CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-408 / S-033

Trade Name: **Trusopt**

Generic Name: **Dorzolamide hydrochloride ophthalmic solution**

Sponsor: **Merck Inc**

Approval Date: **April 15, 2004**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-408 / S-033

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	X
Summary Review	X
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-408 / S-033

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-408/S-033

Merck & Co., Inc.
Attention: Jeffrey R. Tucker, M.D.
Regulatory Affairs, Domestic
Merck Research Laboratories
Sumneytown Pike
BLA-20
P.O. Box 4
West Point PA 19486

Dear Dr. Tucker:

Please refer to your supplemental new drug application dated October 16, 2003, received October 17, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trusopt (dorzolamide hydrochloride ophthalmic solution) 2%.

We acknowledge receipt of your submissions dated November 3, 2003, and April 9, 2004.

This supplemental new drug application provides for revisions in the label to reflect the safe and effective use of Trusopt (dorzolamide hydrochloride ophthalmic solution) 2% in pediatric patients with elevated intraocular pressure.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert, as submitted on April 9, 2004.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated **"FPL for approved supplement NDA 20-408/S-033."** Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug products, HFD-550 and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Nancy Halonen, Regulatory Project Manager, at (301) 827-2199.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure:

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

/s/

Wiley Chambers
4/15/04 09:48:56 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-408 / S-033

LABELING

TRUSOPT®

(dorzolamide hydrochloride ophthalmic solution)
Sterile Ophthalmic Solution 2%

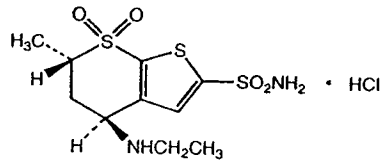
DESCRIPTION

TRUSOPT* (dorzolamide hydrochloride ophthalmic solution) is a carbonic anhydrase inhibitor formulated for topical ophthalmic use.

Dorzolamide hydrochloride is described chemically as: (4*S-trans*)-4-(ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride. Dorzolamide hydrochloride is optically active. The specific rotation is

$$\alpha \begin{matrix} 25° \\ 405 \end{matrix} \quad (C=1, \text{water}) = \sim -17°.$$

Its empirical formula is $C_{10}H_{16}N_2O_4S_3 \cdot HCl$ and its structural formula is:



Dorzolamide hydrochloride has a molecular weight of 360.9 and a melting point of about 264°C. It is a white to off-white, crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

TRUSOPT Sterile Ophthalmic Solution is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous solution of dorzolamide hydrochloride. The pH of the solution is approximately 5.6, and the osmolarity is 260-330 mOsM. Each mL of TRUSOPT 2% contains 20 mg dorzolamide (22.3 mg of dorzolamide hydrochloride). Inactive ingredients are hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide (to adjust pH) and water for injection. Benzalkonium chloride 0.0075% is added as a preservative.

CLINICAL PHARMACOLOGY

Mechanism of Action

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBCs), but also in other tissues. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

TRUSOPT Ophthalmic Solution contains dorzolamide hydrochloride, an inhibitor of human carbonic anhydrase II. Following topical ocular administration, TRUSOPT reduces elevated intraocular pressure. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

---

* Registered trademark of MERCK & CO., Inc.

Pharmacokinetics/Pharmacodynamics

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of binding to CA-II. The parent drug forms a single N-desethyl metabolite, which inhibits CA-II less potently than the parent drug but also inhibits CA-I. The metabolite also accumulates in RBCs where it binds primarily to CA-I. Plasma concentrations of dorzolamide and metabolite are generally below the assay limit of quantitation (15 nM). Dorzolamide binds moderately to plasma proteins (approximately 33%). Dorzolamide is primarily excreted unchanged in the urine; the metabolite also is excreted in urine. After dosing is stopped, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about four months.

To simulate the systemic exposure after long-term topical ocular administration, dorzolamide was given orally to eight healthy subjects for up to 20 weeks. The oral dose of 2 mg b.i.d. closely approximates the amount of drug delivered by topical ocular administration of TRUSOPT 2% t.i.d. Steady state was reached within 8 weeks. The inhibition of CA-II and total carbonic anhydrase activities was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function and respiration in healthy individuals.

Clinical Studies

The efficacy of TRUSOPT was demonstrated in clinical studies in the treatment of elevated intraocular pressure in patients with glaucoma or ocular hypertension (baseline IOP $\geq$ 23 mmHg). The IOP-lowering effect of TRUSOPT was approximately 3 to 5 mmHg throughout the day and this was consistent in clinical studies of up to one year duration.

The efficacy of TRUSOPT when dosed less frequently than three times a day (alone or in combination with other products) has not been established.

In a one year clinical study, the effect of TRUSOPT 2% t.i.d. on the corneal endothelium was compared to that of betaxolol ophthalmic solution b.i.d. and timolol maleate ophthalmic solution 0.5% b.i.d. There were no statistically significant differences between groups in corneal endothelial cell counts or in corneal thickness measurements. There was a mean loss of approximately 4% in the endothelial cell counts for each group over the one year period.

INDICATIONS AND USAGE

TRUSOPT Ophthalmic Solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

TRUSOPT is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

TRUSOPT is a sulfonamide and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration with TRUSOPT. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

PRECAUTIONS

General

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. TRUSOPT has not been studied in patients with acute angle-closure glaucoma.

TRUSOPT has not been studied in patients with severe renal impairment (CrCl <30 mL/min). Because TRUSOPT and its metabolite are excreted predominantly by the kidney, TRUSOPT is not recommended in such patients.

TRUSOPT has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of TRUSOPT. Many of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of drug therapy. If such reactions are observed, TRUSOPT should be discontinued and the patient evaluated before considering restarting the drug. (See ADVERSE REACTIONS.)

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and TRUSOPT. The concomitant administration of TRUSOPT and oral carbonic anhydrase inhibitors is not recommended.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., dorzolamide) after filtration procedures.

Information for Patients

TRUSOPT is a sulfonamide and although administered topically is absorbed systemically. Therefore the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration. Patients should be advised that if serious or unusual reactions or signs of hypersensitivity occur, they should discontinue the use of the product (see WARNINGS).

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should discontinue use and seek their physician's advice.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

Patients should be advised that TRUSOPT contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following TRUSOPT administration.

Drug Interactions

Although acid-base and electrolyte disturbances were not reported in the clinical trials with TRUSOPT, these disturbances have been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential for such drug interactions should be considered in patients receiving TRUSOPT.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study of dorzolamide hydrochloride administered orally to male and female Sprague-Dawley rats, urinary bladder papillomas were seen in male rats in the highest dosage group of 20 mg/kg/day (250 times the recommended human ophthalmic dose). Papillomas were not seen in rats given oral doses equivalent to approximately 12 times the recommended human ophthalmic dose. No treatment-related tumors were seen in a 21-month study in female and male mice given oral doses up to 75 mg/kg/day (~900 times the recommended human ophthalmic dose).

The increased incidence of urinary bladder papillomas seen in the high-dose male rats is a class-effect of carbonic anhydrase inhibitors in rats. Rats are particularly prone to developing papillomas in response to foreign bodies, compounds causing crystalluria, and diverse sodium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide hydrochloride for one year at 2 mg/kg/day (25 times the recommended human ophthalmic dose) or monkeys dosed topically to the eye at 0.4 mg/kg/day (~5 times the recommended human ophthalmic dose) for one year.

The following tests for mutagenic potential were negative: (1) *in vivo* (mouse) cytogenetic assay; (2) *in vitro* chromosomal aberration assay; (3) alkaline elution assay; (4) V-79 assay; and (5) Ames test.

In reproduction studies of dorzolamide hydrochloride in rats, there were no adverse effects on the reproductive capacity of males or females at doses up to 188 or 94 times, respectively, the recommended human ophthalmic dose.

Pregnancy

Teratogenic Effects. Pregnancy Category C. Developmental toxicity studies with dorzolamide hydrochloride in rabbits at oral doses of $\geq$ 2.5 mg/kg/day (31 times the recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred at doses that caused metabolic acidosis with decreased body weight gain in dams and decreased fetal weights. No treatment-related malformations were seen at 1.0 mg/kg/day (13 times the recommended human ophthalmic dose). There are no adequate and well-controlled studies in pregnant women. TRUSOPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

In a study of dorzolamide hydrochloride in lactating rats, decreases in body weight gain of 5 to 7% in offspring at an oral dose of 7.5 mg/kg/day (94 times the recommended human ophthalmic dose) were seen during lactation. A slight delay in postnatal development (incisor eruption, vaginal canalization and eye openings), secondary to lower fetal body weight, was noted.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TRUSOPT, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and IOP-lowering effects of TRUSOPT have been demonstrated in pediatric patients in a 3-month, multi-center, double masked, active-treatment-controlled trial.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Controlled clinical trials:

The most frequent adverse events associated with TRUSOPT were ocular burning, stinging, or discomfort immediately following ocular administration (approximately one-third of patients). Approximately one-quarter of patients noted a bitter taste following administration. Superficial punctate keratitis occurred in 10-15% of patients and signs and symptoms of ocular allergic reaction in approximately 10%. Events occurring in approximately 1-5% of patients were conjunctivitis and lid reactions (see PRECAUTIONS, *General*), blurred vision, eye redness, tearing, dryness, and photophobia. Other ocular events and systemic events were reported infrequently, including headache, nausea, asthenia/fatigue; and, rarely, skin rashes, urolithiasis, and iridocyclitis.

In a 3-month, double-masked, active-treatment-controlled, multicenter study in pediatric patients, the adverse experience profile of TRUSOPT was comparable to that seen in adult patients.

Clinical practice

The following adverse events have occurred either at low incidence (<1%) during clinical trials or have been reported during the use of TRUSOPT in clinical practice where these events were reported voluntarily from a population of unknown size and frequency of occurrence cannot be determined precisely. They have been chosen for inclusion based on factors such as seriousness, frequency of reporting, possible causal connection to TRUSOPT, or a combination of these factors: signs and symptoms of systemic allergic reactions including angioedema, bronchospasm, pruritus, and urticaria; dizziness, paresthesia; ocular pain, transient myopia, choroidal detachment following filtration surgery, eyelid crusting; dyspnea; contact dermatitis, epistaxis, dry mouth and throat irritation.

OVERDOSAGE

Electrolyte imbalance, development of an acidotic state, and possible central nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

DOSAGE AND ADMINISTRATION

The dose is one drop of TRUSOPT Ophthalmic Solution in the affected eye(s) three times daily.

TRUSOPT may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

HOW SUPPLIED

TRUSOPT Ophthalmic Solution is a slightly opalescent, nearly colorless, slightly viscous solution.

No. 3519 — TRUSOPT Ophthalmic Solution 2% is supplied in OCUMETER®* PLUS container, a white, opaque, plastic ophthalmic dispenser with a controlled drop tip as follows:

NDC 0006-3519-35, 5 mL

NDC 0006-3519-36, 10 mL.

Storage

Store TRUSOPT Ophthalmic Solution at 15-30°C (59-86°F). Protect from light.

Rx only

Manuf. for:
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

By: Laboratories Merck Sharp & Dohme-Chibret
63963 Clermont-Ferrand Cedex 9, France

Issued

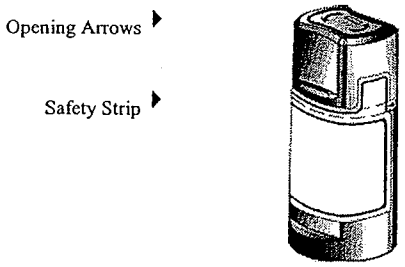
INSTRUCTIONS FOR USE

Please follow these instructions carefully when using TRUSOPT*. Use TRUSOPT as prescribed by your doctor.

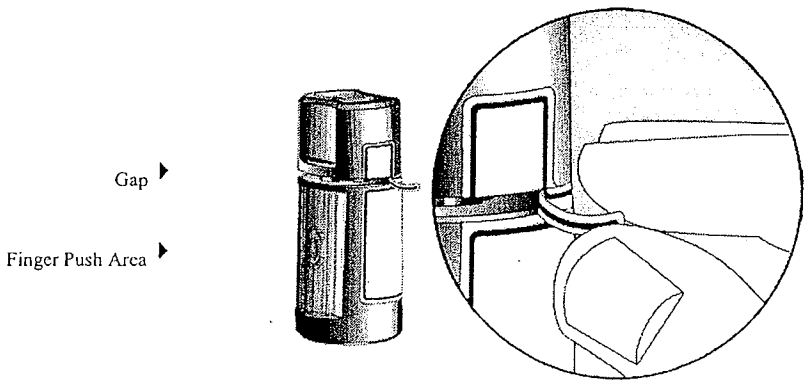
1. If you use other topically applied ophthalmic medications, they should be administered at least 10 minutes before or after TRUSOPT.

2. Wash hands before each use.

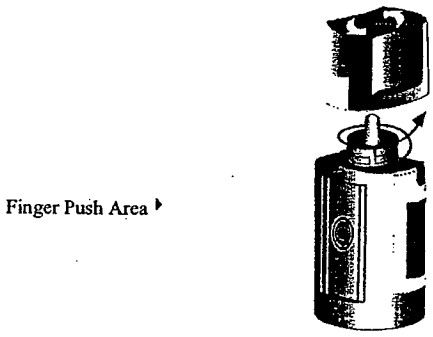
3. Before using the medication for the first time, be sure the Safety Strip on the front of the bottle is unbroken. A gap between the bottle and the cap is normal for an unopened bottle.



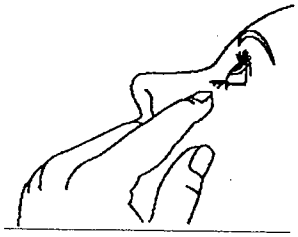
4. Tear off the Safety Strip to break the seal.



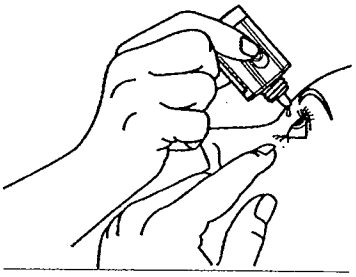
5. To open the bottle, unscrew the cap by turning as indicated by the arrows.

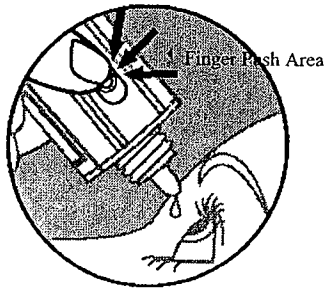


6. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.



