Conforms to standard (b) (4)
Identity of timolol		HPLC	Conforms to standard
Identity of timolol		TLC	Conforms to standard
Viscosity			(b) (4)
Deliverable volume		EP 2.9.28	≥ 0.2 mL
pH		EP 2.2.3	5.5-5.8
Osmolality		FP depression	242-323 mOsm

Assay			
	Dorzolamide	HPLC	90.0-110.0%
	Timolol	HPLC	90.0-110.0%
(b) (4) related degradants	(b) (4)	HPLC	(b) (4)
	Any unspecified		
	Total		(Release (b) (4))
(b) (4) related degradants	(b) (4)	HPLC	(b) (4)
	Any unspecified		
	Total		(Release (b) (4))
Sterility		USP <71>	Sterile
Endotoxins		USP <85>	≤ 5 EU/mL
Particulate matter		USP<789>	
	≥10 μm		≤ 50 particles/mL
	≥25 μm		≤ 5 particles/mL
	≥50 μm		≤ 2 particles/mL

Note: The specifications are lacking for a control for unspecified impurities which should be no more than (b) (4)

CDTL Review
 William M. Boyd, M.D.
 NDA 202514
 Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

FACILITIES INSPECTIONS:

On 3/14/11 an Establishment Evaluation Request was submitted by Althea Cuff and on 6/27/11 an overall recommendation of Withhold was made. In an e-mail of 8/25/11 April Inyard, OC, indicated that Merck site at Elkton, VA is under consideration for a warning letter.

**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
Priority:	5	Estab. Name:	
Org. Code:	590	Generic Name:	
Application Comment:		Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION; DORZOLAMIDE HYDROCHLORIDE; 2% 001; SOLUTION; TIMOLOL MALEATE; .5%
FDA Contacts:	A. CUFF L. NG	Project Manager Team Leader	(HF-01) 301-796-4061 301-796-1426

Overall Recommendation:	WITHHOLD	on 26-OCT-2011	by D. SMITH	()
	PENDING	on 19-SEP-2011	by EES_PROD	
	WITHHOLD	on 27-JUN-2011	by EES_PROD	

CDTL Review
 William M. Boyd, M.D.
 NDA 202514
 Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

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.: RFPRTM12 (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

CDTL Review
 William M. Boyd, M.D.
 NDA 202514
 Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

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

Establishment: CFN: 1036761 FEI: 1036761
 MERCK AND CO INC
 4633 MERCK RD W
 WILSON, NC 278939613

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: DRUG SUBSTANCE 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

CDTL Review
 William M. Boyd, M.D.
 NDA 202514
 Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

Establishment: CFN: 1112271 FEI: 1112271
 MERCK AND CO INC
 2778 SOUTH EAST SIDE HWY
 ELKTON, VA 22827

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)
 DISTRICT IS SEEKING REGULATORY ACTION DUE TO DEFICIENCIES CITED IN THE APRIL/MAY 2011 INSPECTION. INSPECTIONAL DEFICIENCIES RELATE TO STERILE API MANUFACTURING PROCESS. (on 25-JUL-2011 by B. HIGGINS (HFR-CE2545) 804-747-0124)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** POTENTIAL OAI

<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
SUBMITTED TO DO INSPECTION WAS PERFORMED AFTER PROFILE-BASED DECISION WAS ENTERED FOR THIS APPLICATION.	27-JUN-2011	10-Day Letter			STOCKM
DO RECOMMENDATION PENDING CORPORATE WARNING LETTER. RECOMMENDATION SUBMITTED BY PHI-DO TO CDER 9/11.	13-SEP-2011			WITHHOLD PEND REG ACTION - WARNING LTR	BSEEMAN
OC RECOMMENDATION CDER OC REVIEWING CORPORATE WARNING LETTER (TWO SITES: VA AND PA).	26-OCT-2011			WITHHOLD DISTRICT RECOMMENDATION	SMITHDE

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

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.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 6/14/2011:

Dorzolamide hydrochloride and timolol maleate were first introduced for the reduction of intraocular pressure 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 applicant 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 20,408, **TRUSOPT**, Dorzolamide hydrochloride (Approval date: December 9, 1994)
- NDA 18,086, **TIMOPTIC**, Timolol maleate (Approval date: August 17, 1978)
- 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.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 5/31/2011:

Cosopt PF is nearly identical to a previously marketed product (Cosopt, NDA 20-869 approved 4/7/98) with the only difference being the removal of the preservative benzalkonium chloride. The applicant has requested a waiver of the requirement for the submission of in vivo bioavailability data on the grounds that there is no strong empirical evidence to expect that removal of the preservative would alter bioavailability. Accordingly, no clinical pharmacology studies of the COSOPT PF formulation were conducted, and no pharmacokinetic samples were obtained in the Phase 3 trial conducted in support of this NDA.

The Reviewer concurs with the applicant's request for a waiver of the in vivo bioavailability requirement. The clinical pharmacology program conducted for the approval of the original Cosopt product is sufficient for the approval of the Cosopt PF product.

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 6/24/2011:

In the Product Quality Microbiology Filing Review of NDA 202667 dated March 23, 2011, the applicant was sent an additional comment regarding the lack of bacterial endotoxins specification in this submission. This comment together with additional CMC questions were sent to the applicant in an Information Request Letter dated April 19, 2011. The comment and the applicant's response dated May 27, 2011 are provided below. Agency's Product Quality Microbiology Response follows.

Comment:

3. Test the drug product for endotoxins at release and on stability, at least annually.

Applicant's Response:

The applicant believes that bacterial endotoxin testing is not a necessary test for Dorzolamide Hydrochloride (+) Timolol Maleate Preservative Free Ophthalmic Solution. Endotoxins produce a pyrogenic reaction and in severe cases septic shock when injected. As described in the proposed product labeling, Dorzolamide Hydrochloride (+) Timolol Maleate Preservative Free Ophthalmic Solution is administered to the intact surface of the eyeball and (b) (4) the patient would not be exposed to such a reaction.

Currently, bacterial endotoxin is not a critical quality attribute for sterile ophthalmic solutions as shown in USP <1151> "Pharmaceutical Dosage Forms" and the sponsor proposed specifications without endotoxin testing is in alignment with this compendial standard. This is further reinforced by the observation that there are approximately 80 USP monographs for sterile ophthalmic solutions and suspensions without bacterial endotoxin requirements.

FDA Response:

It is the policy of the ophthalmic review division that endotoxin should be controlled in topical ophthalmic products. Therefore, it recommended that applicants include an endotoxin specification for topical ophthalmic products targeted at an acceptance level of 0.5 EU/mL.

Note: In the amendment of 9/9/11 the applicant agreed, at the request of FDA, to add a specification for endotoxins. See page 5 this review.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 12/7/2011:

Analyses of Endpoints

Study P-081 was submitted in support of the proposed indication, the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers.

The mean intraocular pressure treatment group comparisons and the 95% confidence intervals around the mean differences at all time points are presented below for the All Patients Treated - Last Observation Carried Forward (APT-LOCF) population.

The pre-specified primary efficacy comparison was between the relative ocular hypotensive effect of preservative-free 2.0% dorzolamide/0.5% timolol combination administered BID to that of 2.0% dorzolamide/0.5% timolol combination with preservative administered BID at trough (just prior to the morning dose).

In order to conclude that the two treatment groups were equivalent it was required that the 95% confidence interval around the true treatment group difference between mean changes from Day -1 to Week 12 in trough (Hour 0) IOP was less than 1.5 mm Hg.

Study P-081

Chart 6.1.4-1

Mean IOP Comparison of PF Dorzolamide/Timolol and Dorzolamide/Timolol at Morning Dose Peak and Trough - APT-LOCF Worse Eye

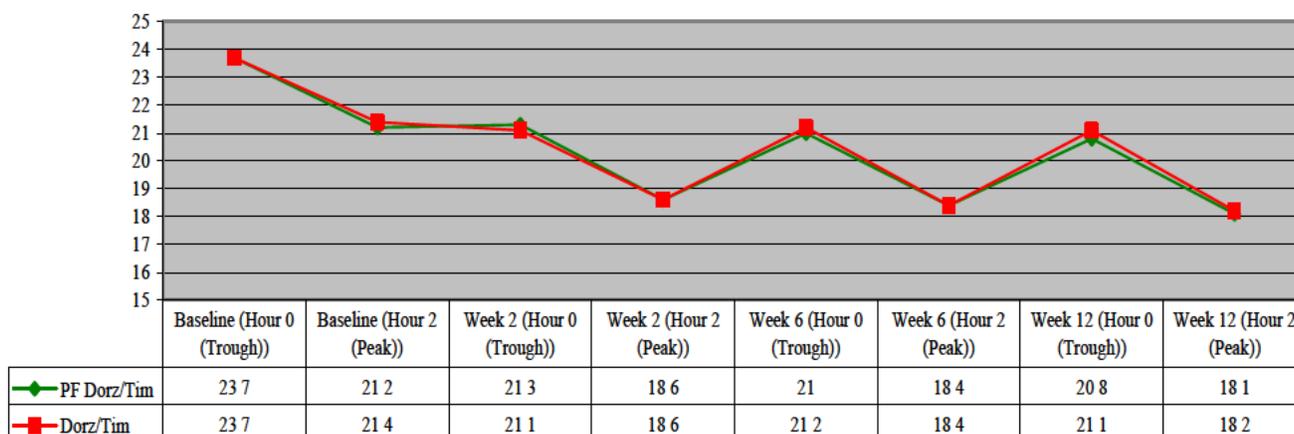


Chart 6.1.4-2

**95% Confidence Intervals of the IOP Mean Difference Between
 PF Dorzolamide/Timolol and Dorzolamide/Timolol at Morning Dose Peak and Trough
 APT LOCF - Worse Eye**

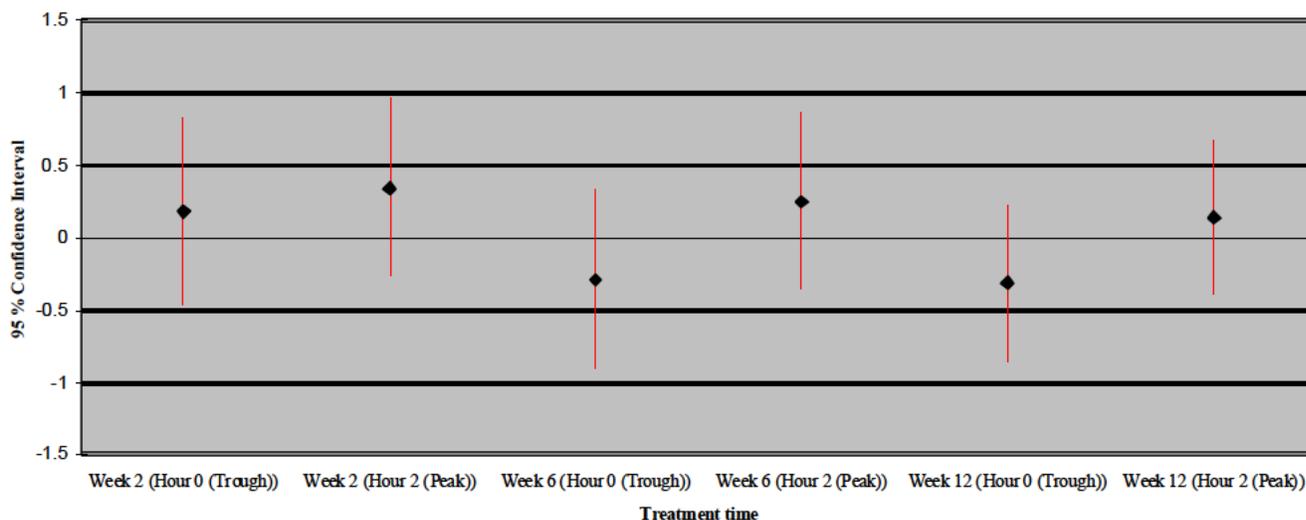


Chart 6.1.4-1

The difference between the IOP lowering effect of preservative free dorzolamide 2% / timolol 0.5% ophthalmic solution and dorzolamide 2% / timolol 0.5% ophthalmic solution with preservative at peak and trough around the morning dose were neither clinically relevant nor statistically significant in the All Patients Treated-LOCF population.

Chart 6.1.4-2

As requested by the Agency at a pre-NDA meeting, the applicant presented the following analysis to demonstrate the bioequivalence of the two dorzolamide/timolol formulations. The 95% confidence interval for the mean difference in IOP between the preservative free dorzolamide/timolol and preservative containing dorzolamide/timolol treatment groups is less than 1.0 mmHg for all peak and trough time points from Week 2 through Week 12 in the All Patients Treated-LOCF population.

The additional sensitivity analyses of raw IOP and change from baseline IOP using both ANOVA (unadjusted for baseline IOP) and ANCOVA (adjusted for baseline IOP) methods for both the All Patients Treated-Last Observation Carried Forward (APT LOCF) and Per Protocol- Observed Cases (PP-OC) approaches provided results similar to the primary and secondary efficacy analyses.

For each of these additional analyses, the 95% confidence interval for the difference in mean raw IOP or mean change from baseline IOP between the treatment groups is less than 1.0 mmHg for all peak and trough time points from Week 2 through Week 12 in the All Patients Treated-LOCF or the Per Protocol populations. Therefore, these supportive analyses also demonstrate that preservative-free dorzolamide/timolol and preservative-containing dorzolamide/timolol are clinically equivalent.

Efficacy Summary Statement

The difference between the IOP lowering effect of preservative free dorzolamide 2% / timolol 0.5% ophthalmic solution and dorzolamide 2% / timolol 0.5% ophthalmic solution with preservative at peak and trough around the morning dose were neither clinically relevant nor statistically significant in the All Patients Treated-LOCF or the Per Protocol populations in Study P-081.

Supportive analyses also demonstrate that preservative-free dorzolamide/timolol and preservative-containing dorzolamide/timolol are clinically equivalent.

The data support Cosopt PF (dorzolamide hydrochloride – timolol maleate ophthalmic solution) 2%/0.5% administered twice daily 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.

There were no significant treatment group interactions ($p > 0.05$) with regard to age, iris color, gender or race for changes in trough or peak IOP from Baseline Day -1 and Week 12.

8. Safety

From the original Medical Officer Review dated 12/7/2011:

Submitted under Section 505(b) of the Food, Drug and Cosmetic Act, this application relies in part on the Agency's findings in three previously approved NDAs. These applications are for Cosopt (NDA 20-869), Trusopt (NDA 20-408) and Timoptic (NDA 18-086) for demonstration of the safety of dorzolamide hydrochloride/ timolol maleate. In order to demonstrate comparable safety for Cosopt and Cosopt PF (dorzolamide hydrochloride / timolol maleate) preservative free ophthalmic solution, Study P081 was performed.

All 261 patients who entered the study were included in the analysis of clinical safety.

Table 7.2.1 Overall Exposure

	Cosopt PF	Cosopt
0 to 7 days	1	0
8 to 22 days	1	2
23 to 49 days	2	1
50 to 80 days	1	1
81 to 94 days	126	126

Ninety six percent of patients in each treatment group remained on therapy for at least 81 days.

There were no deaths reported during the study.

Table 7.3.2 -1 Serious Clinical Adverse Experiences

Patient No.	Gender/Age	Relative Day of Onset	Adverse Experience	Outcome
0313	M / 64	43	Neoplasm, Thyroid, Benign	Recovered
0356	F / 84	42	Osteoarthritis	Recovered

Table 7.3.3-1 Subjects Discontinued from Treatment or Study Safety Population

Reason for Discontinuation	Treatment	Patient Number
Adverse event – dermatitis, itching	Cosopt PF	0178
Adverse event – blurred vision, stinging upon instillation	Cosopt PF	0219
Adverse event – burning upon instillation	Cosopt PF	0354
Adverse event – sinus congestion, sinus headache, itching, stinging upon instillation	Cosopt PF	0357
Adverse event – Nausea, loss of appetite	Cosopt	0264
Adverse event – Dermatitis, itching	Cosopt	0273
Adverse event – Burning upon instillation	Cosopt	0355

All study discontinuations were due to non-serious adverse events.

No specific clinical adverse experiences were reported by more than 4 patients in either treatment group for any body system other than special senses.

Table 7.4.1-1 Common Adverse Experiences Occurring > 0 % in Any Treatment Group by Body System Safety Population

Body System or Adverse Experience	Cosopt PF N=131		Cosopt N=130	
	n	(%)	n	(%)
Patients with one or more adverse experiences	35	(26.7)	44	(33.8)
Patients with no adverse experience	96	(73.3)	86	(66.2)
Body as a Whole / Site Unspec.	1	(0.8)	2	(1.5)
Asthenia/Fatigue	1	(0.8)	0	(0.0)
Flu-like Illness	0	(0.0)	2	(1.5)
Digestive System	0	(0.0)	1	(0.8)
Anorexia	0	(0.0)	1	(0.8)

Body System or Adverse Experience	Cosopt PF N=131		Cosopt N=130	
	n	(%)	n	(%)
Nausea	0	(0.0)	1	(0.8)
Endocrine System	1	(0.8)	0	(0.0)
Neoplasm, Thyroid, Benign	1	(0.8)	0	(0.0)
Musculoskeletal System	1	(0.8)	0	(0.0)
Osteoarthritis	1	(0.8)	0	(0.0)
Nervous System and Psychiatric	4	(3.1)	2	(1.5)
Depression	1	(0.8)	0	(0.0)
Dizziness	1	(0.8)	0	(0.0)
Headache	2	(1.5)	2	(1.5)
Insomnia	1	(0.8)	0	(0.0)
Respiratory System	2	(1.5)	2	(1.5)
Influenza	0	(0.0)	1	(0.8)
Pharyngitis	1	(0.8)	0	(0.0)
Rhinorrhea	0	(0.0)	1	(0.8)
Sinus Disorder	1	(0.8)	0	(0.0)
Skin & Skin Appendage	4	(3.1)	2	(1.5)
Dermatitis	2	(1.5)	1	(0.8)
Pruritus	2	(1.5)	1	(0.8)
Urticaria	1	(0.8)	1	(0.8)
Special Senses	28	(21.4)	38	(29.2)
Abrasion, Corneal	0	(0.0)	1	(0.8)
Blurred Vision	2	(1.5)	2	(1.5)
Burning/Stinging, Eye	21	(16.0)	28	(21.5)
Cataract	0	(0.0)	1	(0.8)
Defect, Visual Field	0	(0.0)	1	(0.8)
Discharge, Eye	0	(0.0)	1	(0.8)
Erosion, Corneal	3	(2.3)	3	(2.3)
Foreign Body Sensation	1	(0.8)	1	(0.8)
Hemianopia	1	(0.8)	0	(0.0)
Hemorrhage, subconjunctival	0	(0.0)	1	(0.8)
Inflammation, eyelid	1	(0.8)	0	(0.0)
Irritation, eyelid	1	(0.8)	0	(0.0)
Itching, eye	1	(0.8)	1	(0.8)
Otitis	0	(0.0)	1	(0.8)
Perversion, Taste	4	(3.1)	7	(5.4)
Photophobia	0	(0.0)	1	(0.8)
Tearing	1	(0.8)	1	(0.8)
Urogenital System	0	(0.0)	1	(0.8)
Infection, Urinary Tract	0	(0.0)	1	(0.8)

Note: Although a patient may have had two or more adverse experiences, the patient is counted only once within a category and in the overall total. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had an adverse experience.

Most patients did not experience any adverse events. The most common specific adverse events for both treatment groups were ocular burning/stinging and taste perversion.

Safety Summary Statement

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate the safety of Cosopt PF (dorzolamide hydrochloride – timolol maleate ophthalmic solution) 2%/0.5% administered twice daily 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.

The most frequently reported adverse events occurring in up to 30% of patients were taste perversion (bitter, sour, or unusual taste) or ocular burning and/or stinging. The following adverse reactions were reported in 5-15% of patients: conjunctival hyperemia, blurred vision, superficial punctate keratitis or eye itching.

9. Advisory Committee Meeting

No Advisory Committee Meeting has been scheduled. There are no outstanding clinical issues which are believed to benefit from an advisory committee discussion at this time.

10. Pediatrics

The safety and effectiveness of preservative-containing dorzolamide hydrochloride ophthalmic solution and preservative-containing timolol maleate ophthalmic solution have been established when administered individually in pediatric patients aged 2 years and older and this is reflected in the approved Cosopt label in the US. Based on these data and the demonstrated clinical equivalence of preservative-free formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate to the preservative-containing formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate, no additional pediatric studies were required in support of NDA 202-667.

11. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. Per the DSI review finalized 6/16/2011:

CDTL Review
William M. Boyd, M.D.
NDA 202514
Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

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.

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.

FINANCIAL DISCLOSURE

Merck has attempted to comply with the FDA regulation, Financial Disclosure by Clinical Investigators. Protocol 081 was a single investigator clinical study for which Robert A. Laibovitz, MD served as clinical investigator in 1997. Dr. Laibovitz has since retired. Dr. Laibovitz did not provide the requested financial disclosure information by the cut-off date and therefore could not be certified. In compliance with the regulatory requirement for the Sponsor to demonstrate "due diligence" (21 CFR 54.4), multiple requests for this information were made, when possible, to the investigator who did not respond within the required time frame.

Dr. Laibovitz did not return the certification form with requested information. The form was sent by Merck & Co., on April 19, 2010, April 23, 2010 and May 18, 2010.

Dr. Laibovitz was the primary investigator at site 0001 for MK507A-081 in 1997. Dr. Laibovitz retroactively completed a Certification/ Disclosure form in which he indicated he could not recall his equity interests in Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), as the study was conducted fourteen years ago. Dr. Laibovitz did, however, confirm the absence of a proprietary or financial interest, and compensation for outcome of the study.

Merck completed an internal financial search and it was confirmed no reportable significant payments of other sorts were made to the investigator by Merck.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Cosopt PF, acceptable in OSE Review 2010-510, dated May 13, 2011, and in a second pre-action OSE Review 2011 – 2609, dated October 14, 2011.

DMEPA was invited to all internal labeling meetings and provided recommendations on the packaging configuration and the package insert labeling.

DPP (i.e. DDMAC)

The Division of Professional Promotion (DPP) was invited to all internal labeling meetings and provided recommendations on the packaging configuration and the package insert labeling in a review dated September 30, 2011.

BIOSTATISTICS

Per the Biostatistics consultative review finalized 8/29/11:

In this submission, the applicant is seeking approval of preservative-free (PF) 2.0% dorzolamide/0.5% timolol combination for the treatment for lowering elevated Intra-ocular pressure (IOP). The applicant compared the efficacy and tolerability of preservative-free and preservative-containing (PC) formulations of the dorzolamide/timolol fixed combination (Cosopt) in patients with elevated IOP.

Based on the evaluation of the efficacy and safety data in this submission, this [biostatistician] reviewer has made the following conclusions:

In an active-treatment-controlled, parallel, double-masked study in 261 patients with elevated Intraocular pressure 22 mmHg in one or both eyes, Cosopt Preservative-Free treatment is non-inferior to Cosopt Preservative-Containing in lowering IOP (using non-inferiority margin of 1.5 mmHg). The safety profile of Cosopt Preservative-Free was similar to Cosopt Preservative-Containing.

12. Labeling

NDA 202514, Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% is not recommended for approval 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.

The original Medical Officer's review dated 12/7/2011 contains revisions to the applicant's proposed package insert submitted via email on September 30, 2011 and proposed carton and container labeling submitted via email on October 19, 2011.

Final labeling negotiation is deferred until outstanding Chemistry Manufacturing issues (i.e. facilities not in compliance with good manufacturing practice regulations) are resolved.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 202514, Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5% is not currently recommended for approval 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.

Manufacturing facilities for the drug substance are not in compliance with current good manufacturing practice. Satisfactory resolution of this deficiency is required before this application may be approved.

CDTL Review
William M. Boyd, M.D.
NDA 202514
Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2%/0.5%

The drug product specifications should include a control for unspecified impurities which should be no more than (b) (4)

RISK BENEFIT ASSESSMENT:

The difference between the IOP lowering effect of preservative free dorzolamide 2% / timolol 0.5% ophthalmic solution and dorzolamide 2% / timolol 0.5% ophthalmic solution with preservative at peak and trough around the morning dose were neither clinically relevant nor statistically significant in the All Patients Treated-LOCF or the Per Protocol populations in Study P-081.

Supportive analyses also demonstrate that preservative-free dorzolamide/timolol and preservative-containing dorzolamide/timolol are clinically equivalent.

The data support Cosopt PF (dorzolamide hydrochloride – timolol maleate ophthalmic solution) 2%/0.5% administered twice daily 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.

The most frequently reported adverse events occurring in up to 30% of patients were taste perversion (bitter, sour, or unusual taste) or ocular burning and/or stinging. The following adverse reactions were reported in 5-15% of patients: conjunctival hyperemia, blurred vision, superficial punctate keratitis or eye itching.