7. Invert the bottle, and press lightly with the thumb or index finger over the "Finger Push Area" (as shown) until a single drop is dispensed into the eye as directed by your doctor.





DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.

Ophthalmic medications, if handled improperly, can become contaminated by common bacteria known to cause eye infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated ophthalmic medications. If you think your medication may be contaminated, or if you develop an eye infection, contact your doctor immediately concerning continued use of this bottle.

8. Repeat steps 6 & 7 with the other eye if instructed to do so by your doctor.

9. Replace the cap by turning until it is firmly touching the bottle. Do not overtighten the cap.

10. The dispenser tip is designed to provide a pre-measured drop; therefore, do NOT enlarge the hole of the dispenser tip.

11. After you have used all doses, there will be some TRUSOPT left in the bottle. You should not be concerned since an extra amount of TRUSOPT has been added and you will get the full amount of TRUSOPT that your doctor prescribed. Do not attempt to remove excess medicine from the bottle.

WARNING: Keep out of reach of children.
If you have any questions about the use of TRUSOPT, please consult your doctor.

MERCK & CO., Inc.

Whitehouse Station, NJ 08889, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-408 / S-033

SUMMARY REVIEW

Medical Officer's Review of NDA 20-408
BPCA Summary

Proprietary Name:	**Trusopt Ophthalmic Solution 2%**
Established Name:	**dorzolamide HCL ophthalmic solution**
Sponsor:	**Merck & Co. Inc** **BLA-20, P.O. Box 2** **West Point, PA 19486**
NDA Supplement:	**SE5**
Proposed Indication:	**Treatment of increased intraocular pressure in pediatric patients with glaucoma or ocular hypertension**
Date of Submission:	October 16, 2003
Date of Review:	April 14, 2004

BPCA Summary

I. Recommendations

A. Recommendation on Approvability

NDA 20-408 /SE5-033 is recommended for approval. The clinical study contained in this supplement supports the use of dorzolamide 2% in the pediatric population. The benefits of using this drug product outweigh the risks in the treatment of elevated intraocular pressure in pediatric patients.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no recommendations for phase 4 studies.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Dorzolamide HCL was approved in 1994 as the first topical carbonic anhydrase inhibitor for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or glaucoma. To date the safety and effectiveness of this product has not been established in the pediatric population.

Currently, the only approved drug for the treatment of elevated IOP in the pediatric population is brimonidine tartrate ophthalmic solution. This drug product is labeled for pediatric patients over the age of 2 years old.

A pediatric written request for dorzolamide 2% was issued by the Agency in 1999 with subsequent amendments in 2000 and 2002. The sponsor has conducted a 12-week multicenter, randomized, masked, active-control trial comparing dorzolamide 2% to timolol GFS in response to this written request. The primary objective of the written request and submitted trial was to obtain data on the safety and clinical response of dorzolamide 2% in the pediatric population.

B. Efficacy

The clinical response data contained in this supplement demonstrates that dorzolamide 2% effectively lowers IOP in the pediatric population. IOP is lowered approximately 7-9mmHg in this population with a baseline IOP of approximately 30 mmHg.

C. Safety

Dorzolamide 2% is safe for use in the pediatric population below the age of 6 years old. Overall, less than 2.5% of patients in the dorzolamide 2% treatment group discontinued from the study due to an adverse event. The safety profile of dorzolamide is similar to that seen in adults. The types of adverse events seen are those commonly expected with topical ophthalmic medications.

D. Dosing

Dosing for this pediatric trial was based on the currently labeled dosing frequency for adult patients. No further dose ranging was warranted. The currently labeled dosing level and frequency is safe in the pediatric population.

E. Special Populations

The sponsor has adequately addressed the safety and clinical response of this drug product in two age cohorts The two age cohorts analyzed were: "patients < 2 years old" and "patients ≥ 2 years but <6 years old". The effects of gender, race, age and iris color were analyzed during the review of the original NDA. Gender effects were not analyzed in this pediatric supplement because the study population is not large enough to perform this analysis and no effects were found in the original NDA submission. There is no additional data needed in other populations for this drug product. Safety and efficacy have been adequately characterized in the target populations.

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

/s/

Jennifer Harris
4/14/04 01:40:20 PM
MEDICAL OFFICER

Wiley Chambers
4/14/04 02:17:00 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-408 / S-033

MEDICAL REVIEW(S)

CLINICAL REVIEW

Medical Officer's Review of NDA 20-408
Pediatric Supplement

Proprietary Name:	**Trusopt Ophthalmic Solution 2%**
Established Name:	**dorzolamide HCL ophthalmic solution**
Sponsor:	**Merck & Co. Inc** **BLA-20, P.O. Box 2** **West Point, PA 19486**
NDA Supplement:	**SE5**
Proposed Indication:	[ ]

Date of Submission:	October 16, 2003
Date of Review:	February 25, 2004

Table of Contents

Clinical Review for NDA 20-408 Pediatric Supplement

Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 20-408 /SE5-033 is recommended for approval after labeling revisions are made consistent with the recommendations listed in this review. The clinical study contained in this supplement supports the use of dorzolamide 2% in the pediatric population. The benefits of using this drug product outweigh the risks in the treatment of elevated intraocular pressure in pediatric patients.

F [ ]

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Dorzolamide HCL was approved in 1994 as the first topical carbonic anhydrase inhibitor for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or glaucoma. To date the safety and effectiveness of this product has not been established in the pediatric population.

Currently, the only approved drug for the treatment of elevated IOP in the pediatric population is brimonidine tartrate ophthalmic solution. This drug product is labeled for pediatric patients over the age of 2 years old.

A pediatric written request for dorzolamide 2% was issued by the Agency in 1999 with subsequent amendments in 2000 and 2002. The sponsor has conducted a 12-week multicenter, randomized, masked, active-control trial comparing

dorzolamide 2% to timolol GFS in response to this written request. The primary objective of the written request and submitted trial was to obtain data on the safety and clinical response of dorzolamide 2% in the pediatric population.

B. Efficacy

The clinical response data contained in this supplement demonstrates that dorzolamide 2% effectively lowers IOP in the pediatric population. IOP is lowered approximately 7-9mmHg in this population with a baseline IOP of approximately 30 mmHg.

C. Safety

Dorzolamide 2% is safe for use in the pediatric population below the age of 6 years old. Overall, less than 2.5% of patients in the dorzolamide 2% treatment group discontinued from the study due to an adverse event. The safety profile of dorzolamide is similar to that seen in adults. The types of adverse events seen are those commonly expected with topical ophthalmic medications.

D. Dosing

Dosing for this pediatric trial was based on the currently labeled dosing frequency for adult patients. No further dose ranging was warranted. The currently labeled dosing level and frequency is safe in the pediatric population.

E. Special Populations

The sponsor has adequately addressed the safety and clinical response of this drug product in two age cohorts The two age cohorts analyzed were: "patients < 2 years old" and "patients ≥ 2 years but <6 years old". The effects of gender, race, age and iris color were analyzed during the review of the original NDA. Gender effects were not analyzed in this pediatric supplement because the study population is not large enough to perform this analysis and no effects were found in the original NDA submission. There is no additional data needed in other populations for this drug product. Safety and efficacy have been adequately characterized in the target populations.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Proprietary Name :	Trusopt Ophthalmic Solution
Established Name:	dorzolamide HCl ophthalmic solution
Sponsor:	Merck & Co., Inc. BLA-20, P.O. Box 4 West Point PA 19486
NDA Supplement:	SE5
Pharmacologic Category:	carbonic anhydrase inhibitor
Dosage Form and Route of Administration:	Ophthalmic solution for topical ocular administratic
Proposed Indication:	treatment of ntraocular pressure in pediatric patients with glaucoma or ocular hypertension

B. State of Armamentarium for Indication(s)

Dorzolamide HCL was approved in 1994 as the first topical carbonic anhydrase inhibitor for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or glaucoma. To date the safety and effectiveness of this product has not been established in the pediatric population.

Currently, the only approved drug for the treatment of elevated IOP in the pediatric population is brimonidine tartrate ophthalmic solution. This drug product is labeled for pediatric patients over the age of 2 years old.

C. Important Milestones in Product Development

Milestones leading up to this pediatric efficacy supplement submission:

12/9/94 – Original NDA approved
6/24/99 – Original pediatric written request issued by the Agency
5/19/00 – Amended written request issued to revise the age group enrollment criteria.

2/12/02 – Amended written request issued to revise the timeframe for submission of pediatric studies.

D. Other Relevant Information

As of July 7, 2003, dorzolamide HCL has received marketing approval for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma in approximately 69 countries. This product has not been withdrawn from the market in any country as of this date.

E. Important Issues with Pharmacologically Related Agents

There are no safety concerns associated with other topical ophthalmic agents in this pharmacologic class.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There were no new consultant reviews required for this efficacy supplement. Full reviews for all disciplines were completed during the review of the original NDA.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

A full pharmacokinetics review was completed for this product in the original NDA review. No new pharmacokinetic data is contained in this pediatric supplement.

B. Pharmacodynamics

No new pharmacodynamic data is contained in this pediatric supplement.

IV. Description of Clinical Data and Sources

A. Overall Data

This pediatric supplement includes one study (P1001C1) that was conducted at 22 U.S. sites and 13 international sites. This material is contained in NDA 20-408/SE5-033 Volume 1. The materials were submitted in hard copy and electronic formats.

B. Tables Listing the Clinical Trials

Protocol Number	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	Demographics	Total Subjects
P100C1	Multicenter, double-masked, randomized, active-controlled	12 weeks	Pediatric patients with glaucoma or ocular hypertension	Trusopt 2% Timolol GFS 0.25% Timolol GFS 0.5%	TID QD QD	Age (1 month – 6 years) 106 males 78 females	184

C. Postmarketing Experience

The existing postmarketing data available in the adult population has been reviewed by the division. The events reported are consistent with the events reported in the clinical study included in this efficacy supplement.

The sponsor searched their own Worldwide Adverse Experience System (WAES) database for reports of adverse experiences with dorzolamide hydrochloride in patients aged <6 years of age. A total of 8 reports were identified. There were 3 reports of local nonserious adverse experiences; skin irritation, ocular burning and corneal clouding. The corneal clouding resolved with the discontinuation of dorzolamide and did not reappear when dorzolamide was restarted.

Two (2) reports described serious adverse experiences that persisted after dorzolamide was discontinued (metabolic acidosis and respiratory acidosis).

Two (2) cases of presumed dorzolamide overdose were received. One patient developed somnolence that resolved within hours. In another patient, rash, red eye, and dehydration occurred after 8 days of treatment.

D. Literature Review

The sponsor has reviewed the medical literature for adverse events in patients

under the age of six. One report of lethargy, hypotension, and hypothermia in a 4 week old patient was published in the medical literature. The patient was taking dorzolamide, betaxolol and brimonidine drops. This report attributed the adverse events to the use of brimonidine tartrate.

V. Clinical Review Methods

A. How the Review was Conducted

The primary objective of this review was to determine the safety profile of dorzolamide HCL in the pediatric population. Clinical response data was also analyzed; however, the division believes that efficacy for this drug product can be reliably extrapolated from the adult population. Safety was assessed by evaluating the adverse event profile, discontinuation data and the drug specific safety concerns addressed in the pediatric written request. This included vital signs, pulse, blood pressure, alertness, intraocular pressure, visual acuity, dilated ophthalmoscopy and corneal diameter.

B. Overview of Materials Consulted in Review

This review was based on the review of a single trial (P100C1) submitted by the sponsor in both paper and electronic format.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits were not conducted for this efficacy supplement. The data was reviewed internally for consistency with other safety and efficacy data available for this drug product.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

There is no evidence to indicate that this trial was not conducted in accordance with accepted ethical standards. The sponsor attests that the study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

E. Evaluation of Financial Disclosure

The sponsor has certified that they have not entered into any financial arrangement with the clinical investigators of this trial whereby the value of compensation to the investigator could be affected by the outcome of the study.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The clinical response data contained in this supplement demonstrates that dorzolamide 2% effectively lowers IOP in the pediatric population. IOP is lowered approximately 7-9mmHg in this population.

B. General Approach to Review of the Efficacy of the Drug

The purpose of this submission was to determine the safety profile of dorzolamide HCL in the pediatric population. It is the division's view that efficacy for this product can be reliably extrapolated from the existing adult database; therefore, this trial was not designed to establish efficacy. Clinical response data was collected and is presented below along with the study design.

C. Detailed Review of Trials by Indication

Title: Three-Month, Double-Masked, Active Treatment Controlled, Multicenter Study of 2% Dorzolamide T.I.D. and of Timolol Maleate in Gel-Forming Solution Q.D. in Pediatric Patients Age <6 Years With Elevated Intraocular Pressure or Glaucoma

Objective:
Primary
To document an acceptable safety profile for initial therapy with dorzolamide 2% t.i.d. taken for up to 3 months in patients <6 years of age with elevated IOP or glaucoma.

The primary safety endpoint for each treatment group will be the proportion of patients who discontinue therapy due to a drug-related adverse experience prior to completing 3 months of therapy.

Secondary
To characterize the IOP-lowering effect of dorzolamide 2% t.i.d., and the need for additional therapy in patients <6 years of age with elevated IOP or glaucoma. To characterize the effect of dorzolamide 2% t.i.d. on total CO2 in patients <6 years of age with elevated IOP or glaucoma.

Study Design: This was a 3-month, double-masked, active-treatment-controlled, multicenter study to investigate the safety and ocular hypotensive effect of dorzolamide 2% t.i.d. in pediatric glaucoma patients younger than 6 years. Timolol maleate gel-forming solution (timolol GFS) once daily (q.d.) was the active treatment control. Patients were randomized 2:1, dorzolamide to timolol GFS therapy. If IOP was inadequately controlled on monotherapy, a change was made to open-label concomitant therapy of dorzolamide 2% t.i.d. and timolol GFS 0.25% q.d. (for patients <2 years of age) or combination therapy of dorzolamide 2%/ timolol 0.5% twice daily (b.i.d.) (for patients ≥2 years but <6 years of age).

Study Medications:

Dosage	**Formulation Nos.**
Dorzolamide 2% topical	E-9943, E-9990
Dorzolamide placebo topical	E-9887, E-9991
Timolol GFS 0.25% topical	E-9963, E-9994, E-10432
Timolol GFS 0.5% topical	E-9353, E-9995, E-10209
Dorzolamide 2%/Timolol 0.5% topical	E-9817, E-9993

Clinical Sites

Site No.	Investigator	Country	Age Cohort < 2 years		Age Cohort ≥ 2 years but < 6 years	
			Dorzolamide 2% (N=56)	Timolol GFS 0.25% (N=27)	Dorzolamide 2% (N=66)	Timolol GFS 0.5% (N=35)
100004	Coats, David K.	U.S.	1	0	2	2
100005	Gandham, Sai B.	U.S.	1	0	0	1
100009	Lueder, Gregg T.	U.S.	3	2	2	1
100010	Medow, Norman B.	U.S.	0	1	2	0
100011	Mills, Monte D.	U.S.	1	0	2	2
100012	Plager, David A.	U.S.	3	1	5	2
100013	Samples, John R.	U.S.	0	0	1	0
100014	Scher, Colin Allen	U.S.	0	0	0	1
100015	Summers, C. Gail	U.S.	3	1	2	1
100016	Wilson, M. Edward	U.S.	1	0	3	1
100017	Zwaan, Johan T.	U.S.	3	2	1	1
100018	May, Michael J.	U.S.	1	0	0	0
100019	Godfrey, David G.	U.S.	0	0	2	1
100022	Wright, Kenneth W.	U.S.	4	2	0	0
100023	Kubacki, Joseph J.	U.S.	0	0	1	0
100027	Song, Jonathan C.	U.S.	3	3	4	2
125001	Aquino, Norman M.	Philippines	5	2	4	2
125002	Hurtado, Maria Isabel	Colombia	0	0	2	1
125004	Arango, Santiago	Colombia	8	3	6	4
125005	Galvez, Flor	Peru	2	1	2	1
125006	Debess, Pedro	Venezuela	0	1	1	0
125007	Spagarino, Manuela	Venezuela	2	0	1	1
125009	Rodriguez, Manuel	Mexico	1	0	2	1

2. History or evidence of goniotomy or trabeculotomy within 1 month of study start, filtration or implant surgery within 3 months of study start, or cyclodestructive surgery within 3 months of study start. Patients may have had intraocular laser surgery up to 3 months prior to study start.
3. History or evidence of significant ocular trauma within 3 months prior to study start.
4. Evidence of acute or recent ocular inflammation and/or infection within 1 month prior to study start.
5. Chronic conjunctivitis, chronic keratitis, or lacrimal deficiency.

Pharmacologic

1. Concomitant systemic or topical nonocular medication known to affect intraocular pressure.
2. Participation in a study involving an investigational drug within 4 weeks prior to study start.

General/Systemic

1. History of hypersensitivity to any components of dorzolamide or timolol GFS ophthalmic solutions; known severe or serious hypersensitivity to sulfonamides.
2. Any contraindication to the use of timolol GFS ophthalmic solutions.
3. History or evidence of impaired renal function.

Safety Assessment

The primary study objective was to document an acceptable safety profile for initial therapy with dorzolamide 2% taken for up to 3 months in patients 1 week to <2 years and in patients ≥2 years but <6 years of age. The primary measure of safety for each group was the proportion of patients who discontinued therapy due to a drug-related adverse experience prior to completing 3 months of therapy.

Safety Measures Assessed:

Ocular Examinations (visual acuity, biomicroscopy, dilated fundus exam)
Vital Signs (blood pressure, pulse and respiratory rate)
Alertness Assessment
Laboratory test (CO_2)
Physical Examination
Adverse Experience monitoring

Efficacy Assessment

The efficacy objective of this 3-month study was to characterize the IOP lowering effect of dorzolamide 2% t.i.d., and the need for additional therapy. IOP was measured on Study Day 1, and Weeks 1, 4, and 12, and on Weeks 2 or 5 if a change in therapy was implemented.

Study Schedule

Procedure	Prestudy Screening Day –21 to –1	Study Day 1, Weeks 1, 4, 12[#]	Weeks 2 or 5 if change in therapy was made	Poststudy visit
Ocular and medical history	X			
Physical examination	X[+]			X
Alertness assessment	X	X	X	
Visual acuity	X	X	X	
External and anterior ocular examination	X	X	X	
Intraocular pressure	X	X	X	
Corneal diameter measurements*		X		
Lens and ophthalmoscopy	X			X
Patient Report Card		X	X	X
Vital signs	X	X	X	
Total CO_2		X[@]		
Adverse experience monitoring		X	X	X

[#] Week 12 and Poststudy examinations were to be completed for patients who discontinued prior to Week 12
[+] A complete physical examination by a pediatrician, if not already performed within 3 months of study start.
[*] Corneal diameter measurements were performed on Study Day 1 and Week 12.
[@] Total CO2 levels were to be measured at Study Day 1 and Week 12.

Subject Disposition and Demographics

Patient Disposition (Age Cohort < 2 years)

	Dorzolamide 2%	Timolol GFS 0.25%
Entered (Randomized)	56	27
Masked Monotherapy Phase		
Completed	28	16
Discontinued	6	3
Patient switched to open-label concomitant therapy	22	8
Open-label Concomitant therapy Phase		
Completed	15	7
Discontinued	7	1

Patient Disposition (Age Cohort≥2 years but 6 years)

	Dorzolamide 2%	Timolol GFS 0.25%
Entered (Randomized)	66	35
Masked Monotherapy Phase		
Completed	41	21
Discontinued	6	3
Patient switched to open-label concomitant therapy	19	11
Open-label Concomitant therapy Phase		
Completed	12	7
Discontinued	7	4

Reviewer's Comments:
Approximately 30-40% of patients in each treatment group for both age cohorts were switched to concomitant therapy due to lack of IOP control on monotherapy.

Discontinued Patients and Reason

Patient	Age	Treatment	Reason	Days in Study
2003	2	Dorzolamide 2%	IOP not controlled - surgery	62
2009	7 months	Dorzolamide 2%	IOP not controlled - surgery	39
2031	11 months	Dorzolamide 2%	IOP not controlled - surgery	6
2033	6 months	Dorzolamide 2%	IOP not controlled - surgery	14
2034	1 month	Dorzolamide 2%	IOP not controlled - surgery	21
2044	1	Dorzolamide 2%	IOP not controlled - medication	78
2049	1	Dorzolamide 2%	bradycardia	113
2053	4 months	Dorzolamide 2%	IOP not controlled – surgery	28
2058	2 months	Dorzolamide 2%	IOP not controlled – surgery	3
2079	1	Dorzolamide 2%	IOP not controlled – surgery	4
2094	3 months	Dorzolamide 2%	Lost to follow-up	35
2182	4	Dorzolamide 2%	IOP not controlled – surgery	50
2187	2	Dorzolamide 2%	IOP not controlled – surgery	73
2212	4	Dorzolamide 2%	IOP not controlled – surgery	49
2243	3	Dorzolamide 2%	IOP not controlled – surgery	42
2331	6 months	Dorzolamide 2%	Withdrew consent	89
2342	2 months	Dorzolamide 2%	IOP not controlled – surgery	119
2351	6 months	Dorzolamide 2%	Withdrew consent	17
2355	1	Dorzolamide 2%	IOP not controlled – surgery	15
2385	1	Dorzolamide 2%	IOP not controlled – surgery	16
2389	2 months	Dorzolamide 2%	IOP not controlled – medication	16
2508	5	Dorzolamide 2%	IOP not controlled – surgery	29
2527	4	Dorzolamide 2%	Loss of appetite, malaise, eye pain/redness	61
2535	4	Dorzolamide 2%	Withdrew consent	14
2541	4	Dorzolamide 2%	IOP not controlled – medication	51
2554	2	Dorzolamide 2%	Eye burning/itching	97
2557	2	Dorzolamide 2%	IOP not controlled – medication	15
2580	4	Dorzolamide 2%	IOP not controlled – surgery	16

Patient	Age	Treatment	Reason	Days in Study
2585	5	Dorzolamide 2%	IOP not controlled – surgery	32
2002	6 months	Timolol GFS 0.25%	IOP not controlled – medication	9
2032	2 months	Timolol GFS 0.25%	Corneal diameter/IOP decrease	111
2334	1	Timolol GFS 0.25%	bronchospasm	19
2341	1	Timolol GFS 0.25%	IOP not controlled – surgery	85
2381	1	Timolol GFS 0.25%	IOP not controlled – surgery	16
2161	5	Timolol GFS 0.5%	IOP not controlled – surgery	36
2181	4	Timolol GFS 0.5%	Glaucomatous cupping	50
2189	3	Timolol GFS 0.5%	Eye redness	8
2213	2	Timolol GFS 0.5%	IOP not controlled – surgery	19
2244	4	Timolol GFS 0.5%	IOP not controlled – medication	29
2551	5	Timolol GFS 0.5%	IOP not controlled – medication/completed	88
2555	5	Timolol GFS 0.5%	IOP not controlled – surgery	36
2565	4	Timolol GFS 0.5%	Withdrew consent	37

Reviewer's Comment:

The majority of patients, 30 (73%), discontinued the study due to poor IOP control. Seventy-three (73%) of these patients were in the dorzolamide treatment group versus 8% in the timolol group.

Baseline Patient Characteristics by Treatment Group (Age Cohort < 2 years)

	Dorzolamide 2% (N=56)	Timolol GFS 0.25% (N=27)
Gender		
Male	35 (62.5%)	20 (74.1%)
Female	21 (37.5%)	7 (25.9%)
Race		
Asian	5 (8.9%)	2 (7.4%)
Bi-racial	1 (1.8%)	0
Black	4 (7.1%)	2 (7.4%)
Caucasian	16 (28.6%)	7 (25.9%)
Egyptian	8 (14.3%)	4 (14.8%)
Hispanic	22 (39.3%)	11 (40.7%)
Hispanic/White	0	1 (3.7%)
Age (months)		
Mean	9.7	11.5
Range	1 to 23	0.25 to 22
Iris Color		
Blue	10 (17.9%)	8 (29.6%)
Brown	20 (35.7%)	9 (33.3%)
Dark brown	22 (39.3%)	8 (29.6%)
Hazel	1 (1.8%)	0
Other*	3 (5.4%)	2 (7.4%)
Baseline IOP (mmHg) – Worse Eye		
Mean	32.6	29.9
range	17.3 to 64	14 to 48.7

*other = aniridia or unable to evaluate

Reviewer's Comment:

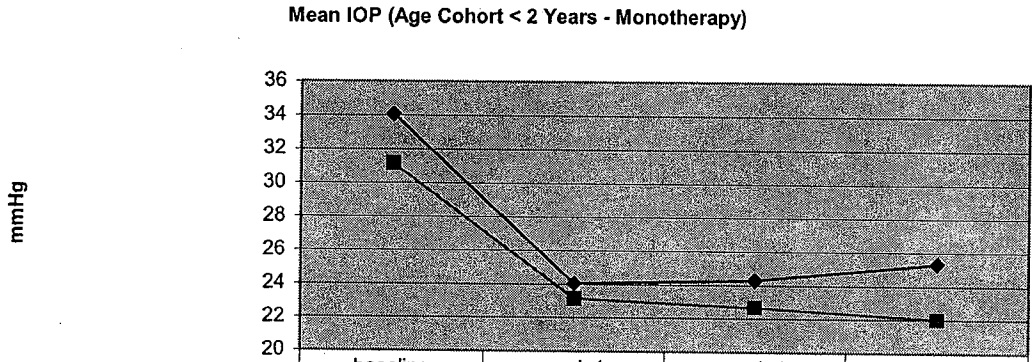
The treatment groups were well balanced at baseline for both age cohorts.

Baseline Patient Characteristics by Treatment Group (Age Cohort ≥2 years but < 6 years)

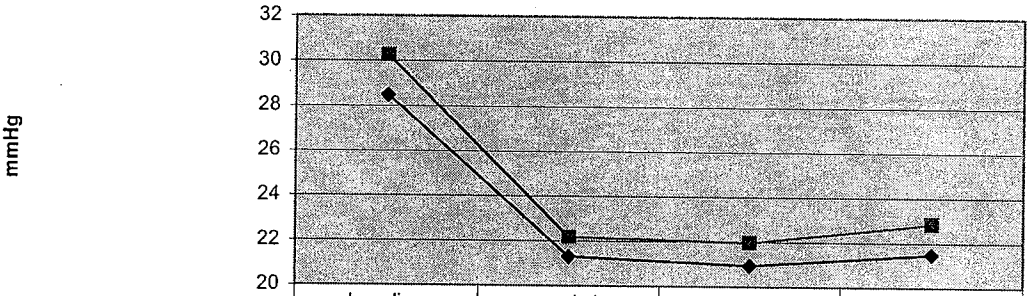
	Dorzolamide 2% (N=56)	Timolol GFS 0.25% (N=27)
Gender		
Male	33 (50%)	18 (51.4%)
Female	33 (50%)	17 (48.6%)
Race		
Asian	5 (7.6%)	2 (5.7%)
Black	4 (6.1%)	1 (2.9%)
Caucasian	23 (34.8%)	14 (40.0%)
Egyptian	8 (12.1%)	4 (11.4%)
Hispanic	26 (39.4%)	12 (34.3%)
Indian	0	2 (5.7%)
Age (years)		
Mean	3.4	3.5
Range	2 to 6	2 to 6
Iris Color		
Blue	9 (13.6%)	7 (20%)
Brown	19 (28.8%)	7 (20%)
Dark brown	26 (39.4%)	15 (42.9%)
Green	1 (1.5%)	0
Hazel	6 (9.1%)	3 (8.6%)
Other*	5 (7.6%)	3 (8.6%)
Baseline IOP (mmHg) – Worse Eye		
Mean	28.7	30.3
range	18 - 55	22 – 45.5

*other = aniridia or unable to evaluate

Clinical Response Analyses



	baseline	week 1	week 4	week 12
dorzolamide HCL 2%	34.07	24.05	24.3	25.33
timolol GFS 0.25%	31.15	23.15	22.67	22.03

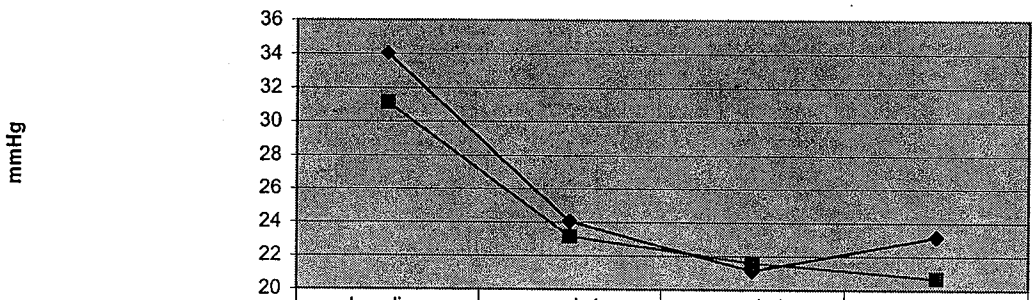


	baseline	week 1	week 4	week 12
dorzolamide HCL 2%	28.49	21.32	20.96	21.49
timolol GFS 0.5%	30.26	22.19	21.97	22.85

Reviewers Comments:

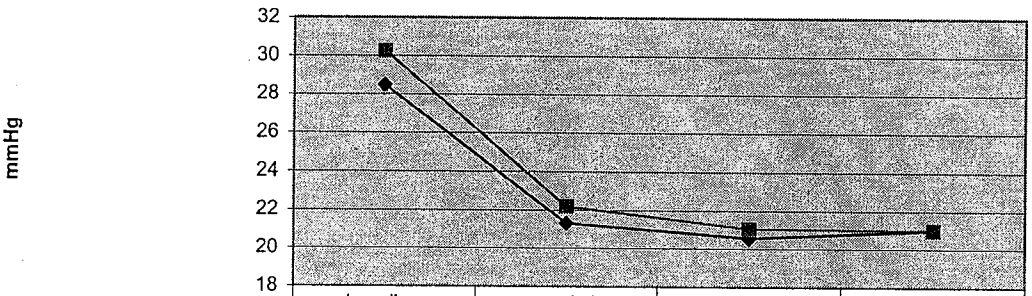
Dorzolamide 2% and timolol GFS have similar IOP lowering ability in the pediatric population. Both drugs lower IOP of approximately 7-9mmHg. The response was similar in both the age groups (i.e. < 2 and ≥ 2 but < 6 years of age).