Pharmacology/Toxicology, Biostatistics, Clinical, and Clinical Pharmacology have recommended approval for this application. CMC does not recommend approval.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

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

/s/

WILLIAM M BOYD
12/12/2011

WILEY A CHAMBERS
12/12/2011

CLINICAL REVIEW

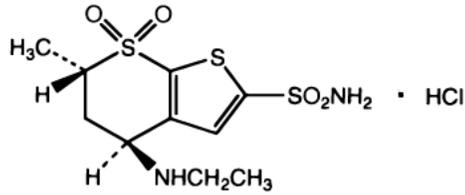
Application Type NDA
Application Number(s) 202-667
Priority or Standard Standard

Submit Date(s) 2/16/2011
Received Date(s) 2/16/2011
PDUFA Goal Date 12/16/2011
Division / Office DTOP/OAP

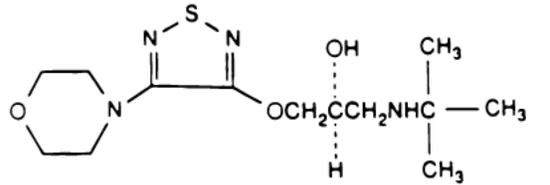
Reviewer Name(s) Rhea A. Lloyd, MD
Review Completion Date 8/5/11

Established Name dorzolamide hydrochloride
and timolol maleate
ophthalmic solution 2%/0.5%
(Proposed) Trade Name Cosopt PF
Therapeutic Class carbonic anhydrase inhibitor
and beta blocker
Applicant Merck Sharp & Dohme Corp.
126 East Lincoln Avenue
P.O. Box 2000
Mail Drop: RY33-204
Rahway, NJ 01065-0900

Formulation(s) Dorzolamide hydrochloride
 $C_{10}H_{16}N_2O_4S_3 \cdot HCl$



Timolol maleate
 $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$



Dosing Regimen One drop of Cosopt PF in the affected eye(s) two times daily

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

Intended Population(s) Patients 2 years of age or older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 202-667, Cosopt PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution) 2%/0.5% with the labeling changes listed in this review is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone.

This application relies upon the Agency's findings of safety and efficacy for NDA 20-869, Cosopt (dorzolamide hydrochloride / timolol maleate ophthalmic solution) approved April 7, 1998. Cosopt PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution) 2%/0.5% is the same in strength, dosage form and route of administration as Cosopt (dorzolamide hydrochloride / timolol maleate ophthalmic solution).

The approval of this application is based upon the proof of bioequivalence of Cosopt PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution) 2%/0.5% which is preservative-free and Cosopt (NDA 20-869 approved 1998) which contains 0.0075% benzalkonium chloride. The bioequivalence study contained in this application was required to establish that the removal of the preservative from Cosopt maintained a similar safety and efficacy profile for Cosopt PF. The bioequivalence of Cosopt PF to Cosopt was demonstrated in an adequate and well-controlled study, Study P-081, which had a clinical endpoint. Statistical significance in the test for equivalence was achieved in that the two-sided, 95% confidence interval for the mean difference in intraocular pressure at peak and trough for treatment groups was within 1.5 mmHg for all intraocular pressure measurement time points and within 1.0 mmHg for the majority of IOP measurement time points.

1.2 Risk Benefit Assessment

Study P081, the bioequivalence study, submitted in this application revealed no clinically relevant difference in safety or efficacy between Cosopt PF and Cosopt. Thus, the risk benefit assessment is the same as that for the currently marketed product, Cosopt.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name:	dorzolamide hydrochloride and timolol maleate 2%/5%
Proposed Trade Name:	Cosopt PF
Chemical Class:	new formulation
Pharmacological Class:	carbonic anhydrase inhibitor and beta blocker
Indication:	for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers.
Dosing Regimen:	Instill one drop of Cosopt PF in the affected eye(s) twice daily
Age Groups:	Patients 2 years of age or older

NDA 20-869 for Cosopt (dorzolamide hydrochloride and timolol maleate ophthalmic solution) was first approved for marketing in the US on April 7, 1998. Cosopt combines a beta blocker, a common first-line IOP lowering therapy with a topical carbonic anhydrase inhibitor (CAI), a common add-on therapy for lowering IOP and is preserved with benzalkonium chloride. Both active components in this fixed-dose combination of 2.0% dorzolamide hydrochloride and 0.5% timolol maleate lower IOP by decreasing aqueous humor production. Dorzolamide hydrochloride inhibits carbonic anhydrase isoenzyme II (CA-II) in the ciliary process of the eye. Timolol maleate inhibits aqueous humor inflow presumably by blocking catecholamine stimulation at the ciliary body. When both are used together, either as concomitant therapy or as a fixed combination, the IOP lowering effect is greater than with either product used alone.

In this NDA 202-667, Cosopt PF is the fixed combination of 2% dorzolamide hydrochloride and 0.5% timolol maleate ophthalmic solution formulated without the preservative benzalkonium chloride. Cosopt PF is otherwise identical to Cosopt, the currently marketed formulation of preservative containing dorzolamide hydrochloride / timolol maleate ophthalmic solution.

**Composition of Preservative Free
Dorzolamide Hydrochloride and Timolol Maleate 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)	(b) (4)
Hydroxyethylcellulose ¹	Ph. Eur., NF	(b) (4)	(b) (4)
Sodium Hydroxide ²	Ph. Eur., NF	pH Adjustment	qs pH 5.60
Mannitol	Ph. Eur., USP	(b) (4)	(b) (4)
Water for Injection	Ph. Eur., USP (b) (4)	(b) (4)	(b) (4)

**Specification for Preservative Free
Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution**

Tests	Acceptance Criteria	Test Methods
Appearance (Release and Shelf life)	Clear, colorless to nearly colorless, slightly viscous solution which is practically free from particles.	Visual
Identity (Release) Dorzolamide Hydrochloride	HPLC – The chromatogram of the sample solution exhibits a peak with essentially the same retention time as the standard reference material. TLC – The R _f value of the spot from the sample preparation corresponds to that obtained from the standard preparation.	HPLC TLC
Identity (Release) Timolol Maleate	HPLC – The chromatogram of the sample solution exhibits a peak with essentially the same retention time as the standard reference material. TLC – The R _f value of the spot from the sample preparation corresponds to that obtained from the standard preparation.	HPLC TLC
Viscosity	(Release): (b) (4) centipoise (mPa.s) (Shelf Life) (b) (4) centipoise (mPa.s)	
Deliverable Volume (Release)	Minimum 0.2 mL	
pH (Release and Shelf Life)	5.5 – 5.8	Ph. Eur. 2.2.3, Potentiometric Determination of pH
Osmolality / Freezing Point Depression (Release)	242 to 323 mOsm	Ph. Eur. 2.2.35 "Osmolality"
Assay – Dorzolamide Hydrochloride (as base) (Release and Shelf Life)	Label Claim: 20.00 mg/mL 90.00 – 110.0% of label claim	HPLC
Degradation Products fo (b) (4)	(b) (4)	
Any Individual Degradates	(b) (4)	HPLC

Tests	Acceptance Criteria	Test Methods
Total Degradates	(b) (4) (Release)	
(b) (4)	(b) (4) Shelf life)	
	(b) (4) Shelf life)	
Any unspecified degradates	(b) (4) Shelf life)	
Total Degradates	(b) (4) Shelf life)	
Assay Timolol Maleate (as base) (Release and Shelf life)	Label Claim: 20.00 mg/mL 90.00 – 110.0% of label claim	
Degradation Products for (b) (4)		
Any Individual Degradates	(b) (4) (Release)	
Total Degradates	(b) (4) (Release)	
(b) (4)	(b) (4) (Shelf life)	
	(b) (4) (Shelf life)	
Any Unspecified Degradates	(b) (4) (Shelf life)	
Total Degradates	(b) (4) (Shelf life)	
Sterility (Release and End of Shelf Life)	No microbial growth observed	Ph. Eur. 2.6.1, Sterility
Particulate Matter (Release)	No more than 50 per mL ($\geq 10 \mu\text{m}$) No more than 5 per mL ($\geq 25 \mu\text{m}$) No more than 2 per mL ($\geq 50 \mu\text{m}$)	USP <789> (Microscopic)

1 Identity by TLC may be an alternate test to Identity by HPLC.

Reviewer's Comment:

A specification for unidentified impurities (b) (4) should be included. A specification for endotoxin should be included, (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

There are many products of different pharmacologic classes including beta blocking agents, cholinergic medications, carbonic anhydrase inhibitors and prostaglandin analogues marketed for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Drug Products with Approved NDAs

Pharmacologic Class/Applicant	Tradename	Established Name
Alpha-2 agonists		
Alcon	Iopidine	Apraclonidine
Allergan, Inc.	Alphagan/	brimonidine tartrate

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2/0.5%

Pharmacologic Class/Applicant	Tradename	Established Name
	Alphagan P	
Beta-adrenergic antagonists		
Alcon	Betoptic/ Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharmaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan	travoprost
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/ pilocarpine hydrochloride
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

2.3 Availability of Proposed Active Ingredient in the United States

In April 1998, Cosopt (dorzolamide hydrochloride and timolol maleate ophthalmic solution) was approved in Merck's NDA 20-869. It is currently being marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no specific issues that need to be addressed.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In a Pre-NDA meeting held on April 28, 2010, the Agency agreed that Protocol 081 together with cross reference to the studies submitted in support of NDA 20-869 Cosopt would be sufficient to enable review of an NDA for the preservative-free dorzolamide/timolol formulation. Requirements for the establishment of clinical equivalence between the two formulations were given. Additionally, the Agency requested that both ANCOVA (adjusting for baseline) and ANOVA (unadjusted for baseline) results be presented. Presentation of these analyses for two endpoints, change from baseline in IOP and raw IOP, at every efficacy visit (Weeks 2, 6, and 12) and time point (peak and trough) were requested.

2.6 Other Relevant Background Information

As of December 1, 2010, Cosopt PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution) 2%/0.5% has been approved in 22 countries. The first marketing authorization of preservative-free COSOPT® was in Canada on 01-Oct-2004. Other countries that subsequently provided marketing authorization of preservative-free COSOPT® include Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Korea, Luxembourg, Netherlands, Norway, Portugal, Slovenia, Sweden, Switzerland, Turkey and United Kingdom.

The application relies on the Agency's determination of the safety and efficacy in the following applications:

- NDA 18-086, Timoptic (timolol maleate ophthalmic solution) 0.5% approved August 17, 1978.
- NDA 20-408, Trusopt (dorzolamide hydrochloride ophthalmic solution) 2.0% approved December 9, 1994.
- NDA 20-869, Cosopt (dorzolamide hydrochloride and timolol maleate ophthalmic solution) approved April 7, 1998.

The bioequivalence study contained in this application was required to establish that the removal of the benzalkonium chloride (BAK) from the dorzolamide hydrochloride / timolol maleate formulation in Cosopt PF maintained a similar safety and efficacy profile with Cosopt. The bioequivalence of Cosopt PF and Cosopt was demonstrated in an

adequate and well-controlled study, Study P-081. Statistical significance in the test for equivalence was achieved in that the two-sided, 95% confidence interval for the mean difference in intraocular pressure at peak and trough for treatment groups was within 1.5 mmHg for all intraocular pressure measurement time points and within 1.0 mmHg for the majority of IOP measurement time points.