Mean IOP (Age Cohort < 2 Years - Overall)



	baseline	week 1	week 4	week 12
dorzolamide HCL 2%	34.07	24.05	21.12	23.15
timolol GFS 0.25%	31.15	23.15	21.6	20.68

Mean IOP (Age Cohort >= 2 Years but < 6 Years - Overall)



	baseline	week 1	week 4	week 12
dorzolamide HCL 2%	28.49	21.32	20.57	20.99
timolol GFS 0.5%	30.26	22.19	21.06	21

D. Efficacy Conclusions

It was the division's view that efficacy for this product could be reliably extrapolated from the existing adult database. The clinical response data contained in this study confirms that dorzolamide 2% effectively lowers IOP in pediatric patients under the age of 6.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Dorzolamide 2% is safe for use in the pediatric population below the age of 6 years old. Overall, less than 2.5% of patients in the dorzolamide 2% treatment group discontinued from the study due to an adverse event. The safety profile of dorzolamide is similar to that seen in adults. The types of adverse events seen are those commonly expected with topical ophthalmic medications.

B. Description of Patient Exposure

Age Cohort <2 Years

Monotherapy Phase
Twenty-nine (29) patients took dorzolamide 2% BID for at least 61 days. Sixteen (16) patients took timolol GFS 0.25% QD for at least 61 days.

Concomitant Therapy Phase
Twenty-one (21) patients took dorzolamide 2% TID and timolol GFS 0.25% QD for at least 41 days of the study.

Age Cohort ≥2 Years but <6 Years

Monotherapy Phase
Forty-two (42) patients took dorzolamide 2% TID for at least 61 days. Twenty one (21) patients took timolol GFS 0.5% QD for at least 61 days.

Combination Therapy Phase
Eighteen (18) patients took the dorzolamide 2%/timolol 0.5% combination BID for at least 51 days.

C. Methods and Specific Findings of Safety Review

The primary objective of study P100C1 was to document an acceptable safety profile for initial therapy with dorzolamide 2% taken for up to 3 months in patients 1 week to <2 years and in patients ≥ 2 years but < 6 years of age. The primary measure of safety for each group was the proportion of patients who discontinued therapy due to a drug-related adverse experience prior to completing 3 months of therapy.

Primary Safety Variable

In the age cohort <2 years, 1 patient (1.79%) of 56 initially randomized to the dorzolamide 2% treatment group discontinued study therapy due to a drug-related adverse event. None of the 27 patients initially randomized to the timolol GFS 0.25% treatment group discontinued study therapy due to a drug-related adverse experience.

The drug related adverse event was experienced by a patient (AN 2049) in the dorzolamide 2% group who switched to open-label concomitant therapy (dorzolamide/timolol) on study day 8 because of inadequate IOP control. A drug-related serious adverse experience of bradycardia was observed on study day 24. Timolol administration was discontinued for the patient on the same day that the bradycardia was noted, but the patient was continued on dorzolamide 2% monotherapy. The bradycardia resolved after 8 days, and the subject continued on dorzolamide 2% monotherapy.

Discontinuations Due to Adverse Experiences (Age Cohort < 2 years)

	Dorzolamide 2% (N=56)	**Timolol GFS 0.25% (N=27)**
Masked Monotherapy Phase		
Discontinued due to any drug-related adverse experience[+]	0	0
Discontinued due to any adverse event	0	2 (7.4%)
Open-Label Concomitant Therapy Phase	N=22	N=9
Discontinued due to any drug-related adverse experience[+]	1 (4.6%)	0
Discontinued due to any adverse event	1 (4.6%)	0

[+] determined by the investigator to possibly, probably, or definitely drug related.

In the age cohort ≥2 years but <6 years, 2 patients (3.03%) of 66 initially randomized to the dorzolamide 2% treatment group discontinued study therapy due to a drug-related adverse experience. Both of these patients discontinued due to at least one of the following adverse experiences: eye pain, ocular injection, burning/stinging eye, or eye itching associated with dorzolamide 2% monotherapy treatment. One (2.86%) of the 35 patients initially randomized to the timolol GFS 0.25% treatment group discontinued study therapy due to the drug-related adverse experience of ocular injection.

Discontinuations Due to Adverse Experiences (Age Cohort ≥ 2 years but < 6 years)

	Dorzolamide 2% (N=66)	**Timolol GFS 0.25% (N=35)**
	N (%)	N (%)
Masked Monotherapy Phase		
Discontinued due to any drug-related adverse experience[+]	2 (3%)	1 (3%)
Discontinued due to any adverse event	2 (3%)	2 (5.7%)
Open-Label Concomitant Therapy Phase	N=19	N=11
Discontinued due to any drug-related adverse experience[+]	0	0
Discontinued due to any adverse event	0	0

[+] determined by the investigator to possibly, probably, or definitely drug related.

Reviewer's comments:
Overall, less than 2.5% of patients in the dorzolamide 2% treatment group discontinued from the study due to an adverse event compared to the discontinuation rate in the timolol GFS group of 6.5%.

Adverse Events Leading to Discontinuation

Patient	Treatment	Age	Reason	Day of Onset	Days in Study	Phase
02049	Dorzolamide 2%	1 year	Bradycardia	24	113	Concomitant
02527	Dorzolamide 2%	4 years	Loss of appetite, malaise, eye pain, eye redness	32	61	Monotherapy
02554	Dorzolamide 2%	2 years	Eye burning, eye itching	1	97	Monotherapy
02032	Timolol GFS 0.25%	2 months	Decrease corneal diameter, decreased IOP	31	111	Monotherapy
02334	Timolol GFS 0.25%	1 year	Bronchospasm	17	19	Monotherapy
02181	Timolol GFS 0.5%	4 years	Glaucomatous cupping	49	50	Monotherapy
02189	Timolol GFS 0.5%	3 years	Eye redness	4	8	Monotherapy

Clinical Adverse Event Experiences

Adverse Events in Age Cohort <2 Years

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence > 0 % in One or More Treatment Groups) by Body System (Age Cohort <2 Years)

	Masked Monotherapy Phase				Open-label Concomitant Therapy Phase Dorzolamide 2% + Timolol GFS 0.25% (N=31)			
	Dorzolamide 2% (N=56)		Timolol GFS 0.25% (N=27)		Dorzolamide 2% (m=22)		Timolol GFS 0.25% (m=9)	
	n	(%)	n	(%)	n	(%)‡	n	(%)‡
Patients with one or more adverse experiences	42	(75.0)	17	(63.0)	16	(72.7)	7	(77.8)
Patients with no adverse experience	14	(25.0)	10	(37.0)	6	(27.3)	2	(22.2)
Body as a Whole/Site Unspecified	**18**	**(32.1)**	**5**	**(18.5)**	**1**	**(4.5)**	**3**	**(33.3)**
Infection, viral	1	(1.8)	0	0	0	0	0	0
Infection, RSV	1	(1.8)	0	0	0	0	0	0
Fever	14	(25.0)	5	(18.5)	1	(4.5)	3	(33.3)
Hyperemia	1	(1.8)	0	0	0	0	0	0
Pain, abdominal	1	(1.8)	0	0	0	0	0	0
Failure to thrive	1	(1.8)	0	0	0	0	0	0
Pain, postoperative	1	(1.8)	0	0	0	0	0	0
Cardiovascular System	**0**	**(0)**	**0**	**(0)**	**1**	**(4.5)**	**0**	**(0)**
Bradycardia	0	(0)	0	(0)	1	(4.5)	0	(0)
Digestive System	**13**	**(23.2)**	**2**	**(7.4)**	**5**	**(22.7)**	**2**	**(22.2)**
Anorexia	3	(5.4)	0	(0)	0	(0)	0	(0)
Constipation	2	(3.6)	0	(0)	0	(0)	1	(11.1)
Diarrhea	10	(17.9)	1	(3.7)	3	(13.6)	1	(11.1)
Vomiting	3	(5.4)	0	(0)	2	(9.1)	0	(0)
Enterocolitis, pseudomembranous	0	(0)	0	(0)	1	(4.5)	0	(0)
Gastroenteritis	1	(1.8)	1	(3.7)	1	(4.5)	0	(0)
Stomatitis	0	(0)	0	(0)	1	(4.5)	0	(0)
Ulcer, mouth	1	(1.8)	0	0	0	0	0	0
Pain, dental	1	(1.8)	0	0	0	0	0	0
Hemic and Lymphatic System	**1**	**(1.8)**	**0**	**(0)**	**0**	**(0)**	**1**	**(11.1)**
Anemia	1	(1.8)	0	0	0	0	0	0
Anemia, hypochromic	0	(0)	0	(0)	0	(0)	1	(11.1)
Metabolic/Nutritional/Immune	**1**	**(1.8)**	**1**	**(3.7)**	**2**	**(9.1)**	**0**	**(0)**
Hypovolemia	1	(1.8)	0	0	0	0	0	0
Nutritional abnormality	0	(0)	0	(0)	1	(4.5)	0	(0)
Weight loss	0	(0)	1	(3.7)	1	(4.5)	0	(0)
Musculoskeletal System	**0**	**(0)**	**1**	**(3.7)**	**1**	**(4.5)**	**0**	**(0)**
Pain, foot	0	(0)	1	(3.7)	0	(0)	0	(0)
Sprain, wrist	0	(0)	0	(0)	1	(4.5)	0	(0)
Nervous System and Psychiatric	**6**	**(10.7)**	**2**	**(7.4)**	**2**	**(9.1)**	**1**	**(11.1)**
Hemiplegia	1	(1.8)	0	0	0	0	0	0
Developmental Delay	1	(1.8)	0	0	0	0	0	0
Seizure disorder	1	(1.8)	0	0	0	0	0	0
Depression	1	(1.8)	0	0	0	0	0	0
Anxiety	1	(1.8)	0	0	0	0	0	0
Behavior disturbance	1	(1.8)	0	0	0	0	0	0
Pseudotumor cerebri	0	(0)	0	(0)	0	(0)	1	(11.1)
Intracranial pressure increased	0	(0)	0	(0)	0	(0)	1	(11.1)

	Masked Monotherapy Phase				Open-label Concomitant Therapy Phase Dorzolamide 2% + Timolol GFS 0.25% (N=31)			
	Dorzolamide 2% (N=56)		Timolol GFS 0.25% (N=27)		Dorzolamide 2% (m=22)		Timolol GFS 0.25% (m=9)	
	n	(%)	n	(%)	n	(%)‡	n	(%)‡
Somnolence	0	(0)	0	(0)	1	(4.5)	0	(0)
Irritability	1	(1.8)	1	(3.7)	1	(4.5)	0	(0)
Hypersomnia	0	(0)	1	(3.7)	0	(0)	0	(0)
Insomnia	1	(1.8)	0	0	0	0	0	0
Respiratory System	**25**	**(44.6)**	**9**	**(33.3)**	**8**	**(36.4)**	**4**	**(44.4)**
Bronchoconstriction	0	(0)	1	(3.7)	0	(0)	0	(0)
Bronchitis	2	(3.6)	2	(7.4)	0	(0)	1	(11.1)
Bronchitis, chronic	0	(0)	0	(0)	0	(0)	1	(11.1)
Bronchial disorder	1	(1.8)	0	0	0	0	0	0
Congestion, nasal	3	(5.4)	0	(0)	1	(4.5)	0	(0)
Congestion, pulmonary	0	(0)	0	(0)	1	(4.5)	0	(0)
Cough	12	(21.4)	6	(22.2)	2	(9.1)	0	(0)
Infection, respiratory, upper	7	(12.5)	4	(14.8)	2	(9.1)	2	(22.2)
Influenza	4	(7.1)	1	(3.7)	2	(9.1)	1	(11.1)
Pharyngitis	2	(3.6)	0	(0)	0	(0)	1	(11.1)
Pneumonia	3	(5.4)	0	(0)	1	(4.5)	0	(0)
Rhinitis	2	(3.6)	0	(0)	1	(4.5)	1	(11.1)
Rhinorrhea	2	(3.6)	1	(3.7)	0	(0)	0	(0)
Sinusitis	0	(0)	0	(0)	1	(4.5)	0	(0)
Tonsillitis	0	(0)	1	(3.7)	0	(0)	0	(0)
Skin & Skin Appendage	**5**	**(8.9)**	**3**	**(11.1)**	**3**	**(13.6)**	**0**	**(0)**
Alopecia	0	(0)	0	(0)	1	(4.5)	0	(0)
Flushing	0	(0)	1	(3.7)	0	(0)	0	(0)
Infection, would, postoperative	1	(1.8)	0	0	0	0	0	0
Laceration	0	(0)	1	(3.7)	0	(0)	0	(0)
Rash	4	(7.1)	1	(3.7)	2	(9.1)	0	(0)
Special Senses	**20**	**(35.7)**	**10**	**(37.0)**	**12**	**(54.5)**	**3**	**(33.3)**
Blepharitis	1	(1.8)	1	(3.7)	0	(0)	0	(0)
Burning/stinging, eye	1	(1.8)	0	(0)	1	(4.5)	0	(0)
Cataract	0	(0)	0	(0)	1	(4.5)	0	(0)
Conjunctivitis	2	(3.6)	0	(0)	2	(9.1)	0	(0)
Conjunctivitis, bacterial	1	(1.8)	0	(0)	1	(4.5)	0	(0)
Corneal enlargement	2	(3.6)	0	(0)	0	(0)	0	(0)
Corneal diameter decrease	0	(0)	1	(3.7)	0	(0)	0	(0)
Detachment, retinal	0	(0)	1	(3.7)	0	(0)	0	(0)
Discharge, eye	3	(5.4)	3	(11.1)	1	(4.5)	1	(11.1)
Edema, corneal	1	(1.8)	1	(3.7)	0	(0)	0	(0)
Edema, eyelid	2	(3.6)	0	(0)	1	(4.5)	1	(11.1)
Epiphora	0	(0)	0	(0)	0	(0)	1	(11.1)
Haze, corneal	2	(3.6)	0	(0)	1	(4.5)	0	(0)
Infection, eye	0	(0)	0	(0)	1	(4.5)	1	(11.1)
Injection, ocular	4	(7.1)	3	(11.1)	1	(4.5)	2	(22.2)
Intraocular pressure decrease	0	(0)	1	(3.7)	0	(0)	0	(0)
Irritation, eye	0	(0)	2	(7.4)	1	(4.5)	0	(0)
Inflammation, eyelid	1	(1.8)	1	(3.7)	1	(4.5)	0	(0)
Itching, eye	1	(1.8)	0	0	0	0	0	0
Opacity, corneal	0	(0)	0	(0)	0	(0)	1	(11.1)
Otitis	2	(3.6)	0	(0)	1	(4.5)	0	(0)
Otitis media	1	(1.8)	0	(0)	1	(4.5)	1	(11.1)
Pain, eye	1	(1.8)	0	0	0	0	0	0
Rupture, Descemet's membrane	0	(0)	0	(0)	0	(0)	1	(11.1)
Swelling, eye	1	(1.8)	1	(3.7)	0	(0)	0	(0)