Table 2.6.2-1 Clinical Studies Submitted in NDA 20-869 Cosopt

Protocol No.	Location No. of Sites	Study Design	IOP Inclusion Requirement at 0830 and 1030 hours	Open-label Run-in Duration	Treatment Arms	Enrollment	Completed (Dropout)
043	US 19 sites	Multiple dose Double masked Parallel 3 months + 9 month extension	≥ 22 mmHg in at least 1 eye	Timolol 0.5% BID (all pts) 0830, bedtime 2 weeks	Combo BID Concomitant TID	50 ♂ 71 ♀ 71 ♂ 50 ♀	99 (22) 104 (17)
044	Non-US 22 European sites	Multiple dose Double masked Parallel 3 months + 12 month extension	≥ 24 mmHg in at least 1 eye	None (washout period)	Combo BID Dorz 2% TID Timolol 0.5% BID	48 ♂ 67 ♀ 71 ♂ 47 ♀ 55 ♂ 62 ♀	99 (16) 102(16) 100 (17)
047	US 27 sites	Multiple dose Double masked Parallel 3 months	≥ 24 mmHg in at least 1 eye	None (washout period)	Combo BID Dorz 2% TID Timolol 0.5% BID	54 ♂ 60 ♀ 55 ♂ 54 ♀ 62 ♂ 50 ♀	105 (9) 98(11) 101 (11)
058	Non-US Multiple continents 16 sites	Multiple dose Double masked Parallel 3 months	≥ 22 mmHg in at least 1 eye	Timolol 0.5% BID (all pts), 0830, bedtime 2 weeks	Combo BID Concomitant BID	65 ♂ 86 ♀ 48 ♂ 100 ♀	145 (6) 145 (3)
063	US 23 sites	Multiple dose Double masked Parallel 3 months	≥ 22 mmHg in at least 1 eye	Timolol 0.5% BID (all pts), 0900, bedtime 3 weeks	Combo BID Dorz 2% TID Timolol 0.5% BID	42 ♂ 62 ♀ 22 ♂ 29 ♀ 47 ♂ 51 ♀	94 (10) 49 (2) 89 (9)
064	US 23 sites	Multiple dose Double masked Parallel 3 months	≥ 22 mmHg in at least 1 eye	Timolol 0.5% BID (all pts), 0900, bedtime 3 weeks	Combo BID Dorz 2% TID Timolol 0.5% BID	54 ♂ 47 ♀ 32 ♂ 17 ♀ 44 ♂ 53 ♀	97 (4) 47 (2) 91 (6)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information requests for the sponsor.

3.2 Compliance with Good Clinical Practices

The clinical trial for Protocol 081 was conducted by Robert A. Laibovitz, MD in 1997. Dr. Laibovitz has since retired and source documentation is no longer available to be inspected by the Division of Scientific Investigations (DSI). The applicant, Merck, has access to copies of case report forms, drug accountability records and labels.

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) for NDA (b) (4)), on May 9, 1989 (Sponsor: (b) (4)) and on December 28, 1995 (Sponsor (b) (4)). (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.

All studies that are cross referenced in this application were conducted in accordance with the current standard research approaches with regard to the design, conduct, and analysis of such trials including the archiving of essential documents. These trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trial was performed. All studies that are cross-referenced in this application have been previously submitted to the FDA as part of the NDAs for approved drugs.

3.3 Financial Disclosures

Merck has attempted to comply with the FDA regulation, Financial Disclosure by Clinical Investigators. Protocol 081 was a single investigator clinical study for which Robert A. Laibovitz, MD served as clinical investigator in 1997. Dr. Laibovitz has since retired. Dr. Laibovitz did not provide the requested financial disclosure information by the cut-off date and therefore could not be certified. In compliance with the regulatory requirement for the Sponsor to demonstrate "due diligence" (21 CFR 54.4), multiple requests for this

information were made, when possible, to the investigator who did not respond within the required time frame.

Dr. Laibovitz did not return the certification form with requested information. The form was sent by Merck & Co., on April 19, 2010, April 23, 2010 and May 18, 2010.

Dr. Laibovitz was the primary investigator at site 0001 for MK507A-081 in 1997. Dr. Laibovitz retroactively completed a Certification/ Disclosure form in which he indicated he could not recall his equity interests in Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), as the study was conducted fourteen years ago. Dr. Laibovitz did, however, confirm the absence of a proprietary or financial interest, and compensation for outcome of the study.

Merck completed an internal financial search and it was confirmed no reportable significant payments of other sorts were made to the investigator by Merck.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to Section 2.1.

Reviewer's Comment:

At the time of completion of this review, the CMC review was not yet complete.

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

The preclinical pharmacology, pharmacokinetic and toxicology profiles of the individual components and the combination have been well characterized in preclinical studies previously submitted to the FDA as part of the NDAs for the preservative-containing formulations of Cosopt, Trusopt and Timoptic.

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 ophthalmic solution), Approval date: August 17, 1978.

- NDA 20-408, Trusopt (dorzolamide hydrochloride ophthalmic solution), Approval date: December 9, 1994.
- NDA 20-869, Cosopt (dorzolamide hydrochloride and timolol maleate ophthalmic solution), Approval date: April 7, 1998.

4.4 Clinical Pharmacology

Both components in this fixed-dose combination of 2.0% dorzolamide hydrochloride / 0.5% timolol maleate lower IOP by decreasing aqueous humor production. Dorzolamide hydrochloride is a topically active inhibitor of carbonic anhydrase isoenzyme II (CA-II) in the ciliary process of the eye. Specifically, dorzolamide acts by decreasing the secretion of aqueous humor from the ciliary process. Timolol maleate is a non-specific beta-adrenergic receptor antagonist which also inhibits aqueous humor inflow presumably by blocking catecholamine stimulation at the ciliary body. When both are used together, either as concomitant therapy or as a fixed combination, the IOP lowering effect is greater than with either product used alone.

The applicant requested and was granted a waiver of the requirement for the submission of in vivo bioavailability data. Removal of the preservative is likely to decrease bioavailability, however, clinical equivalence was demonstrated in Study P081. No clinical pharmacology studies of the COSOPT PF formulation were conducted, and no pharmacokinetic samples were obtained in the Phase 3 trial conducted in support of this NDA.

The preclinical pharmacology, pharmacokinetic and toxicology profiles of the individual components and the combination have been well characterized in preclinical studies previously submitted to the FDA as part of the NDAs for the preservative-containing formulations of Cosopt, Trusopt and Timoptic.

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

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- NDA 20-869, Cosopt (dorzolamide hydrochloride and timolol maleate ophthalmic solution), Approval date: April 7, 1998.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
Protocol 081 Bioequivalence Study	Randomized, double-masked, parallel, multiple dose, active-controlled, single center	Patients at least 21 years of age with open angle glaucoma or ocular hypertension	2% Dorzolamide / 0.5% Timolol combination 2% Dorzolamide / 0.5% Timolol combination with BAK	1 drop in each eye at 0900 hours and bedtime for 12 weeks	3 week run-in period with timolol alone followed by 12 weeks	261

5.2 Review Strategy

This application contains a single bioequivalence trial to support the approval of Cosopt PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution) 2%/0.5% for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers alone. The study was randomized, single center, double-masked, active-controlled, two-arm and parallel group in design.

The submitted clinical study reports, clinical protocols, and literature reports related to Study P081 were reviewed in depth. The majority of the application was submitted in electronic CTD format. Modules 1, 2, and 5 were reviewed in depth.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study P081: 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

Investigator

This study was performed at a single center in the United States. The primary investigator's name and address are as follows:

Robert A. Laibovitz, MD
Eye Research Associates
3307 Northland Drive
Suite 470
Austin, TX 78731

Study Design

A 3-week open-label run-in of 0.5% timolol BID preceded the 12-week, single center, double-masked, randomized (1:1), 2-arm, active controlled, parallel-group study comparing preservative-free (PF) dorzolamide/timolol combination twice daily with the preservative containing dorzolamide/timolol combination twice daily.

Primary Objective:

- To compare the relative ocular hypotensive effect of preservative-free 2.0% dorzolamide / 0.5% timolol combination administered BID to that of 2.0% dorzolamide / 0.5% timolol combination with preservative administered BID at trough (just prior to morning dose).

Secondary Objective:

- To compare the relative ocular hypotensive effect of preservative-free 2.0% dorzolamide / 0.5% timolol combination administered BID to that of 2.0% dorzolamide / 0.5% timolol with preservative administered BID at peak (2 hours after the morning dose).
- To compare the safety and tolerability of both preservative-free dorzolamide/timolol and dorzolamide/timolol with preservative.

This was a randomized, double masked, active treatment controlled, multiple-dose, parallel study.

Run-in Period / Screening (Day -21 to -2)

At the start of the run-in period, patients discontinued their ocular hypotensive therapy and began taking 0.5% timolol ophthalmic solution BID at 0900 hours and bedtime. During the 3-week run-in period, patients completed a prestudy screening evaluation to determine if they fulfilled the admission/exclusion criteria. The prestudy evaluation included visual acuity, external ocular examination, slit lamp examination. In order to be entered into the study, women of childbearing potential were required to undergo a urine beta-HCG pregnancy test, the results of which had to be negative. These women also had to agree to use adequate means of contraception throughout the study and for the 8 months thereafter.

Baseline (Day -1)

On study Day -1, patients returned to the clinic prior to instillation of the 0.5% timolol ophthalmic solution run-in treatment for an examination at 0830 hours which included an evaluation of visual acuity, slit lamp and external ocular examination, and IOP. If the

IOP was ≥ 22 mmHg in at least one eye at 0830 hours, patients were eligible to continue with the Day -1 examinations. The run-in 0.5% timolol ophthalmic solution was instilled in both eyes at 0900 hours. The examinations were repeated at 1100 hours.

Masked Treatment Period (Day 1)

On Day 1, patients returned to the clinic at 0830 hours. Each patient was assigned to one treatment sequence according to a randomized allocation schedule. The examination schedule was as follows:

0830 hours External ocular exam, slit lamp exam
0900 hours First administration of one drop of study drug medication to each eye
0930 hours External ocular exam, slit lamp exam
1100 hours Goldmann applanation (IOP)

Prior to leaving the clinic, patients were instructed in the proper use of the study drug in unit-dose containers, i.e., at each dosing time, instill 1 drop in each eye using 1 unit-dose container and immediately discard the remaining drug in that container. The patients were instructed to administer their drops at approximately 0900 hours and at bedtime. Patients were given a sufficient number of unit-dose containers to supply them until the next scheduled visit.

Weeks 2, 6, and 12

Patients returned to the clinic at 0830 hours prior to the instillation of study drug and brought any unused study drug with them to the clinic. The examinations were performed as follows:

0830 hours Visual acuity, external ocular exam, slit lamp exam, Goldmann applanation (IOP)
0900 hours Administration of study drug
1100 hours Visual acuity, external ocular exam, slit lamp exam, Goldmann applanation (IOP)

Prior to leaving the clinic at Weeks 2 and 6, patients received a sufficient quantity of unit-dose containers of study drug until the next scheduled visit. The patient was reminded of the proper use of the unit-dose containers, and to administer the study drug daily at 0900 hours and bedtime.

Week 12 or Termination from the Study

In addition to the above evaluations, a visual field examination and dilated ophthalmoscopy were performed following the 1100 hour IOP measurement at Week 12 to complete the post-study evaluation. Mydriatic agents were not instilled in the eyes until after the 1100 hour IOP measurement to prevent the mydriatic agent from influencing the evaluation of IOP.

If a patient was discontinued from the study for any reason prior to Week 12, a complete ophthalmic examination was performed including the following: visual acuity, external

ocular examination, slit lamp examination, IOP measurement, dilated ophthalmoscopy and visual field examination.

14 Day Telephone Follow-Up

All patients were contacted by telephone 14 days after the final dose of study drug was administered. Patients were questioned about their general health since completing the study. Merck Research Laboratory (MRL) was notified immediately if a patient had a serious adverse experience during this period.

Table 5.3.1-2 Schedule of Clinical Observations

	Prestudy Day - 21 to -2	Baseline Day -1		Day 1				Weeks 2 and 6			Week 12 ⁶		
	Prestudy	0830	1100	0830	0900	0930	1100	0830	0900	1100	0830	0900	1100
Informed Consent	X												
Inclusion / Exclusion criteria	X												
Randomization				X									
Visual acuity	X	X	X					X		X	X		X
External ocular examination (lids)	X	X	X	X		X		X		X	X		X
Slit lamp examination	X	X	X	X		X		X		X	X		X
Dilated Ophthalmoscopy	X												X ⁴
Goldmann applanation IOP ¹	X	X ²	X				X	X ²		X	X ²		X
Urine pregnancy test	X												
Instill Timoptic 0.5%		X											
Instill study drug					X				X			X	
Visual field exam ³	X												X ⁵
Dispense and Instruct on administration of study drug							X			X			
Review of adverse events		X	X	X				X			X		X
Collection of all study drug													X

1 Measurements of IOP were obtained within ± one-half hour of the 0830 hour and 1100 hour time points. IOP measurements on Days -1, and Weeks 2, 6, and 12 were efficacy measures. IOP on Day 1 was a safety measure only.

2 IOP measurement obtained prior to morning dose (trough: 0830 hours).

3 If patient did not complete a computerized visual field evaluation within 1 year of the pre-study exam, a learning visual field was performed and discarded. A second visual field evaluation was conducted as the official pre-study visual field examination.

4 Mydriatic agents were instilled after 1100 IOP measurement.

5 If a clinically significant change from baseline was noted in the visual field, the exam was repeated within 2 weeks.

6 14 day follow-up phone call was made to patients to inquire about whether any serious adverse experiences had occurred following final study drug instillation.

NOTE: All examinations were to be scheduled within ± 2 days of the prespecified date.

Study Population

Approximately 260 patients with elevated intraocular pressure were to be enrolled in the study to provide a minimum of 120 patients in each treatment group who would complete the study. Men and women over the age of 21 were enrolled. Women of childbearing potential had a negative urine β -HCG (beta human chorionic gonadotropin) test prior to entry and agreed to practice adequate means of contraception during the study and for 8 months following the completion of this study.

Inclusion Criteria

1. Open-angle glaucoma or ocular hypertension in both eyes.
2. Treatment with open-label 0.5% timolol ophthalmic solution bid for at least 3 weeks prior to Day -1 (baseline).
3. IOP of ≥ 22 mmHg in one or both eyes at 0830 hours on Day -1, after the 3-week run-in period.

Exclusion Criteria

Ocular

1. History or evidence of intraocular surgery or significant ocular trauma within 6 months of study start. However, patients may have had intraocular laser therapy up to within 3 months of study start.
2. Evidence of acute or recent ocular inflammation and/or infection within 3 months of study start.
3. Significant ocular symptoms or signs such as photophobia, flashes or streaks of light, metamorphopsia, diplopia, or transient loss of vision.
4. Evidence of acute or chronic angle closure.
5. Pupil would not dilate sufficiently for adequate evaluation of the retina.
6. Having worn contact lenses or having discontinued contact lens use within 3 weeks of study start.

Pharmacologic

1. Current use of illicit drugs or chronic alcohol abuse.
2. Participation in a study involving administration of investigational drugs within 4 weeks of study start.
3. Previous exposure to treatment with 2.0% dorzolamide / 0.5% timolol combination.
4. Concomitant systemic or dermatologic medication known to affect intraocular pressure, e.g., clonidine, carbonic anhydrase inhibitors, corticosteroids, scopolamine, etc. However, calcium channel blockers and angiotensin converting enzyme inhibitors were not prohibited. Oral β -blocking agents were allowed if their administration remained constant during the study.

General / Systemic

1. History of hypersensitivity to any components of dorzolamide/timolol ophthalmic solution. Any patient with known severe or serious hypersensitivity to sulfonamides was discussed with the clinical monitor before inclusion.
2. Contraindication to either component of the combination.
3. History of evidence of bronchial asthma, clinically significant chronic obstructive pulmonary disease, or impaired renal function.
4. History of evidence of sinus bradycardia (50 bpm or less); second- or third-degree atrioventricular block; uncompensated heart failure; overt cardiac failure or cardiogenic shock. Athletes were not excluded for having a low pulse rate.
5. Any situation or condition relating to a patient which, in the opinion of the investigator, may have confounded the results of the study, may have interfered with a patient's optimal participation in the study, or may have produced a significant risk to the patient.
6. Pregnant or nursing women and women of childbearing potential not using adequate means of contraception and who were not willing to use adequate means of contraception during and for 8 months following the completion of this study.
7. Substantial renal disease, hematologic abnormality or disease, or electrolyte imbalances.

Identity of Investigational Product

For the 3-week Run-In Period, Timoptic 0.5% was provided in 10 mL open-label, market image ocumeters.

For the double-masked treatment period, the study medications, preservative free 2.0% dorzolamide/0.5% timolol ophthalmic solution and 2.0% dorzolamide/0.5% timolol ophthalmic solution with BAK were provided as sterile ophthalmic solutions in unit-dose containers. The unit dose containers were packaged in pouches of 15 unit dose containers per pouch, and 13 pouches per box.

Study Drugs	Formulation No.
3-Week Run-In	
Timolol ophthalmic solution, 0.5%	1383D
12-Week Double-Masked Period	
Preservative-free 2.0% dorzolamide/0.5% timolol ophthalmic solution	FE-1542
BAK-containing 2.0% dorzolamide/0.5% timolol ophthalmic solution	FE-1543

Evaluation Criteria

Efficacy

IOP measurements (by Goldmann applanation) used in the efficacy evaluation were performed at Day -1 (baseline), Week 2, 6, and 12. IOP measured at trough at approximately 0830 hours (prior to morning dose; Hour 0) and peak at approximately 1100 hours (2 hours after morning dose; Hour 2) were analyzed. Ocular hypotensive

effects were assessed using changes in IOP measurements from Day -1 (baseline) to those obtained at Weeks 2, 6, and 12. The primary hypothesis is based on the change in IOP from baseline at Week 12. The analysis was performed on the measurements from the patient's worse eye. The worse eye was defined as follows:

- The eye with the higher intraocular pressure at 0830 hours on Day -1. If both eyes were equal, then
- The eye with the higher intraocular pressure at 1100 hours on Day -1. If both eyes were equal, then
- The right eye was selected.

Safety

Visual acuity, external ocular examination, slit-lamp evaluation, Goldmann applanation IOP (measured on Day 1), ophthalmoscopy, and visual field evaluation, as well as monitoring of adverse experiences were safety parameters in this study.

Statistical and Analytical Plans

Study Hypotheses

In patients with elevated IOP, the ocular hypotensive effect of preservative-free 2.0% dorzolamide/0.5% timolol combination administered BID will be equivalent (i.e., within 1.5 mmHg) to that of 2.0% dorzolamide/0.5% timolol combination with preservative administered BID at morning trough (just prior to morning dose).

In patients with elevated IOP, the ocular hypotensive effect of preservative-free 2.0% dorzolamide/0.5% timolol combination administered BID will be equivalent (i.e., within 1.5 mmHg) to that of 2.0% dorzolamide/0.5% timolol combination containing preservative administered BID at peak (approximately 2 hours post morning dose).

The safety profiles of preservative-free dorzolamide/timolol combination and dorzolamide/timolol containing preservative will be similar.

Statistical Power

Power analyses were performed during the planning phase of this study. These analyses indicated that for morning trough (Hour 0), a sample size of 240 patients (120 in each treatment group) provided a 97% probability of concluding equivalency based on the above criterion if the response to the 2 treatments was indeed equal. This computation assumed that the between-patient standard deviation (SD) for changes in IOP was equal to 3.0 mmHg.

An analogous computation was performed for the secondary outcome of Week 12 peak IOP (Hour 2). A sample size of 120 patients per treatment group provided a 93% probability of concluding equivalency if the response to the two treatments was indeed

equal. This computation assumed a between-patient change in peak IOP SD of 3.5 mmHg.

Statistical Analysis

Two approaches were used to define samples for analysis of the efficacy data. These are:

- All patients treated, last-observation-carried-forward (APT-LOCF)
- Per Protocol, observed cases (PP-OC)

All Patients Treated, Last Observation Carried Forward (APT-LOCF)

In the primary analysis of interest, the APT-LOCF approach, all patients were included who were randomized to study medication and who had an IOP measurement of their worse eye after Day 1. Thus, the primary APT-LOCF analysis was carried out by imputing any missing Week 12 IOP values by using the following rule which was carried out separately for trough and peak values relevant to the worse eye:

Week 12 IOP was set equal to:

- the Week 12 value if available, if not available then;
- the Week 6 value if available, if not available then;
- the Week 2 value if available, if not available then;
- the Week 12 value was set to missing and patient was excluded from the comparison.

The Day 1 value was not used in the imputation algorithm because it was not defined as an efficacy outcome (Day 1 IOP assessment was for safety evaluation only). Similarly, patients were included in the APT-LOCF secondary analyses for peak IOP if the worse eye peak IOP was available for any follow up visit beyond Day 1.

Per Protocol, Observed Cases (PP-OC)

The Per Protocol, observed cases (PP-OC) analyses were performed without imputing missing data and after excluding patients who were serious protocol violators. Patients could also be excluded for failure to meet any inclusion/ exclusion criteria or for taking a prohibited concomitant medication. No patient was excluded for these reasons. In addition, other potential serious protocol violations were assessed on a per visit bases including not taking study medication at key prescribed times. Serious per-visit protocol violations did not necessarily imply that all follow-up data was excluded. PP-OC results are summarized in the efficacy results section.

Analytical Methods

Baseline Comparisons

Demographic patient characteristics (age, gender, race, and iris color), baseline IOP, secondary diagnoses, and prior and concomitant therapy usage were summarized by assigned treatment group. Fisher's exact tests (two-tailed) were used to compare the treatment groups with regard to dichotomous outcomes. Unpaired t-tests were used to

compare treatment groups with regard to baseline IOP at both trough and peak measurements.

Safety Comparisons

All patients who received study medication were included in the evaluation of safety parameters. Safety parameters included measures of visual acuity, external ocular and slit-lamp evaluations, ophthalmoscopy, visual field evaluations, and changes in the optic nerve cup/disc ratio. IOP measured 2 hours after the first drop of study drug on Day 1 was also evaluated as a safety measure only. Incidence rates for dichotomous safety parameters were compared using Fisher's exact tests employing two-sided type I error rates of $\alpha = 0.05$. Day 1 IOP measurements were compared using Student's t-tests, Wilcoxon's rank sum tests were used to compare distributions of visual field global indices between treatment groups. Wilcoxon's signed rank tests were used to compare prestudy to poststudy values of the global indices within treatment group. All p-values were rounded to three decimal places and statistical significance was declared if the rounded p-value was ≤ 0.050 .

Efficacy Analyses

At a pre-NDA meeting held between the sponsor and the Agency, additional analyses were requested by the Agency. For these analyses, the Agency specified the following:

Equivalence between the two formulations is recommended to be defined as the two sided 95% confidence interval being less than 1.5 mmHg at each direct group comparison over multiple times over the three month period and being less than 1.0 mmHg for the majority of direct group comparisons; the time points should include both the peak and trough efficacy times for both the test and control agents.

Based upon this request, the following analyses were conducted on both the change from baseline in IOP as well as the raw IOP using the All Patients Treated Last Observation Carried Forward (APT LOCF) and Per-Protocol Observed Cases (PP OC) approaches:

- ANOVA including a term for treatment;
- ANCOVA including terms for treatment and baseline IOP.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Study P-081 was submitted in support of the proposed indication, the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers.

6.1.1 Methods

This application relies upon safety and efficacy established for Cosopt (NDA 20-869), Trusopt (NDA 20-408) and Timoptic (NDA 18-086). The applicant is the NDA holder for Cosopt and Trusopt. A Letter of Authorization from Aton Pharma permitting the applicant to cross reference NDA 18-086 was submitted in the application. This study was to establish bioequivalence of Cosopt PF and Cosopt.

6.1.2 Demographics

Table 6.1.2-1 Demographic Data

	Cosopt PF N=131	Cosopt N=130	Total N=261
Age (years)			
Mean	56.0	54.8	
SD	15.0	15.4	
Range	22-90	22-86	
No. Enrolled			
> 65	37	31	68
56-65	34	35	69
46-55	23	33	56
36-45	23	14	37
< 36	14	17	31
Sex, N (%)¹			
Male	64 (48.9)	43 (33.1)	107 (41.0)
Female	67 (51.1)	87 (66.9)	154 (59.0)
Race/ Ethnicity, N (%)			
White	96 (73.3)	88 (67.7)	184 (70.5)
Black	14 (10.7)	17 (13.1)	31 (11.9)
Asian	2 (1.5)	1 (0.8)	3 (1.1)
Hispanic	19 (14.5)	22 (16.9)	41 (15.7)
Hawaiian	0	1 (0.8)	1 (0.4)
Arabic	0	1 (0.8)	1 (0.4)
Iris Color, N, (%)			

	Cosopt PF N=131	Cosopt N=130	Total N=261
Dark Brown	21 (16.0)	26 (20.0)	47 (18.0)
Brown	55 (42.0)	49 (37.7)	104 (39.8)
Hazel/Light Brown	19 (14.5)	22 (16.9)	41 (15.7)
Green	3 (2.3)	1 (0.8)	4 (1.5)
Blue	33 (25.2)	32 (24.6)	65 (24.9)
Iris Color Category¹			
Dark	76 (58.0)	75 (57.7)	151 (57.9)
Light	55 (42.0)	55 (42.3)	110 (42.1)
Baseline IOP (mmHg) – Worse Eye			
Hour 0 (Trough)			
Mean	23.7	23.7	23.7
Median	23.0	23.0	23.0
SD	1.5	1.5	1.5
Range	22 to 29	22 to 30	22 to 30
Hour 2 (Peak)			
Mean	21.2	21.4	21.3
Median	21.0	21.5	21.0
SD	2.5	2.7	2.6
Range	14 to 27	15 to 28	14 to 28

¹ Dark = dark brown and brown; Light = hazel/light brown, green, and blue

Note: This study was completed in 1998 prior to the publication of the September 2005 FDA Guidance for Industry Collection of Race and Ethnicity Data in Clinical Trials. A conversion to the FDA's categories of race is challenging because ethnicity was not collected.