	Masked Monotherapy Phase				Open-label Concomitant Therapy Phase Dorzolamide 2% + Timolol GFS 0.25% (N=31)			
	Dorzolamide 2% (N=56)		Timolol GFS 0.25% (N=27)		Dorzolamide 2% (m=22)		Timolol GFS 0.25% (m=9)	
	n	(%)	n	(%)	n	(%)‡	n	(%)‡
Tearing	2	(3.6)	1	(3.7)	0	(0)	1	(11.1)
Urogenital System	**1**	**(1.8)**	**0**	**(0)**	**0**	**(0)**	**1**	**(11.1)**
Infection, urinary tract	1	(1.8)	0	(0)	0	(0)	1	(11.1)

† Indicates total number of patients (across treatments) who switched to open-label combination therapy.
‡ The percent = Number of patients in each category (n)/ number of patients who switched to open-label combination therapy (m), based on the therapy to which the patient was randomized in the monotherapy phase.

Reviewer's Comments:
There is a higher rate of adverse reactions in the dorzolamide 2% treatment group during monotherapy. This is no longer present during the concomitant therapy phase. The rates appear to be equivalent. There is a four-fold higher rate of diarrhea in the dorzolamide 2% treatment group during the monotherapy phase. This difference is no longer present during concomitant treatment.

Monotherapy Phase
The most common clinical adverse experiences in both treatment groups were fever, cough, and upper respiratory infections. A greater proportion of patients who were randomized to dorzolamide 2% had a digestive system adverse experience compared with the timolol GFS 0.25% group (23.2% versus 7.4%). Specifically, more patients randomized to dorzolamide 2% reported diarrhea (17.9% versus 3.7%). A greater proportion of patients who were randomized to timolol GFS 0.25% had eye discharge (11.1% versus 5.4%) and eye irritation (7.4% versus 0%) compared with the dorzolamide 2% group.

Concomitant Therapy Phase
The most common clinical adverse experience was diarrhea in the dorzolamide 2% group and fever in the timolol GFS 0.25% group. A greater proportion of patients who were initially randomized to dorzolamide 2% had vomiting (9.1% versus 0%), cough (9.1% versus 0%), and conjunctivitis (9.1% versus 0%) compared with the timolol GFS 0.25% group. A greater proportion of these patients also had a skin & skin appendage disorder (13.6% versus 0%); specifically, 2 patients initially randomized to dorzolamide 2% reported rash (9.1% versus 0%). Neither of these 2 patients discontinued the study due to the adverse experience of rash. A greater proportion of patients who were randomized to timolol GFS 0.25% had fever (33.3% versus 4.5%), upper respiratory infection (22.2% versus 9.1%), and ocular injection (22.2% versus 4.5%) compared with the dorzolamide 2% group.

Adverse Events in Age Cohort >2 Years but <6 Years

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence > 0 % in One or More Treatment Groups) by Body System (Age Cohort ≥2 Years but <6 Years)

	Masked Monotherapy Phase				Open-Label Combination Therapy Phase Dorzolamide 2% + Timolol 0.5% (N=30)†			
	Dorzolamide 2% (N=66)		Timolol GFS 0.5% (N=35)		Dorzolamide 2% (m=19)		Timolol GFS 0.5% (m=11)	
	n	(%)	n	(%)	n	(%)‡	n	(%)‡
Patients with one or more adverse experiences	50	(75.8)	24	(68.6)	8	(42.1)	9	(81.8)
Patients with no adverse experience	16	(24.2)	11	(31.4)	11	(57.9)	2	(18.2)
Body as a Whole/Site Unspecified	**14**	**(21.2)**	**10**	**(28.6)**	**2**	**(10.5)**	**3**	**(27.3)**
Cold sensation	0	0	1	(2.9)	0	0	0	0
Edema, swelling	1	1.5	0	0	0	0	0	0
Fever	11	(16.7)	9	(25.7)	0	(0)	3	(27.3)
Infection, viral	1	(1.5)	0	(0)	1	(5.3)	0	(0)
Malaise	1	1.5	0	0	0	0	0	0
Pain, abdominal	2	(3.0)	0	(0)	0	(0)	0	(0)
Pain, postoperative	0	(0)	0	(0)	1	(5.3)	0	(0)
Trauma	0	0	1	(2.9)	0	0	0	0
Cardiovascular System	**0**	**0**	**1**	**(2.9)**	**0**	**0**	**0**	**0**
Hypertension	0	0	1	(2.9)	0	0	0	0
Tachycardia	0	0	1	(2.9)	0	0	0	0
Digestive System	**14**	**(21.2)**	**6**	**(17.1)**	**2**	**(10.5)**	**3**	**(27.3)**
Anorexia	2	(3.0)	1	(2.9)	0	(0)	0	(0)
Constipation	0	(0.0)	1	(2.9)	1	(5.3)	0	(0)
Dental caries	0	(0)	0	(0)	0	(0)	1	(9.1)
Diarrhea	7	(10.6)	4	(11.4)	1	(5.3)	2	(18.2)
Nausea	1	(1.5)	1	(2.9)	0	0	0	0
Vomiting	6	(9.1)	1	(2.9)	1	(5.3)	1	(9.1)
Gastroenteritis, infectious	1	1.5	0	0	0	0	0	0
Gastroenteritis	0	0	1	(2.9)	0	0	0	0
Stomatitis	1	1.5	0	0	0	0	0	0
Hemic and Lymphatic	**1**	**(1.5)**	**0**	**0**	**0**	**0**	**0**	**0**
Lymphadenopathy	1	(1.5)	0	0	0	0	0	0
Metabolic/Nutritional/Immune	**0**	**0**	**1**	**(2.9)**	**0**	**0**	**0**	**0**
Dehydration	0	0	1	(2.9)	0	0	0	0
Musculoskeletal System	**1**	**(1.5)**	**0**	**(0.0)**	**1**	**(5.3)**	**0**	**(0)**
Fracture	1	1.5	0	0	0	0	0	0
Pain, neck	0	(0)	0	(0)	1	(5.3)	0	(0)
Nervous System and Psychiatric	**10**	**(15.2)**	**3**	**(8.6)**	**1**	**(5.3)**	**0**	**(0)**
Headache	7	(10.6)	2	(5.7)	1	(5.3)	0	(0)
Somnolence	1	(1.5)	2	(5.7)	0	(0)	0	(0)
Anxiety	0	0	1	(2.9)	0	0	0	0
Agitation	1	1.5	0	0	0	0	0	0
Irritability	1	1.5	0	0	0	0	0	0
Respiratory System	**29**	**(43.9)**	**11**	**(31.4)**	**3**	**(15.8)**	**3**	**(27.3)**
Bronchitis	2	(3.0)	1	(2.9)	0	(0)	0	(0)
Congestion, nasal	0	(0)	0	(0)	1	(5.3)	0	(0)
Cough	10	(15.2)	3	(8.6)	0	(0)	1	(9.1)
Infection, respiratory, upper	12	(18.2)	5	(14.3)	0	(0)	1	(9.1)
Influenza	7	(10.6)	2	(5.7)	0	(0)	1	(9.1)

	Masked Monotherapy Phase				Open-Label Combination Therapy Phase Dorzolamide 2% + Timolol 0.5% (N=30)†			
	Dorzolamide 2% (N=66)		Timolol GFS 0.5% (N=35)		Dorzolamide 2% (m=19)		Timolol GFS 0.5% (m=11)	
	n	(%)	n	(%)	n	(%)‡	n	(%)‡
Pharyngitis	2	(3.0)	0	(0.0)	1	(5.3)	0	(0)
Pneumonia	0	(0)	0	(0)	0	(0)	1	(9.1)
Rhinitis	4	(6.1)	1	(2.9)	0	(0)	0	(0)
Rhinorrhea	5	(7.6)	3	(8.6)	1	(5.3)	0	(0)
Sinus disorder	2	(3.0)	0	(0.0)	0	(0)	0	(0)
Sneezing	1	1.5	0	0	0	0	0	0
Hoarseness	1	1.5	0	0	0	0	0	0
Skin & Skin Appendage	**5**	**(7.6)**	**2**	**(5.7)**	**1**	**(5.3)**	**1**	**(9.1)**
Bite/sting, nonvenomous	0	(0)	0	(0)	1	(5.3)	0	(0)
Contusion	0	0	1	(2.9)	0	0	0	0
Dry skin	0	(0)	0	(0)	1	(5.3)	0	(0)
Varicella	1	1.5	0	0	0	0	0	0
Impetigo	1	1.5	0	0	0	0	0	0
Dermatitis, contact	1	1.5	0	0	0	0	0	0
Pallor	0	(0)	0	(0)	0	(0)	1	(9.1)
Rash	2	(3.0)	1	(2.9)	0	(0)	0	(0)
Sunburn	1	1.5	0	0	0	0	0	0
Sweating	0	(0)	0	(0)	0	(0)	1	(9.1)
Special Senses	**22**	**(33.3)**	**13**	**(37.1)**	**3**	**(15.8)**	**5**	**(45.5)**
Blurred Vision	1	(1.5)	0	(0)	0	(0)	0	(0)
Burning/stinging, eye	9	(13.6)	3	(8.6)	0	(0)	1	(9.1)
Conjunctivitis	2	(3.0)	2	(5.7)	1	(5.3)	1	(9.1)
Conjunctivitis, bacterial	1	1.5	0	0	0	(0)	0	(0)
Conjunctivitis, follicular	0	(0)	1	(2.9)	0	(0)	0	(0)
Conjunctival disorder	1	1.5	0	(0)	0	0	0	(0)
Cupping, optic disc	0	(0.0)	1	(2.9)	0	(0)	1	(9.1)
Cyst, iris	0	(0.0)	1	(2.9)	0	(0)	0	(0)
Discharge, eye	0	(0.0)	4	(11.4)	0	(0)	0	(0)
Edema, eyelid	1	(1.5)	1	(2.9)	1	(5.3)	0	(0)
Foreign body sensation	1	(1.5)	0	(0)	0	(0)	0	(0)
Heterochromia	1	(1.5)	0	(0)	0	(0)	0	(0)
Hordeolum	1	(1.5)	0	(0)	0	(0)	0	(0)
Infection, eye	0	(0)	1	(2.9)	0	(0)	0	(0)
Inflammation, eyelid	2	(3.0)	0	(0.0)	0	(0)	0	(0)
Injection, conjunctival	2	(3.0)	1	(2.9)	0	(0)	1	(9.1)
Injection, ocular	7	(10.6)	6	(17.1)	0	(0)	2	(18.2)
Itching, eye	2	(3.0)	1	(2.9)	0	(0)	0	(0)
Opacity, vitreous	1	(1.5)	0	(0)	0	0	0	(0)
Otitis media	3	(4.5)	0	(0.0)	0	(0)	0	(0)
Pain, eye	4	(6.1)	2	(5.7)	0	(0)	1	(9.1)
Ptosis	0	(0.0)	1	(2.9)	0	(0)	0	(0)
Tearing	0	(0.0)	3	(8.6)	2	(10.5)	0	(0)
Uveitis	0	(0.0)	1	(2.9)	0	(0)	0	(0)
Urogenital System	**1**	**(1.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Infection, urinary tract	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)

† Indicates total number of patients (across treatments) who switched to open-label combination therapy.
‡ The percent = Number of patients in each category (n)/ number of patients who switched to open-label combination therapy (m), based on the therapy to which the patient was randomized in the monotherapy phase.

Reviewer's Comments:
There are approximately twice as many adverse events documented during the open-label treatment phase in the patient population initially randomized to timolol GFS 0.5% therapy. The clinical significance of this is uncertain since both patient populations were being treated with Cosopt. The adverse event profile would be expected to be similar.

Monotherapy Phase
The two most common clinical adverse experiences in both treatment groups were fever and upper respiratory infections. A greater proportion of patients who were randomized to dorzolamide 2% had reported vomiting (9.1% versus 2.9%), headache (10.6% versus 5.7%), cough (15.2% versus 8.6%), and influenza (10.6% versus 5.7%) compared with the timolol GFS 0.5% group. A greater proportion of patients who were randomized to timolol GFS 0.5% had eye discharge (11.4% versus 0%) and tearing (8.6% versus 0%) compared with the dorzolamide 2% group.