Reviewer's Comment:

There was a significant difference between the percentages of males and females randomized to the treatment groups, $p = 0.012$ (Fisher's exact test). No significant differences were found between treatment groups for race, iris color, iris color category or baseline IOP.

6.1.3 Subject Disposition

A total of 261 patients were enrolled and 254 patients (97.3%) completed the study. Of these, three patients were not included in the primary efficacy evaluation (APT LOCF) of change in trough IOP from baseline Day -1 to Week 12. All 3 patients were missing trough IOP data for Weeks 2, 6, and 12. There were noon treatment values to be carried forward.

Table 6.1.3-1 Analysis Populations

	Cosopt PF	Cosopt
Demographics		
Number of Patients Entered (N)	131	130
Efficacy		
Number of patients with data available APT-LOCF	130	128
Safety		
Number of patients	131	130

Table 6.1.3-2 Subjects Discontinued from Treatment or Study Safety Population

Reason for Discontinuation	Treatment	Patient Number
Adverse event – dermatitis, itching	Cosopt PF	0178
Adverse event – blurred vision, stinging upon instillation	Cosopt PF	0219
Adverse event – burning upon instillation	Cosopt PF	0354
Adverse event – sinus congestion, sinus headache, itching, stinging upon instillation	Cosopt PF	0357
Adverse event – Nausea, loss of appetite	Cosopt	0264
Adverse event – Dermatitis, itching	Cosopt	0273
Adverse event – Burning upon instillation	Cosopt	0355

Reviewer’s Comment:

All study discontinuations were due to adverse events. None of the adverse events were serious.

Table 6.1.3-3 Number (%) of Patients in the Primary and Secondary Week 12 Efficacy Analyses – Trough (Hour 0)

	Cosopt PF n(%)	Cosopt n(%)	Total
All Patients Treated (APT-LOCF) Analysis			
Total Number Entered	131(100)	130 (100)	261 (100)
Week 12 trough IOP observed	127 (96.9)	127 (97.7)	254 (97.3)
Week 12 carried forward from Week 6 ^a	2	1	3
Week 12 carried forward from Week 2 ^b	1	0	1
Total with Last Observation Carried Forward	3 (2.3)	1 (0.8)	4 (1.5)
Total All Patients Treated (APT-LOCF) analysis	130 (99.2)	128 (98.5)	258 (98.9)

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Per Protocol (PP-OC) Analysis			
Total Number Entered	131 (100)	130 (100)	261 (100)
Excluded from PP-OC due to Missing Week 12			
Weeks 12, 6, and 2 all missing ^c	1 (0.8)	2 (1.5)	3 (1.2)
Weeks 2 or 6 not missing ^d	3 (2.3)	1 (0.8)	4 (1.5)
Other PP-OC exclusions			
Insufficient washout of ocular antihypertensive therapy prior to entry	0	0	0
Did not meet IOP entrance criteria	0	0	0
Prohibitive concomitant therapy	0	0	0
Off study drug	0	0	0
Outside relative day range	0	(1) ^e	(1) ^e
Total included in per protocol analysis (PP-OC)	127 (96.9)	127 (97.7)	254 (97.3)

a APT-LOCF from Week 6: PF dorzolamide/timolol: AN 0219; AN 0357; dorzolamide/timolol: AN 0264.

b APT-LOCF from Week 2: PF dorzolamide/timolol: AN 0354; dorzolamide/timolol: none.

c APT-LOCF- Missing all IOP efficacy measurements (Weeks 2, 6, and 12): PF dorzolamide/timolol: AN0178; dorzolamide/timolol: AN 0273; AN 0355.

d PF dorzolamide/timolol: AN 0219; AN 0354/ AN 0357; dorzolamide/timolol: AN 0264.

e AN 0264 had an unscheduled visit due to AE on Relative Day 46 after a Week 6 visit on Relative Day 42. This exclusion from the PP-OC analysis is already counted as excluded due to Week 12 missing (^d) and so does not also appear in Total additional PP-OC exclusions.

Reviewer's Comment:

Three patients were not included in the primary efficacy evaluation (APT-LOCF) of change in trough IOP from baseline Day -1 to Week 12. All three patients were missing trough IOP data; therefore, no values could be carried forward. One of the patients was in the PF dorzolamide/timolol group and two were in the dorzolamide/timolol group. All discontinued the study due to adverse events.

6.1.4 Analysis of Primary Endpoint(s)

In order to conclude that the two treatment groups were equivalent it was required that the 95% confidence interval around the true treatment group difference between mean changes from Day -1 to Week 12 in trough (Hour 0) IOP was less than 1.5 mm Hg.

Chart 6.1.4-1

Mean IOP Comparison of PF Dorzolamide/Timolol and Dorzolamide/Timolol at Morning Dose Peak and Trough - APT-LOCF Worse Eye

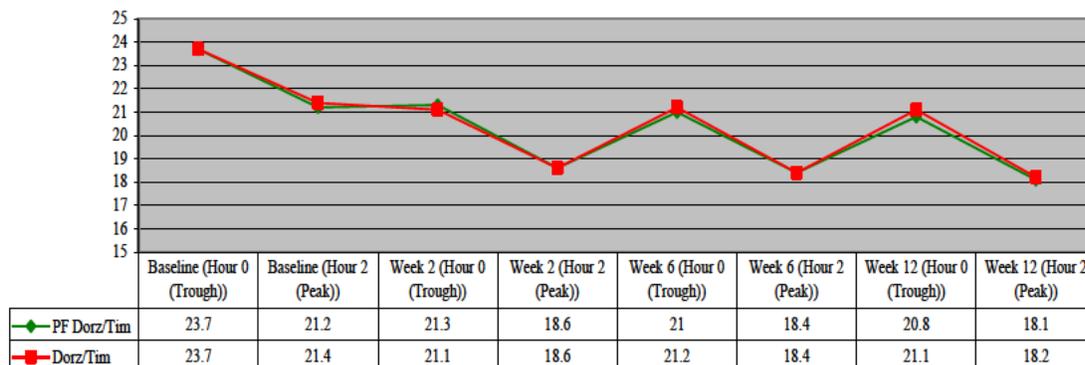
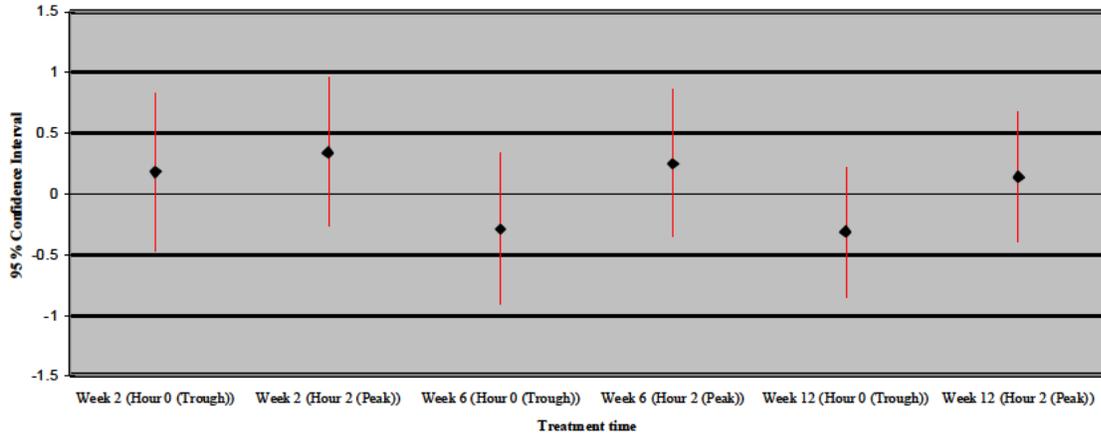


Chart 6.1.4-2

**95% Confidence Intervals of the IOP Mean Difference Between
 PF Dorzolamide/Timolol and Dorzolamide/Timolol at Morning Dose Peak and Trough
 APT LOCF - Worse Eye**



Sensitivity Analysis

Chart 6.1.4-3

**Mean IOP Comparison of PF Dorzolamide/Timolol and Dorzolamide/Timolol at Morning Dose Peak
 and Trough - Per Protocol, Observed Cases - Worse Eye**

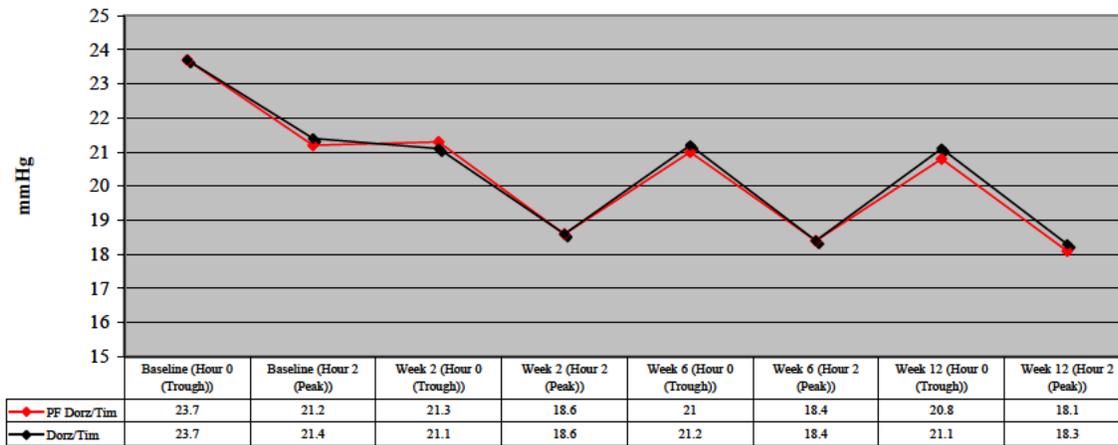
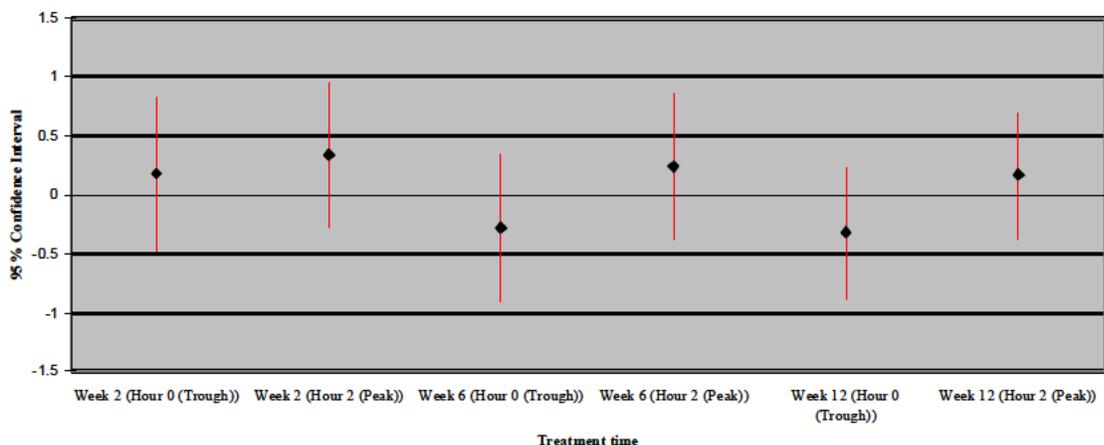


Chart 6.1.4-4

95% Confidence Intervals of the IOP Mean Difference Between
PF Dorzolamide/Timolol and Dorzolamide/Timolol at Morning Dose Peak and Trough
PP Observed Cases - Worse Eye



Reviewer's Comments:

The difference between the IOP lowering effect of preservative free dorzolamide 2% / timolol 0.5% ophthalmic solution and dorzolamide 2% / timolol 0.5% ophthalmic solution with preservative at peak and trough around the morning dose were neither clinically relevant nor statistically significant in the All Patients Treated-LOCF or the Per Protocol populations.

As requested by the Agency at a pre-NDA meeting, the sponsor presented the following analysis to demonstrate the bioequivalence of the two dorzolamide/timolol formulations. The 95% confidence interval for the mean difference in IOP between the preservative free dorzolamide/timolol and preservative containing dorzolamide/timolol treatment groups is less than 1.0 mmHg for all peak and trough time points from Week 2 through Week 12 in the All Patients Treated-LOCF or the Per Protocol populations.

6.1.5 Analysis of Secondary Endpoints(s)

Refer to Charts 6.1.4-1 and 6.1.4-2 above.

6.1.6 Other Endpoints

No additional endpoints were required to establish the efficacy of the drug product.

6.1.7 Subpopulations

Treatment group differences were examined based on subpopulations. There were no significant treatment group interactions ($p > 0.05$) with regard to age, iris color, gender or race for changes in trough or peak IOP from Baseline Day -1 and Week 12.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The clinical efficacy of Cosopt PF was demonstrated to be equivalent to that of Cosopt. Dosing of dorzolamide and timolol concomitantly is known to be superior to using Cosopt. It is recommended that the dosing of Cosopt PF be identical to that of Cosopt.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No evidence of tolerance or withdrawal effects has been detected in this trial or in trials for the original NDA 20-869 for Cosopt.

6.1.10 Additional Efficacy Issues/Analyses

Reviewer's Comment:

The additional analyses of raw IOP and change from baseline IOP using both ANOVA (unadjusted for baseline IOP) and ANCOVA (adjusted for baseline IOP) methods for both the All Patients Treated-Last Observation Carried Forward (APT LOCF) and Per Protocol- Observed Cases (PP-OC) approaches provided results similar to the primary and secondary efficacy analyses.

For each of these additional analyses, the 95% confidence interval for the difference in mean raw IOP or mean change from baseline IOP between the treatment groups is less than 1.0 mmHg for all peak and trough time points from Week 2 through Week 12 in the All Patients Treated-LOCF or the Per Protocol populations. Therefore, these supportive analyses also demonstrate that preservative-free dorzolamide/timolol and preservative-containing dorzolamide/timolol are clinically equivalent.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
Protocol 081 Bioequivalence Study	Randomized, double-masked, parallel, multiple dose, active-controlled, single center	Patients at least 21 years of age with open angle glaucoma or ocular hypertension	2% Dorzolamide / 0.5% Timolol combination 2% Dorzolamide / 0.5% Timolol combination with BAK	1 drop in each eye at 0900 hours and bedtime for 12 weeks	3 week run-in period with timolol alone followed by 12 weeks	261

The application relies on the Agency's determination of the safety and efficacy in the following applications:

- NDA 18-086, Timoptic (timolol maleate ophthalmic solution) 0.5% approved August 17, 1978.
- NDA 20-408, Trusopt (dorzolamide hydrochloride ophthalmic solution) 2.0% approved December 9, 1994.
- NDA 20-869, Cosopt (dorzolamide hydrochloride/timolol maleate ophthalmic solution approved April 7, 1998.

7.1.2 Categorization of Adverse Events

The routine clinical testing required to establish the safety of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of this clinical trial.

All adverse events were coded using a MedDRA dictionary and received independent causality assessments from the Investigator and the Medical Monitor.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse events were evaluated individually for this study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All 261 patients who entered the study were included in the analysis of clinical safety. Refer to Table 6.1.2 Demographic Data for further details.

Table 7.2.1 Overall Exposure

	Cosopt PF	Cosopt
0 to 7 days	1	0
8 to 22 days	1	2
23 to 49 days	2	1
50 to 80 days	1	1
81 to 94 days	126	126

Reviewer's Comment:

Ninety six percent of patients in each treatment group remained on therapy for at least 81 days.

7.2.2 Explorations for Dose Response

As its purpose was to establish the bioequivalence of Cosopt PF to Cosopt, the submitted clinical study did not assess dose response.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable. There was no special animal or in vitro testing performed. Refer to the Pharmacology/Toxicology review for additional details.

7.2.4 Routine Clinical Testing

Routine clinical testing and monitoring of study subjects was adequate to elicit adverse events.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance and interaction were not performed due to the negligible systemic absorption of 2 % dorzolamide hydrochloride/ 0.5% timolol maleate ophthalmic solution.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The applicant made adequate efforts to detect specific adverse events. Given the experience with the currently marketed form of this drug product, Cosopt, and published literature, no further studies are recommended.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during the study.

7.3.2 Nonfatal Serious Adverse Events

Table 7.3.2 -1 Serious Clinical Adverse Experiences

Patient No.	Gender/Age	Relative Day of Onset	Adverse Experience	Outcome
0313	M / 64	43	Neoplasm, Thyroid, Benign	Recovered
0356	F / 84	42	Osteoarthritis	Recovered

7.3.3 Dropouts and/or Discontinuations

Table 7.3.3-1 Subjects Discontinued from Treatment or Study Safety Population

Reason for Discontinuation	Treatment	Patient Number
Adverse event – dermatitis, itching	Cosopt PF	0178
Adverse event – blurred vision, stinging upon instillation	Cosopt PF	0219
Adverse event – burning upon instillation	Cosopt PF	0354
Adverse event – sinus congestion, sinus headache, itching, stinging upon instillation	Cosopt PF	0357
Adverse event – Nausea, loss of appetite	Cosopt	0264
Adverse event – Dermatitis, itching	Cosopt	0273
Adverse event – Burning upon instillation	Cosopt	0355

Reviewer’s Comment:

All study discontinuations were due to non-serious adverse events.

7.3.4 Significant Adverse Events

Refer to Common Adverse Events Section 7.4.1.

7.3.5 Submission Specific Primary Safety Concerns

In addition to clinical adverse events, the safety profiles of preservative free dorzolamide/timolol and preservative-containing dorzolamide/timolol were evaluated based on visual acuity, ocular signs, optic nerve cup/disc ratio and visual field examinations.

Visual Acuity

No patients experienced a doubling of their visual angle, compared to their baseline exam at any time during the study.

Ocular Signs

**Table 7.3.5-1 Patients with Emergent or Worsening Ocular Signs
(Incidence \geq 3% on Any Treatment)**

	Cosopt PF N=131	Cosopt N=130
	n (%)	n (%)
External and Anterior Chamber Examination		
Anterior Chamber		
Patients with any sign	0	0
Conjunctiva		
Patients with any sign	4 (3.1)	3 (2.3)
Cornea		
Patients with any sign	22 (16.8)	32 (24.6)
Punctate Epithelial Erosions (or SPK)	22 (16.8)	31 (23.8)
Lids		
Patients with any sign	1 (0.8)	0
Lens and Ophthalmoscopy Exam		
Lens		
Patients with any sign	0	1 (0.8)
Optic Nerve		
Patients with any sign	0	0
Retina		
Patients with any sign	0	0
Vitreous		
Patients with any sign	0	0

Reviewer's Comment: *There was one emergent or worsening ocular sign for both treatment groups, punctate epithelial erosions. There were no clinically relevant treatment group differences in ocular signs.*

Optic Nerve Cup-to-Disc Ratio

No patient had a worsening of 0.2 or greater in the optic nerve cup/disc ratio during the study.

Visual Field Examinations

Visual field data were assessed at two different levels.

- The prestudy and poststudy global indices were collected and changes were statistically analyzed.
- The visual fields were assessed by the investigator who determined whether the overall pattern of any changes suggested clinically significant progression.

**Table 7.3.5-2
Number (%) of Patients with a Clinically Significant Change
Since the Prestudy Visual Field Examination ^a**

	Cosopt PF N=131	Cosopt N=130
	n (%)	n (%)
Degree of Change ^{b, c}		
Improved	1 (0.8%) ^d	3 (2.3%) ^e
No Change	129 (98.5%)	124 (95.4%)
Worsened	1 (0.8%) ^f	1 (0.8%) ^g
Unsure	0	2 (1.5%) ^h

- a Visual field exam completed at baseline and at 12 weeks only.
- b For the patient to be considered "worsened," only one eye had to be reported as worsened, while to be considered "improved," both eyes had to improve.
- c No significant difference between treatment groups was observed.
- d AN 0200
- e AN 0223, AN0228, AN0230
- f AN 0354
- g AN0207
- h AN0148, AN0248

Global indices were obtained using the Humphrey visual field analyzer with the Humphrey 24-2 program. Global indices are as follows:

- Mean Defect (MD): the average difference between the threshold value of the age-corrected normal value for each test location. It is sensitive to generalized depression of the visual field.

- **Pattern Standard Deviation (PSD):** the measure of the uniformity of the visual field and is determined by comparing the shape of the patient's measured field to an age-corrected reference field. A low PSD indicates a smooth hill of vision. A high PSD indicates an irregular hill and may be due to variability in the patient's responses or to actual localized visual field defects.
- **Corrected Pattern Standard Deviation (CPSD):** a measure of the uniformity of the shape of the hill of vision after the effect of short-term fluctuation has been removed. A high CPSD usually indicates the presence of true localized visual field defects even in the presence of a high Short-Term Fluctuation or generalized loss of sensitivity.
- **Short-Term Fluctuation (SF):** a measure of the variability of the patient's responses during a single visual field examination.

Reviewer's Comment:

There were no clinically significant treatment-group differences in any of the global indices at baseline or at Week 12.

Regarding the mean defect, there were statistically significant decreases of less than 1 dB from baseline to Week 12 in both groups ($p < 0.001$ for PF dorzolamide/timolol and $p = 0.002$ for dorzolamide/timolol).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

No specific clinical adverse experiences were reported by more than 4 patients in either treatment group for any body system other than special senses.

**Table 7.4.1-1 Common Adverse Experiences Occurring > 0 %
in Any Treatment Group by Body System
Safety Population**

Body System or Adverse Experience	Cosopt PF N=131		Cosopt N=130	
	n	(%)	n	(%)
Patients with one or more adverse experiences	35	(26.7)	44	(33.8)
Patients with no adverse experience	96	(73.3)	86	(66.2)
Body as a Whole / Site Unspec.	1	(0.8)	2	(1.5)
Asthenia/Fatigue	1	(0.8)	0	(0.0)
Flu-like Illness	0	(0.0)	2	(1.5)
Digestive System	0	(0.0)	1	(0.8)
Anorexia	0	(0.0)	1	(0.8)
Nausea	0	(0.0)	1	(0.8)

Body System or Adverse Experience	Cosopt PF N=131		Cosopt N=130	
	n	(%)	n	(%)
Endocrine System	1	(0.8)	0	(0.0)
Neoplasm, Thyroid, Benign	1	(0.8)	0	(0.0)
Musculoskeletal System	1	(0.8)	0	(0.0)
Osteoarthritis	1	(0.8)	0	(0.0)
Nervous System and Psychiatric	4	(3.1)	2	(1.5)
Depression	1	(0.8)	0	(0.0)
Dizziness	1	(0.8)	0	(0.0)
Headache	2	(1.5)	2	(1.5)
Insomnia	1	(0.8)	0	(0.0)
Respiratory System	2	(1.5)	2	(1.5)
Influenza	0	(0.0)	1	(0.8)
Pharyngitis	1	(0.8)	0	(0.0)
Rhinorrhea	0	(0.0)	1	(0.8)
Sinus Disorder	1	(0.8)	0	(0.0)
Skin & Skin Appendage	4	(3.1)	2	(1.5)
Dermatitis	2	(1.5)	1	(0.8)
Pruritus	2	(1.5)	1	(0.8)
Urticaria	1	(0.8)	1	(0.8)
Special Senses	28	(21.4)	38	(29.2)
Abrasion, Corneal	0	(0.0)	1	(0.8)
Blurred Vision	2	(1.5)	2	(1.5)
Burning/Stinging, Eye	21	(16.0)	28	(21.5)
Cataract	0	(0.0)	1	(0.8)
Defect, Visual Field	0	(0.0)	1	(0.8)
Discharge, Eye	0	(0.0)	1	(0.8)
Erosion, Corneal	3	(2.3)	3	(2.3)
Foreign Body Sensation	1	(0.8)	1	(0.8)
Hemianopia	1	(0.8)	0	(0.0)
Hemorrhage, subconjunctival	0	(0.0)	1	(0.8)
Inflammation, eyelid	1	(0.8)	0	(0.0)
Irritation, eyelid	1	(0.8)	0	(0.0)
Itching, eye	1	(0.8)	1	(0.8)
Otitis	0	(0.0)	1	(0.8)
Perversion, Taste	4	(3.1)	7	(5.4)
Photophobia	0	(0.0)	1	(0.8)
Tearing	1	(0.8)	1	(0.8)
Urogenital System	0	(0.0)	1	(0.8)
Infection, Urinary Tract	0	(0.0)	1	(0.8)

Note: Although a patient may have had two or more adverse experiences, the patient is counted only once within a category and in the overall total. The same patient may appear in different categories.