Combination Therapy Phase
The most common clinical adverse experience was tearing in the dorzolamide 2% group and fever in the timolol GFS 0.5% group. A greater proportion of patients who were initially randomized to timolol GFS 0.5% reported one or more adverse experiences (81.8% versus 42.1%) compared with the dorzolamide 2% group. A greater proportion of patients who were initially randomized to dorzolamide 2% reported tearing (10.5% versus 0%) compared with the timolol GFS 0.5% group. A greater proportion of patients who were initially randomized to timolol GFS 0.5% had fever (27.3% versus 0%), diarrhea (18.2% versus 5.3%), and ocular injection (18.2% versus 0%) compared with the dorzolamide 2% group.

Emergent and Worsening Ocular Symptoms

Number (%) of Patients With Emergent or Worsening Ocular Symptoms (Incidence > 0 % in One or More Treatment Groups) (Age Cohort <2 Years)

	Masked Monotherapy Phase				Open-label Concomitant Therapy Phase Dorzolamide 2% + Timolol GFS 0.25% (N=31)			
	Dorzolamide 2% (N=56)		Timolol GFS 0.25% (N=27)		Dorzolamide 2% (m=22)		Timolol GFS 0.25% (m=9)	
	n	(%)	n	(%)	n	(%)	n	(%)
Burning/stinging, eye	1	(1.8)	0	0	1	(4.5%)	0	0
Discharge, eye	3	(5.4)	3	(11.1%)	1	(4.5%)	1	(11.1%)
Inflammation, eyelid	1	(1.8)	1	(3.7%)	1	(4.5%)	0	0
Injection, ocular	4	(7.1)	3	(11.1%)	1	(4.5%)	2	(22.2%)
Irritation, eye	0	0	2	(7.4%)	1	(4.5%)	0	0
Itching, eye	1	(1.8)	0	0	0	0	0	0
Pain, eye	1	(1.8)	0	0	0	0	0	0
Swelling, eye	1	(1.8)	1	(3.7%)	0	0	0	0
tearing	2	(3.6)	1	(3.7%)	0	0	1	(11.1%)

Number (%) of Patients With Emergent or Worsening Ocular Symptoms (Incidence > 0 % in One or More Treatment Groups) (Age Cohort ≥ 2 Years but < 6 Years)

	Masked Monotherapy Phase				Open-label Concomitant Therapy Phase Dorzolamide 2%/Timolol GFS 0.5% (N=30)			
	Dorzolamide 2% (N=66)		Timolol GFS 0.5% (N=35)		Dorzolamide 2% (m=19)		Timolol GFS 0.5% (m=11)	
	n	(%)	n	(%)	n	(%)	n	(%)
Blurred vision	1	(1.5%)	0	0	0	0	0	
Burning/stinging, eye	9	(13.6%)	3	(8.6%)	0	0	1	0
Discharge, eye	0	0	4	(11.4%)	0	0	0	(9.1%)
Foreign body sensation	1	(1.5%)	0	0	0	0	0	0
Inflammation, eyelid	2	(3.0%)	0	0	0	0	0	0
Injection, conjunctival	2	(3.0%)	1	(2.9%)	0	0	1	(9.1%)
Injection, ocular	7	(10.6%)	6	(17.1%)	0	0	2	(18.2%)
Itching, eye	2	(3.0)	1	(2.9%)	0	0	0	0
Pain, eye	4	(6.1)	2	(5.7%)	0	0	1	(9.1%)
Tearing	0	(0.0)	3	(8.6%)	2	(10.5%)	0	0

Nonfatal Serious Clinical Adverse Experiences

Serious Clinical Adverse Experiences (Age cohort < 2 Years –Masked Monotherapy)

Patient	Age (months)	Day of Onset	Adverse Experience	Disposition
Dorzolamide 2%				
2055	20	77	Hemiplegia	Recovered
2094	3	19	Infection, RSV	Recovered
2048	4	12	Bronchiolitis	Recovered
2326	5	3	Pneumonia	Recovered
2309	3	65	Pneumonia	Recovered
2364	1	30	Seizure disorder	Recovered
Timolol GFS 0.25%				
2334	14	17	Bronchoconstriction	Discontinued

Serious Clinical Adverse Experiences (Age cohort < 2 Years – Open-Label Concomitant Therapy)

Patient	Age (months)	Day of Onset	Adverse Experience	Disposition
Dorzolamide 2%				
2049	18	16	Diarrhea	Recovered
Timolol GFS 0.25%				
2350	5	12	Increase intracranial pressure, pseudotumor cerebri	Recovered
2392	9	47	Fever, pharyngitis, bronchitis	Recovered

Serious Clinical Adverse Experiences (Age cohort ≥ 2 Years but < 6 –Masked Monotherapy)

Patient	Age (years)	Day of Onset	Adverse Experience	Disposition
Dorzolamide 2%				
2003	2	13	Urinary tract infection	Recovered
2374	2	6	Otitis media	Recovered
2592	2	81	Anorexia, stomatitis	Recovered
Timolol GFS 0.5%				
2159	3	35	Gastroenteritis	Recovered

There were no serious clinical adverse experiences reported during the combination therapy phase for the age cohort ≥ 2 Years but < 6.

Deaths

There were no deaths in patients randomized into the study. However, there was one patient who died who was screened but not randomized. This was a 43 day old male with a history of face malformation, facial dysmorphism and congenital glaucoma who died secondary to cerebral edema.

Laboratory Values

The chemistry laboratory test total CO2 was performed at study day 1 and week 12 as the protocol-specified laboratory test. The laboratory tests pCO2 and HCO3 were performed in error at some of the International study sites. These study sites were located in the following countries:

A clinically significant laboratory abnormality (CSLA) for total CO2 was defined as a value ≤ 78% of the lower limit of normal (LLN). Two (2) patients experienced a CSLA during study therapy (both in the age cohort <2 years). Patient AN 2049 was initially on

dorzolamide 2% monotherapy, switched to open-label concomitant therapy on study day 8 , and a CSLA for total CO2 was reported on study day 90. For patient AN 2046, who was randomized to timolol GFS 0.25% monotherapy, no baseline laboratory test was recorded. A CSLA for total CO2 was reported on study day 14. The total CO2 result at the week 12 (study day 112) assessment did not qualify as a CSLA.

Mean Change (SD) in Total CO_2 (mmol/L) to the Last Observation in Treatment Phase (Age Cohort <2 years)

Treatment Phase	Treatment	N	Mean (SD)			
			Baseline	Treatment	Change	% Change
Monotherapy	Dorzolamide 2%	18	21.6 (4.5)	22.9 (3.3)	1.3 (4.3)	10.9 (29.6)
	Timolol GFS 0.25%	10	25.1 (4.5)	23.3 (2.5)	-1.8 (3.0)	-6.0 (9.86)
Overall	Dorzolamide 2%	30	22.3 (4.2)	22.7 (4.0)	0.4 (4.3)	4.6 (25.3)
	Timolol GFS 0.25%	15	24.4 (4.5)	22.8 (3.0)	-1.6 (3.6)	-4.8 (14.07)

Mean Change (SD) in Total CO_2 (mmol/L) to the Last Observation in Treatment Phase (Age Cohort ≥ 2 years but < 6 years)

Treatment Phase	Treatment	N	Mean (SD)			
			Baseline	Treatment	Change	% Change
Monotherapy	Dorzolamide 2%	22	24.3 (2.9)	23.7 (3.4)	-0.6 (3)	-2.0 (12.3)
	Timolol GFS 0.5%	12	25.5 (3.9)	25.6 (4.6)	0.1 (4)	1.2 (16.7)
Overall	Dorzolamide 2%	32	24.7 (2.6)	23.6 (3.1)	-1.1 (3)	-3.9 (11.8)
	Timolol GFS 0.5%	18	24.4 (4.2)	24.4 (4.4)	-0.0 (3.6)	0.9 (15.1)

Reviewer's Comments:
There was no clinically meaningful difference in the mean CO2 values between treatment groups for either of the age cohorts at the end of the study. All mean CO2 values are within normal limits for the pediatric population.

Vital Signs

Summary statistics, including the mean and mean percent change from baseline for the last visit of the study phase (monotherapy, open-label), are presented for each vital sign measure by treatment group. The last monotherapy visit served as the point of reference (baseline) for the concomitant/combination therapy phase analysis.

Mean Change (SD) in Vital Signs to the Last Observation in Treatment Phase (Age Cohort <2 Years—Monotherapy)

Measurement (Unit)	Treatment	Mean (SD)				
		N	Baseline	Treatment	Change	% Change
Systolic BP (mm Hg)	Dorzolamide 2%	53	102.5 (21.16)	101.4 (17.83)	-1.1 (21.26)	2.2 (24.72)
	Timolol GFS 0.25%	26	108.8 (20.30)	109.2 (19.55)	0.3 (15.42)	1.3 (12.74)
Diastolic BP (mm Hg)	Dorzolamide 2%	53	62.4 (16.00)	60.8 (15.27)	-1.6 (19.63)	3.0 (37.15)
	Timolol GFS 0.25%	26	67.9 (12.70)	66.7 (13.81)	-1.2 (11.68)	-0.7 (18.46)
Pulse Rate (beats per minute)	Dorzolamide 2%	52	110.3 (21.13)	108.3 (22.19)	-2.0 (27.04)	1.4 (28.93)
	Timolol GFS 0.25%	26	104.7 (18.43)	115.3 (25.98)	10.6 (24.35)	12.1 (26.19)
Respiratory Rate (breaths per minute)	Dorzolamide 2%	52	29.7 (12.27)	28.0 (10.46)	-1.7 (8.63)	-1.6 (22.66)
	Timolol GFS 0.25%	25	30.2 (16.98)	28.7 (14.20)	-1.4 (6.24)	-1.4 (16.69)

N = Sample size.
SD = Standard deviation; BP = Blood pressure.

Mean Change (SD) in Vital Signs to the Last Observation in Treatment Phase (Age Cohort <2 Years—Concomitant Therapy)

Measurement (Unit)	Treatment	Mean (SD)				
		N	Baseline	Treatment	Change	% Change
Systolic BP (mm Hg)	Dorzolamide 2%	21	99.3 (12.59)	100.0 (17.37)	0.8 (20.35)	2.0 (19.22)
	Timolol GFS 0.25%	9	104.1 (14.34)	105.8 (19.48)	1.7 (17.98)	2.4 (18.99)
Diastolic BP (mm Hg)	Dorzolamide 2%	21	61.1 (14.35)	61.0 (9.78)	-0.2 (15.80)	3.4 (21.87)
	Timolol GFS 0.25%	9	65.6 (9.08)	64.7 (16.95)	-0.8 (18.74)	0.3 (28.45)
Pulse Rate (beats per minute)	Dorzolamide 2%	20	108.3 (18.26)	105.6 (15.79)	-2.7 (20.52)	0.6 (24.66)
	Timolol GFS 0.25%	9	109.3 (18.69)	101.2 (21.55)	-8.1 (15.83)	-7.1 (14.45)
Respiratory Rate (breaths per minute)	Dorzolamide 2%	21	30.5 (14.44)	30.2 (16.28)	-0.3 (7.44)	0.8 (25.81)
	Timolol GFS 0.25%	9	26.9 (8.49)	24.0 (3.61)	-2.9 (6.25)	-6.3 (18.01)

N = Sample size.
SD = Standard deviation.
BP = Blood pressure.

Mean Change (SD) in Vital Signs to the Last Observation in Treatment Phase (Age Cohort ≥2 Years but <6 Years—Monotherapy)

Measurement (Unit)	Treatment	Mean (SD)				
		N	Baseline	Treatment	Change	% Change
Systolic BP (mm Hg)	Dorzolamide 2%	64	109.6 (17.76)	110.3 (14.33)	0.7 (17.81)	2.8 (19.79)
	Timolol GFS 0.5%	35	107.4 (14.28)	104.5 (14.50)	-2.9 (13.32)	-1.9 (12.46)
Diastolic BP (mmHg)	Dorzolamide 2%	64	67.3 (11.83)	66.8 (10.83)	-0.4 (13.69)	2.2 (22.91)
	Timolol GFS 0.5%	35	63.8 (11.22)	61.4 (10.01)	-2.4 (11.49)	-1.6 (18.96)
Pulse Rate (beats per minute)	Dorzolamide 2%	65	98.3 (15.55)	99.3 (15.43)	0.9 (18.08)	2.8 (21.07)
	Timolol GFS 0.5%	35	104.5 (14.58)	99.6 (15.44)	-4.9 (17.16)	-3.2 (20.70)
Respiratory Rate (breaths per minute)	Dorzolamide 2%	61	23.7 (5.86)	23.2 (4.33)	-0.5 (5.43)	1.0 (21.78)
	Timolol GFS 0.5%	34	23.9 (5.29)	23.9 (4.96)	-0.0 (5.01)	2.2 (20.74)

N = Sample size.
SD = Standard deviation.
BP = Blood pressure.

Mean Change (SD) in Vital Signs to the Last Observation in Treatment Phase (Age Cohort ≥2 Years but <6 Years—Combination Therapy)

Measurement (Unit)	Treatment	N	Mean (SD)			
			Baseline	Treatment	Change	% Change
Systolic BP (mm Hg)	Dorzolamide 2%	18	107.9 (11.64)	107.4 (19.34)	-0.5 (17.41)	-0.2 (15.14)
	Timolol 0.5%	11	105.9 (18.38)	104.2 (12.05)	-1.7 (20.54)	1.7 (25.53)
Diastolic BP (mm Hg)	Dorzolamide 2%	18	66.4 (11.06)	63.0 (4.93)	-3.4 (10.07)	-3.2 (13.66)
	Timolol 0.5%	11	59.8 (8.87)	66.6 (8.57)	6.8 (10.21)	13.5 (22.43)
Pulse Rate (bpm)	Dorzolamide 2%	19	102.1 (17.42)	91.3 (18.85)	-10.8 (21.19)	-9.1 (18.49)
	Timolol 0.5%	11	99.5 (20.43)	97.7 (14.46)	-1.8 (15.71)	-0.2 (14.42)
Respiratory Rate (bpm)	Dorzolamide 2%	18	22.2 (4.37)	23.7 (5.74)	1.6 (4.78)	8.0 (19.61)
	Timolol 0.5%	10	25.9 (6.30)	23.2 (3.65)	-2.7 (3.47)	-8.7 (10.65)

N = Sample size.
SD = Standard deviation.
BP = Blood pressure.

Reviewer's Comments:

There were no clinically significant changes in pulse, blood pressure or respiratory rate in either of the treatment groups for both age cohorts. There was an increase in pulse rate noted in the timolol monotherapy treatment group for age cohort < 2. This is counterintuitive based on the mechanism of action of beta-blockers. This event, however, was not clinically significant.