All body systems are listed in which at least 1 patient had an adverse experience.

Reviewer's Comment: *Most patients did not experience any adverse events. The most common specific adverse events for both treatment groups were ocular burning/stinging and taste perversion.*

7.4.2 Laboratory Findings

Laboratory testing was not performed for this study. Extensive clinical laboratory evaluations were a part of the clinical trials in support of the new drug applications for the preservative-containing dorzolamide/timolol combination, as well as for the individual components. Additionally, the safety profiles of these products have been well characterized.

7.4.3 Vital Signs

Vital signs were not performed for this study. Vital sign evaluations were a part of the clinical trials in support of the new drug applications for the preservative-containing dorzolamide/timolol combination, as well as for the individual components. Additionally, the safety profiles of these products have been well characterized.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in this study. The safety profiles for the preservative-containing dorzolamide/timolol combination and for the individual components have been well characterized.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials conducted for this application.

7.4.6 Immunogenicity

Not applicable. The drug product is not expected to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No dose-response or dose-ranging studies were performed for Cosopt or Cosopt PF. The known safety profile of the individual components indicates that the frequency of adverse events increases with repeated instillation and higher concentrations.

7.5.2 Time Dependency for Adverse Events

The known safety profiles of the individual components indicate that the frequency of adverse events increases with repeated instillation and higher concentrations.

7.5.3 Drug-Demographic Interactions

The safety profiles of both the preservative-free and preservative-containing formulations were similar in the subgroup analyses performed by age, race, gender, and iris color. The sample sizes for each subgroup were small making interpretation difficult.

There were no significant new findings. Drug-disease interactions are sufficiently described in the current labeling for the preservative-containing combination.

7.5.4 Drug-Disease Interactions

There were no significant new findings. Drug-disease interactions are sufficiently described in the current labeling for the preservative-containing combination.

7.5.5 Drug-Drug Interactions

There were no significant new findings in this bioequivalence study. Drug-drug interactions are sufficiently described in the current labeling for the preservative-containing combination.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies have not been performed with the combination of dorzolamide hydrochloride and timolol maleate. Studies were performed using the individual components in the previously approved applications for timolol maleate (NDA 18-086) and dorzolamide hydrochloride (NDA 20-408).

7.6.2 Human Reproduction and Pregnancy Data

Reproductive toxicity studies have not been performed with the combination of dorzolamide hydrochloride and timolol maleate. Studies were performed using the individual components in the previously approved applications for timolol maleate (NDA 18-086) and dorzolamide hydrochloride (NDA 20-408).

There have been no adequate and well controlled studies in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of preservative-containing dorzolamide hydrochloride ophthalmic solution and preservative-containing timolol maleate ophthalmic solution have been established when administered individually in pediatric patients aged 2 years and older and this is reflected in the approved Cosopt label in the US. Based on these data and the demonstrated clinical equivalence of preservative-free formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate to the preservative-containing formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate, no additional pediatric studies were required in support of NDA 202-667.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Dorzolamide hydrochloride and timolol maleate are non-narcotic and have no abuse potential. No studies have been performed to evaluate overdose, drug abuse, withdrawal or rebound.

7.7 Additional Submissions / Safety Issues

On June 14, 2011, Merck submitted a 4 Month Safety Update Report which covers the time period from December 2, 2010 through April 1, 2011. No new clinical studies have been performed with Cosopt PF since the original study in 1998. There have been no deaths associated with Cosopt PF (or Cosopt) during the time period. This Safety Update Report will include post-marketing reports of spontaneously reported adverse events (serious and non-serious) from the health care providers (HCPs) from the period of December 2, 2010 to April 1, 2011 for patients using preservative-containing (PC) and PF Cosopt.

Table 7.7-1
Summary of Postmarketing Reports by System Organ Class
Dorzolamide Hydrochloride/Timolol Maleate PC and PF
Received from Health Care Providers
December 2, 2010 to April 1, 2011

System Organ Class	Total Number of Reports ^a	% of Total Reports ^b	Total No. of Serious Reports	% of Serious Reports
Cardiac disorders	6	5	4	20
Ear and labyrinth disorders	1	1	0	0
Eye disorders	54	46	6	30
Gastrointestinal disorder	6	5	1	5
General disorders and administration	23	19	3	15
Immune system disorders	5	4	0	0
Injury, poisoning and procedural	11	9	3	15
Investigations	6	5	1	5

Cosopt PF (dorzolamide hydrochloride - timolol maleate ophthalmic solution) 2/0.5%

Metabolism and nutrition disorders	1	1	0	0
Musculoskeletal and connective tissue	1	1	0	0
Nervous system disorders	15	13	5	25
Psychiatric disorders	2	2	0	0
Respiratory, thoracic and mediastinal	6	5	1	5
Skin and subcutaneous tissue disorders	10	8	2	10
Vascular disorders	3	3	1	5
DISTINCT NUMBER OF REPORTS	118		20	

a A single report may include adverse events in one or more System Organ Classes (SOCs). Therefore, the sum of reports from all SOCs can be greater than the total distinct number of reports received.

b Percentages are the percent of distinct number of reports for events in that SOC.

Reviewer Comments:

Approximately 83% of these reports were considered non-serious. The largest percentage of reports was 'Eye disorders' and 'General disorders and administration site conditions'.

The most common adverse events within the 'Eye disorders' SOC were eye irritation, eye pain, vision blurred and abnormal sensation in eye.

The most common adverse events within the 'General disorders and administration site conditions' SOC were application site irritation, no adverse event, pain and product dropper issue.

The adverse experience reports revealed no new or unexpected safety concerns.

**Table 7.7-2
Summary Tabulation of Serious Postmarketing Events for
Dorzolamide Hydrochloride/Timolol Maleate PC and PF
Received from Health Care Providers
December 2, 2010 to April 1, 2011**

System Organ Class	Preferred Term	Serious Events
Cardiac disorders	Bradycardia	3
	Cardiac arrest	1
	Palpitations	1
Eye disorders	Angle closure glaucoma	1
	Cataract	1
	Conjunctivitis	2
	Eye irritation	1

System Organ Class	Preferred Term	Serious Events
	Eye pain	1
	Lens disorder	1
	Myopia	1
	Visual acuity reduced	1
Gastrointestinal disorders	Nausea	1
	Vomiting	1
General disorders and administration site	Discomfort	1
	Fatigue	1
	Therapeutic response unexpected with drug substitution	1
Injury, poisoning and procedural complications	Overdose	3
	Wrong technique in drug usage process	1
Investigations	Intraocular pressure increased	1
Nervous system disorders	Cerebrovascular accident	1
	Convulsion	1
	Dyskinesia	1
	Syncope	2
Respiratory, thoracic and mediastinal disorders	Oropharyngeal discomfort	1
Skin and subcutaneous tissue disorders	Angioedema	1
	Drug rash with eosinophilia and systemic symptoms	1
	Pruritus generalized	1
Vascular disorders	Orthostatic hypotension	1
TOTAL NUMBER OF EVENTS		34
DISTINCT NUMBER OF REPORTS		20

Reviewer Comments:

The serious adverse experience reports revealed no new or unexpected safety concerns. Many of the reports can be described as an effect of beta blockade or sulfonamide hypersensitivity.

8 Postmarket Experience

Cosopt (dorzolamide hydrochloride and timolol maleate) ophthalmic solution which contains benzalkonium chloride was first approved on February 19, 1998 in Mexico. As of December 2010, it is currently registered and approved in 91 countries. The preservative-free dorzolamide/timolol formulation was first approved on October 1, 2004 in Canada. It is currently registered and approved in 22 countries.

Based on monthly drug distribution data, it is estimated that the cumulative worldwide marketing of dorzolamide/timolol ophthalmic solution from its 1998 market introduction to December 2010 was approximately (b) (4)

Postmarketing data have been collected since each product was launched. For the purposes of this review, the applicant searched the Worldwide Adverse Experiences System (WAES) database for spontaneous reports in patients receiving dorzolamide/timolol from health care providers, including regulatory agencies, from market introduction in February 19, 1998, through December 1, 2010. Notation is not consistently made on the reports as to whether the preservative-containing or preservative-free formulation is being reported. Therefore, the number of reports for the different formulations cannot be determined.

**Table 8-1 Summary of Postmarketing Reports by System Organ Class
Dorzolamide Hydrochloride/Timolol Maleate Received from Health Care Providers
February 19, 1998 through December 1, 2010**

System Organ Class	Total Number of Reports ¹	% of Total Reports ²	Total Number of Serious Reports	% of Serious Reports
Blood and lymphatic system disorders	11	0	6	2
Cardiac disorders	124	4	57	16
Congenital, familial and genetic	9	0	4	1
Ear and labyrinth disorders	36	1	6	2
Endocrine disorders	4	0	1	0
Eye disorders	1839	56	94	26
Gastrointestinal disorders	150	5	12	3
General disorders and administration site conditions	456	14	49	14
Hepatobiliary disorders	4	0	2	1
Immune system disorders	191	6	15	4
Infections and infestations	44	1	5	1
Injury, poisoning and procedural complications	219	7	60	17
Investigations	197	6	31	9
Metabolism and nutrition disorders	28	1	12	3
Musculoskeletal and connective tissue	53	2	8	2

System Organ Class	Total Number of Reports ¹	% of Total Reports ²	Total Number of Serious Reports	% of Serious Reports
disorders				
Neoplasms benign, malignant and unspecified (including cysts and polyps)	8	0	6	2
Nervous system disorders	397	12	49	14
Pregnancy, puerperium and perinatal conditions	7	0	6	2
Psychiatric disorders	69	2	15	4
Renal and urinary disorders	24	1	6	2
Reproductive system and breast disorders	27	1	4	1
Respiratory, thoracic and mediastinal disorders	194	6	31	9
Skin and subcutaneous tissue disorders	350	11	21	6
Surgical and medical procedures	6	0	1	0
Vascular disorders	76	2	13	4
Total number of reports	3313		362	

¹ A single report may include adverse events in one or more System Organ Classes. Therefore, the sum of reports from all System Organ Classes can be greater than the total distinct number of reports received.

² Percentages are the percent of distinct number of reports for events in that System Organ Class

Reviewer's Comment: *Approximately 90% of the submitted reports were non-serious.*

Of all reports with age provided, 62% were in patients aged 65 years and older and 38% were in patients 18 to 64 years of age. Fifty-two percent of the reports were from females, 37% from males and 11% from reports where the sex of the patient was not reported. More than half of the reports came from United States (37%), Canada (11%), Netherlands (6.5%) and Germany (6%).

The System Organ Classes (SOC) with the largest percentage of reports were eye disorders (55.5%), general disorders and administration site conditions (14%), nervous system disorders (12%) and skin and subcutaneous tissue disorders (10.5%).

The most common AEs within the eye disorders SOC were eye irritation, eye pain, ocular hyperemia, vision blurred, and eye pruritus. All these ocular events are listed in the side effects section of the Company Core Data Sheet (CCDS).

The most common AEs within the general disorder and administration site conditions were medication/administrative errors, pain, drug ineffective and asthenia. Medication / administrative errors were routinely captured as "no AE". The majority of the reports containing the event of pain had incomplete information provided (e.g., lack of medical workup) most described 'stinging' and 'burning'. The reports describing lack of efficacy accounted for a relatively small proportion (1%) of all spontaneous reports and the majority of these contained insufficient data including appropriate evaluation of IOP values. The event of asthenia is listed in the side effects section of the approved

Cosopt label under the timolol maleate component. The most common AEs within the nervous system disorders SOC were dysgeusia, headache, dizziness, and burning sensation. The most common AEs within the skin and subcutaneous tissues disorders SOC were pruritus, rash, dermatitis contact and alopecia. These events are described in the approved Cosopt label.

9 Appendices

9.1 Literature Review/References

9.2 Advisory Committee Meeting

No Advisory Committee Meeting is planned for this application.

9.3 Labeling Recommendations

Following is the applicant's proposed package insert submitted via email on September 30, 2011 and proposed carton and container labeling submitted via email on October 19, 2011.

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

/s/

RHEA A LLOYD
12/07/2011

WILLIAM M BOYD
12/07/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1 MK-507A Indication: For the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers.				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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02/28/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	Defer to Statistical team
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	Defer to Statistical team
34.	Are all datasets to support the critical safety analyses available and complete?			X	Defer to Statistical team
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	Defer to Statistical team
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

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02/28/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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02/28/2011

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

/s/

RHEA A LLOYD
03/22/2011

WILLIAM M BOYD
03/22/2011