Alertness Assessment

The response to the alertness assessment at baseline and at Week 12 was summarized by constructing 5x5 contingency tables by treatment group (Grades 1 to 5 at baseline versus Grades 1 to 5 at Week 12). In addition, the number and percent of patients whose responsiveness deteriorated at any point during the study was determined by treatment group. Results were determined for those who completed the study while on monotherapy, and overall.

Patients With Worsening Alertness Assessments for All Patients as Treated – Evaluable* (Age Cohort < 2 Years)

	Dorzolamide 2% (N=55)	Timolol GFS 0.25% (N=27)
Monotherapy	0	1 (3.7%)
Overall	1 (1.8)	1 (3.7)

*Patients who were evaluable had a baseline assessment and at least one on-treatment assessment
N=sample size

Patient Alertness: Change From Baseline to Week 12 (End of Study) for All Patients as Treated—Evaluable† (Age Cohort <2 Years—Monotherapy)

Dorzolamide 2% (N=33)					
Grade at Baseline	Grade at Week 12 (End of Study)				
	1	2	3	4	5
1	30	0	0	0	0
2	1	1	0	0	0
3	1	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
Timolol GFS 0.25% (N=18)					
Grade at Baseline	Grade at Week 12 (End of Study)				
	1	2	3	4	5
1	15	0	0	0	1
2	0	1	0	0	0
3	0	0	0	0	0
4	0	1	0	0	0
5	0	0	0	0	0

† Patients who were evaluable had a baseline assessment and at least one on-treatment assessment.
Note: The last assessment was analyzed for patients who discontinued the study prior to Week 12.
1 = Responds readily to name spoken in normal tone.
2 = Lethargic response to name spoken in normal tone.
3 = Responds only after name is spoken loudly and/or repeatedly.
4 = Responds only after mild prodding or shaking.
5 = Does not respond to mild prodding or shaking.

Reviewer's Comments:
One patient (AN 2035) was assessed as 1 (responds readily) at baseline and 5 (does not respond) at the 12 week visit. Based on the investigator information, this assessment was made during the time that the patient was sedated for IOP measurements. It is not believed to be a clinical adverse event.

Patients With Worsening Alertness Assessments for All Patients as Treated – Evaluable* (Age Cohort ≥ 2 Years but < 6 Years)

	Dorzolamide 2% (N=65)	Timolol GFS 0.5% (N=35)
Monotherapy	0	0
Overall	0	0

*Patients who were evaluable had a baseline assessment and at least one on-treatment assessment
N=sample size

Patient Alertness: Change From Baseline to Week 12 (End of Study) for All Patients as Treated—Evaluable† (Age Cohort ≥2 Years but <6 Years—Monotherapy)

Dorzolamide 2% (N=47)					
Grade at Baseline	Grade at Week 12 (End-of-Study)				
	1	2	3	4	5
1	45	0	0	0	0
2	1	1	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
Timolol GFS 0.5% (N=24)					
Grade at Baseline	Grade at Week 12 (End-of-Study)				
	1	2	3	4	5
1	23	0	0	0	0
2	1	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0

† Patients who were evaluable had a baseline assessment and at least one on-treatment assessment.
Note: The last assessment was analyzed for patients who discontinued the study prior to Week 12.

1 = Responds readily to name spoken in normal tone.
2 = Lethargic response to name spoken in normal tone.
3 = Responds only after name is spoken loudly and/or repeatedly.
4 = Responds only after mild prodding or shaking.
5 = Does not respond to mild prodding or shaking.

Reviewer's Comments:
There were no clinically meaningful changes in patient alertness for this age cohort.

Corneal Diameter

Corneal diameter measurements were obtained at baseline and at Week 12. If the patient discontinued the study prior to Week 12, the corneal diameter was to be measured at the discontinuation visit. The mean and standard deviation at baseline and Week 12, as well as the change and percent change from baseline to Week 12, are presented for the corneal diameter of the study eye. Nominal p-values were calculated on mean change and mean percent change from baseline within treatment groups based on the paired t-test. Results were determined for those who completed the study while on monotherapy, and overall.

Corneal Diameter (mm) Summary Statistics for All Patients as Treated—Evaluable† (Age Cohort <2 Years—Monotherapy)

Treatment	N	Baseline			Week 12			Change			Percent Change (p-Value)
		Mean	SD	Med	Mean	SD	Med	Mean (p-Value)	SD	Med	
Dorzolamide 2%	27	12.89	1.35	13.00	12.96	1.24	12.80	0.1 (0.364)	0.43	0.000	0.8 (0.304)
Timolol GFS 0.25%	15	12.83	1.37	12.50	12.72	1.34	12.50	-0.1 (0.599)	0.84	0.000	-0.7 (0.677)

† Patients who were evaluable had a baseline assessment and at least one on-treatment assessment.
Note: p-Values are for within-group changes from baseline (paired t-test).
SD = Standard deviation.
Med = Median.

Corneal Diameter (mm) Summary Statistics (Age Cohort ≥2 Years but <6 Years—Monotherapy)

Treatment	N	Baseline			Week 12			Change			Percent Change (p-Value)
		Mean	SD	Med	Mean	SD	Med	Mean (p-Value)	SD	Med	
Dorzolamide 2%	42	12.68	2.21	13.00	12.73	2.18	13.00	0.0 (0.493)	0.39	0.000	0.4 (0.417)
Timolol GFS 0.5%	22	12.77	1.53	12.25	12.61	1.48	12.25	-0.2 (0.110)	0.45	0.000	-1.2 (0.106)

Note: p-Values are for within-group changes from baseline (paired t-test).
SD = Standard deviation.
Med = Median.

Reviewer's Comments:

There were no clinically significant changes in corneal diameter in either treatment group for both of the age cohorts. The mean baseline and end of study corneal diameters in this study are outside of normal limits. The values are borderline for megalocornea which is consistent with this disease process.

Visual Acuity

Baseline visual acuity (VA) of the study eye was summarized by age cohort and treatment group. Pre-verbal patients were summarized according to the category listed by the investigator. Patients with results listed in a numerator/denominator format were summarized according to the Snellen equivalent.

One patient in each treatment group (1.8% and 3.7% for dorzolamide 2% and timolol GFS 0.25%, respectively) in the age cohort <2 years experienced a worsening at the Week 12 visit. Three (3) patients (4.5%) in the dorzolamide 2% group and 2 patients (5.7%) in the timolol 0.5% group in the age cohort ≥2 years but <6 years experienced a worsening at the Week 12 visit.

Listing of Patients With a Worsening in Visual Acuity for the Study Eye— Baseline Versus Week 12

Age Cohort	Treatment	Allocation Number (AN)	Baseline Assessment	Week 12 Assessment
<2 Years	Dorzolamide 2%	2058	fixates and follows	poor fixation
	Timolol GFS 0.25%	2329	fixates and follows	no fixation
≥2 Years but <6 Years	Dorzolamide 2%	2157	20/100	20/125
		2169	20/20	20/25
		2204	20/20	20/25
	Timolol GFS 0.5%	2244	20/70	20/200
		2587	5/60	4/60

Three (3) patients who were ≥2 years but <6 years of age, 1 on Dorzolamide 2% (AN 2252) and 2 on Timolol GFS 0.5% (ANs 2253, 2161), were excluded from the analysis due to data entry errors.

Reviewer's Comments:

Two (2) of the seven patients reported as having a worsening in visual acuity had a clinically significant change in vision. Both patients were in the timolol GFS treatment group. Patient 2244 was discontinued from the study at week 29 for poor IOP control. Patient 2329 completed the study.

D. Adequacy of Safety Testing

The submitted study complies with the pediatric written request issued by the Agency and is of adequate duration to assess the safety of this product in the pediatric population. The evaluation methods were appropriate and there is no need for further safety testing.

E. Summary of Critical Safety Findings and Limitations of Data

There were no critical safety findings identified in this study.

VIII. Dosing, Regimen, and Administration Issues

Dosing for this pediatric trial was based on the currently labeled dosing frequency for adult patients. No further dose ranging was warranted. The currently labeled dosing level and frequency is safe in the pediatric population.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor analyzed data for each of 2 age cohorts: "patients <2 years old" and "patients ≥ 2 years but <6 years old". The Sponsor has adequately addressed the safety and clinical response of this drug product in these two cohorts. Gender effects were not analyzed in this pediatric supplement. The effects of gender, race, age and iris color were analyzed during the review of the original NDA.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The sponsor did not analyze the effects of age, race or ethnicity in this pediatric supplement. The effects of gender, race, age and iris color were analyzed during the review of the original NDA.

C. Evaluation of Pediatric Program

The Agency issued a written request for this drug product to gather data on the safety profile in pediatric patients below the age of 6. The Agency believed that efficacy for this product could be reliably extrapolated from the adult population. The study contained in this pediatric efficacy supplement adequately addresses all of the criteria of the pediatric written request. The data has confirmed that this drug product is safe for pediatric use for the labeled indication.

D. Comments on Data Available or Needed in Other Populations

There is no additional data needed in other populations for this drug product. Safety and efficacy have been adequately characterized in the target populations.

X. Conclusions and Recommendations

A. Conclusions

This clinical study supports the use of dorzolamide HCL in the Pediatric population. The benefits of using this drug product outweigh the risks in the treatment of elevated intraocular pressure in pediatric patients below the age of 6. There are no unresolved scientific or regulatory issues.

B. Recommendations

NDA 20-408 /SE5-033 is recommended for approval after labeling revisions are made consistent with the recommendations listed in this review.

9 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1a

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

/s/

Jennifer Harris
3/29/04 12:50:56 PM
MEDICAL OFFICER

Wiley Chambers
3/29/04 04:12:27 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-408 / S-033

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1	1. ORGANIZATION HFD-550	2. NDA Number(s) 20-408
3. Name and Address of Applicant (City & State): Merck & Co., Inc. Sumneytown Pike,P.O.Box 4, BLA-20 West Point, PA 19486 (Virginia Snyder at telephone 484-344-7984)		4. AF No. 5. Supplement(s) Number(s) Date(s) SE5-033 17-Oct-2003
6. Drug Name: TRUSOPT®	7. Nonproprietary Name: Dorzolamide Hydrochloride Ophthalmic Solution	8. Amendments & Other (reports, etc.) - Dates
9. Supplement Provides For: changes in Items 2,3,4,8,10,12,13,16,17,18,19 and 20 of the approved NDA for TRUSORT™ Opthalmic Solution 2% to request pediatric exclusitivity for the use of this drug product.		Annual Report
10. Pharmacological Category: Carbonic anhydrase inhibitor (CAI) and β-blocker	11. How Dispensed: • Rx	12. Related IND(s)/ NDA(s)/DMF(s)
13. Dosage Form(s): Solution	Potency(ies): 2.0%	
15. Chemical Name and Structure: (4S-trans)-4-(ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno [2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide monochloride		16. Records/Reports Current: • Yes • No Reviewed: • Yes • No
17. Comments: A category exclusion from preparing an Environment Assessment is requested. Merck claims that the patient use of the dozolamide hydrochloride meets the requirements of a category exclusion under 21 CFR § 25.32 (b). The estimated concentration of the drug substance at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below — All other formulation containing dorzolamide hydrochloride have been included in this calculation. It is acceptable. Furthermore, no CMC related labeling sections are changed.		
18. Conclusions and Recommendations: From CMC viewpoint this supplement is recommended for an approval action. CC: Original NDA# 20-408 HFD-550/Division File HFD-550/Med/WChambers HFD-550/LNg HFD-550/CSO/RRodriguez HFD-550/YLu R/D initialed by : Linda Ng		
19. REVIEWER		
Name: Yong-de Lu Ph.D.	Signature:	Date Completed: 05-Mar-2004

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

/s/

Yong-De Lu
3/5/04 03:27:00 PM
CHEMIST

Linda Ng
3/5/04 03:48:20 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-408 / S-033

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-408 / S-033
Drug Name:	TRUSOPT (Dorzolamide Hydrochloride) Ophthalmic Solution 2.0%
Indication(s):	The treatment of elevated intraocular pressure in patients with ocular hypertension or open angle glaucoma
Applicant:	Merck & Co., Inc.
Date(s):	Submitted: October 16, 2003 Received: October 16, 2003
Review Priority:	Priority review
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Yongman Kim, Ph.D.
Concurring Reviewers:	Stan Lin, Ph.D.
Medical Division:	Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)
Clinical Team:	Jennifer Harris, M.D.
Project Manager:	Nancy Halonen

Keywords: Pediatric exclusivity, Confidence interval (for binomial proportion), Endpoint analysis with LOCF

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on the data from this pediatric study for marketing exclusivity extension, we conclude that dorzolamide ophthalmic solution resulted in significant reduction of intraocular pressure (IOP) 'after treatment' compared with 'before treatment' in pediatric patients with glaucoma of age less than 6. Also, it appears that the proportion of discontinuation of therapy due to a drug-related adverse experience was within prespecified limits.

1.2 Brief Overview of Clinical Study

The sponsor submitted the results of a study that documents the efficacy and safety of dorzolamide hydrochloride in pediatric patients less than six years of age with a clinical diagnosis of glaucoma or elevated intraocular pressure. This single study was a combination of two identical protocols (Protocols 100 and 125) for U.S. and international sites, respectively. This was a **3-month**, double-masked, active-treatment-controlled, multicenter study to investigate the safety and ocular hypotensive effect of **dorzolamide 2% sterile solution** 3 times a day in pediatric glaucoma patients younger than 6 years of age. Timolol maleate gel-forming solution once daily was the active treatment control.

83 patients younger than 2 years of age were randomized to the dorzolamide arm (n = 56) and the timolol GS arm (n = 27) in 2-to-1 ratio. 101 patients $\geq$ 2 years but < 6 years of age were randomized to the dorzolamide arm (n = 66) and the timolol GS arm (n = 35) in 2-to-1 ratio.

The primary objective of the study was to document an acceptable safety profile for initial therapy with dorzolamide. The primary measure of safety was the proportion of patients who discontinue therapy due to a drug-related adverse experience prior to completing 3 months of therapy.

The secondary objective was to characterize the IOP-lowering effect of dorzolamide. The primary efficacy endpoint was the intraocular pressure change from baseline and percent change from baseline at the end-of-study (Week 12) visit.

Statistical data analyses and presentation were done by age cohort and in all combined patients.

1.3 Statistical Issues and Findings

For the efficacy analysis, the sponsor focused on the statistical significance of decrease in IOP 'before and after' dorzolamide treatment without comparing the decrease with that of the active comparator, timolol.

The comparisons in efficacy between dorzolamide and timolol groups were done using a confidence interval method in a post hoc manner instead of a pre-planned statistical hypothesis testing method. While 95% confidence intervals of difference in IOP decrease after treatment between dorzolamide and timolol included zero indicating that the effect of dorzolamide was not statistically different from that of timolol, a clinical judgment is required regarding similarity in efficacy between the two treatments by assessing the width of the confidence interval.

The safety endpoint was not compared between treatment groups, but was evaluated only within dorzolamide group although the clinical trial was controlled with active comparator.

Based on our review of the data up to 12 weeks we conclude the following:

1. The 95% confidence intervals for the proportion of discontinuation of therapy due to a drug-related adverse experience for dorzolamide group were (0.05%, 9.55%) for age-cohort < 2 years of age and (0.37%, 10.52%) for age-cohort ≥2 years but <6 years of age. Therefore, the safety of dorzolamide in both age-cohorts was shown according to the pre-defined decision rule, which claims the safety if the upper limit is lower than 25%.

2. At Week 12 for age-cohort <2 years of age, there were statistically significant decreases from baseline in IOP in both treatment groups and the decrease were similar in the dorzolamide and timolol groups with mean change changes from baseline (95% CI) in IOP of -7.30 (-9.51, -5.03) vs. -7.80 (-10.90, -4.74) mm Hg. The difference between the two treatments and the 95% CI for the difference were 0.57 (-3.39, 4.54) mm Hg, indicating a similar effect for the two treatment groups.

3. At Week 12 for age-cohort ≥2 years but <6 years of age, there were statistically significant decreases from baseline in IOP in both treatment groups and the decrease were similar in the dorzolamide and timolol groups with mean change changes from baseline (95% CI) in IOP of -7.10 (-8.72, -5.39) vs. -7.40 (-9.67, -5.13) mm Hg. The difference between the two treatments and the 95% CI for the difference were 0.34 (-2.50, 3.19) mm Hg, indicating a similar effect for the two treatment groups.

4. At Week 12 for age-cohorts combined, there were statistically significant decreases from baseline in IOP in both treatment groups and the decrease were similar in the

dorzolamide and timolol groups with mean change changes from baseline (95% CI) in IOP of -7.20 (-8.53, -5.79) vs. -7.60 (-9.45, -5.75) mm Hg. The difference between the two treatments and the 95% CI for the difference were 0.44 (-1.92, 2.79) mm Hg, indicating a similar effect for the two treatment groups.

2. INTRODUCTION

2.1 Overview

2.1.1 Drug class and regulatory history

Dorzolamide, which was approved in 1994, was the first topical carbonic anhydrase inhibitor approved for use in the United States to treat glaucoma.

The FDA has issued a written request for a pediatric study of dorzolamide in June 1999, and amended in May 2000 and February 2002. In the Written Request, the FDA specified that a randomized, double-masked, parallel-comparison study with a minimum 50 patients <2 years of age and a minimum of 50 patients 2 to 5 years of age randomized to dorzolamide monotherapy be conducted.

2.1.2 Indication for TRUSOPT™ (dorzolamide)

TRUSOPT Ophthalmic Solution is indicated in the treatment of elevated IOP in patients with ocular hypertension or open-angle glaucoma. The dosing recommended by the sponsor is one drop of TRUSOPT Ophthalmic Solution in the affected eye(s) three times daily.

2.2 Data Sources

The original electronic submission on October 16, 2003 can be found on the FDA, CDER electronic document room (EDR).

Final Report:
\\Cdsesub1\n20408\S_033\2003-10-16\clinstat\studies

Data set:
\\Cdsesub1\n20408\S_033\2003-10-16\crt\datasets

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

This was a 3-month, double-masked, active-treatment-controlled, multicenter study to investigate ocular hypotensive effect of dorzolamide 2% t.i.d. in pediatric glaucoma patients younger than 6 years. Timolol maleate gel-forming solution (timolol GS) q.d. was the active treatment control. Patients were randomized 2:1, dorzolamide to timolol GS therapy. If IOP was inadequately controlled on monotherapy, a change was made to open-label concomitant therapy of dorzolamide 2% t.i.d. and timolol GS 0.25% q.d. for patients <2 years of age or combination therapy of dorzolamide 2%/ timolol 0.5% b.i.d. for patients ≥2 years but <6 years of age. Figure 1 shows a schematic of the study design of Protocols 100 and 125 in two age cohorts and Table 1 shows change in therapy schedule.

Figure 1. Schematic of Study Design

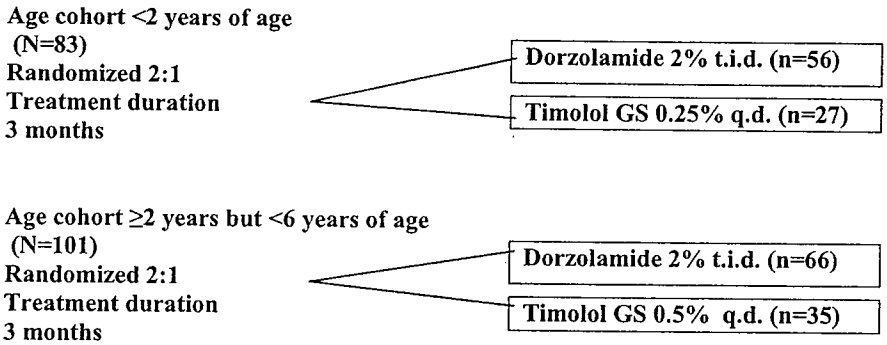


Table 1. Change in Therapy Schedule

Patient Age	Initial Therapy (Masked)	Concomitant/Combination Therapy (Open Label)
<2 years	Dorzolamide 2% t.i.d. Or Timolol GS 0.25% q.d.	Dorzolamide 2% t.i.d. plus Timolol GS 0.25% q.d.
≥2 years but <6 years	Dorzolamide 2% t.i.d. Or Timolol GS 0.5% q.d.	Dorzolamide 2%/ Timolol GS 0.5% fixed combination b.i.d.

The study was an international one. The distribution of the centers by country is as follows:

Protocol 100: USA(22)

Protocol 105: [redacted]

IOP as efficacy outcome was measured on Study Day 1, and Weeks 1, 4, and 12, and at Weeks 2 or 5 if a change in therapy is implemented. The primary efficacy endpoint was the intraocular pressure change from baseline and percent change from baseline at the end-of-study (Week 12) visit. IOP change from baseline and percent change from baseline were tested at each post baseline visit within dorzolamide treatment group using paired t test.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 2 below, about 10% of the patients did not complete the study. For the missing data due to discontinuation, LOCF was used in the efficacy analysis.

Table 2. Patient Disposition

AGE COHORT	<2 Years		≥2 Years but <6 Years		TOTAL
SCREENING FAILURES:	13		19		32
TREATMENT GROUP:	Dorzolamide 2%	Timolol GS 0.25%	Dorzolamide 2%	Timolol GS 0.5%	
RANDOMIZED:	56	27	66	35	184
Masked Monotherapy Phase					
COMPLETED:	28	16	41	21	106
DISCONTINUED:	6	3	4	3	18
Lost to follow-up	1	0	0	0	1
Withdrew consent	0	0	1	0	1
Clinical adverse experience	0	2	2	2	6
IOP not controlled-surgery	4	0	3	1	8
IOP not controlled-medication	0	1	0	0	1
Other reason	1	0	0	0	1
Patient switched to open-label concomitant therapy	22	8	19	11	60

Open-Label Concomitant Therapy Phase					
COMPLETED:	15	7	12	7	41
DISCONTINUED:	7	1	7	4	19
IOP not controlled-surgery	5	1	5	2	13
IOP not controlled-medication	1	0	2	1	4
Other reason	1	0	0	1	
Overall					
COMPLETED:	43	23	53	28	147
DISCONTINUED:	13	4	13	7	37
Lost to follow-up	1	0	0	0	1
Withdrew consent	0	0	1	0	1
Clinical adverse experience	0	2	2	2	6
IOP not controlled-surgery	9	1	8	3	21
IOP not controlled-medication	1	1	2	1	5
Other	2	0	0	1	3

Table 3 and Table 4 below show patient demographics and baseline characteristics by treatment groups, respectively.

Table 3. Patient Demographics

AGE COHORT	<2 Years		≥2 Years but <6 Years		Combined	
TREATMENT GROUP:	Dorzolamide 2%	Timolol GS 0.25%	Dorzolamide 2%	Timolol GS 0.5%	Dorzolamide 2%	Timolol GS 0.25% and 0.5%
N:	56	27	66	35	122	62
Gender						
Male	35 (62.5%)	20 (74.1%)	33 (50%)	18 (51.4%)	68 (55.7%)	38 (61.3%)
Female	21 (37.5%)	7 (25.9%)	33 (50%)	17 (48.6%)	54 (44.3%)	24 (38.7%)
Race						
Asian	5 (8.9%)	2 (7.4%)	5 (7.6%)	2 (5.7%)	10 (8.2%)	4 (6.5%)
Bi-Racial	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Black	4 (7.1%)	2 (7.4%)	4 (6.1%)	1 (2.9%)	8 (6.6%)	3 (4.8%)
Caucasian	16 (28.6%)	7 (25.9%)	23 (34.8%)	14 (40.0%)	39 (32%)	21 (33.9%)
Egyptian	8 (14.3%)	4 (14.8%)	8 (12.1%)	4 (11.4%)	16 (13.1%)	8 (12.9%)
Hispanic	22 (39.3%)	11 (40.7%)	26 (39.4%)	12 (34.3%)	48 (39.3%)	23 (37.1%)
Hispanic/White	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
Indian	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)	0 (0.0%)	2 (3.2%)

Age	(Months)		(Years)		(Months)	
Mean	9.7	11.5	3.4	3.5	29.8	32.2
SD	6.5	6.4	1.2	1.2	21.9	22.2
Median	8	11	3	3	27	29.5
Range	1 to 23	0.25 to 22	2 to 6	2 to 6	1 to 77	0.25 to 83

Table 4. Baseline Characteristics

AGE COHORT	<2 Years		≥2 Years but <6 Years		Combined	
TREATMENT GROUP:	Dorzolamide 2%	Timolol GS 0.25%	Dorzolamide 2%	Timolol GS 0.5%	Dorzolamide 2%	Timolol GS 0.25% and 0.5%
N	56	27	66	35	122	62
Baseline IOP (mmHg) – Worse Eye						
Mean	32.6	29.9	28.7	30.3	30.5	30.1
SD	11.1	8.6	7.4	6.5	9.5	7.4
Median	29	28	26	30	27	29.5
Range	17.3 to 64	14 to 48.7	18 to 55	22 to 45.5	17.3 to 64	14 to 48.7

3.1.3 Statistical Methodologies

Sponsor employed the paired t test to compare 'before' and 'after' treatment IOP measurements. Reviewer did the same analysis adjusting for regional effects (US and non-US) using an analysis of variance (ANOVA) with terms of patient, week, and region. But the re-analyses resulted in the similar p-values for the efficacy comparison as those provided by the sponsor.

3.1.4 Results and Conclusions

Table 5 – Table 7 present the statistical analyses done by sponsor except for the p-values which were recalculated by the reviewer in order to adjust for regional effect.

At Week 12 for age-cohort <2 years of age, there were statistically significant decreases from baseline in IOP in both treatment groups and the decrease were similar in the dorzolamide and timolol groups with mean change changes from baseline (95% CI) in IOP of -7.30 (-9.51, -5.03) vs. -7.80 (-10.90, -4.74) mm Hg. The difference between the two treatments and the 95% CI for the difference were 0.57 (-3.39, 4.54) mm Hg, indicating that the effect of dorzolamide was not statistically different from that of timolol.

At Week 12 for age-cohort ≥2 years but <6 years of age, there were statistically significant decreases from baseline in IOP in both treatment groups and the decrease were similar in the dorzolamide and timolol groups with mean change changes from

baseline (95% CI) in IOP of -7.10 (-8.72, -5.39) vs. -7.40 (-9.67, -5.13) mm Hg. The difference between the two treatments and the 95% CI for the difference were 0.34 (-2.50, 3.19) mm Hg, indicating that the effect of dorzolamide was not statistically different from that of timolol.

At Week 12 for age-cohorts combined, there were statistically significant decreases from baseline in IOP in both treatment groups and the decrease were similar in the dorzolamide and timolol groups with mean change changes from baseline (95% CI) in IOP of -7.20 (-8.53, -5.79) vs. -7.60 (-9.45, -5.75) mm Hg. The difference between the two treatments and the 95% CI for the difference were 0.44 (-1.92, 2.79) mm Hg, indicating that the effect of dorzolamide was not statistically different from that of timolol.

Basically, the sponsor calculated the mean IOP change from baseline and percent change from baseline and tested if these were statistically different from zero. Statistical comparisons were not done between treatment groups. But the sponsor provided the differences between the treatment groups and the 95% confidence intervals, which gave some idea regarding similarity of the IOP between the two treatment groups although it was not clearly stated in the protocol. Therefore, even if the sponsor provided a partial evidence regarding the similarity in IOP lowering effect between the two treatments, the sponsor cannot claim that dorzolamide is similarly effective when compared with the active comparator timolol GS. This claim can be shown by a pre-planned equivalence trial with appropriate equivalence margin.

Table 5. Analysis Results of IOP (mm Hg) (Age Cohort <2 Years - Monotherapy): ITT and LOCF

Visit	Treatment	N	Baseline outcome		Study outcome		Change		% Change (p-Value)
			Mean	SD	Mean	SD	Mean (p-Value)	SD	
Week 1	Dorzolamide 2%	46	34.07	11.61	31.50	24.05	-10.0 (<0.001)	10.77	-27.4 (<0.001)
	Timolol GS 0.25%	22	31.15	9.02	23.15	8.19	-8.0(<0.001)	8.24	-23.8 (<0.001)
Week 4	Dorzolamide 2%	53	33.16	11.29	24.30	9.58	-8.9(<0.001)	8.15	-25.7 (<0.001)
	Timolol GS 0.25%	24	30.26	8.98	22.67	7.75	-7.6(<0.001)	8.11	-23.8 (<0.001)
Week 12	Dorzolamide 2%	58	32.60	11.03	25.33	9.38	-7.3(<0.001) (-9.51, -5.03)	8.69	-20.6 (<0.001) (-26.3, -15.0)
	Timolol GS 0.25%	27	29.88	8.59	22.03	7.32	-7.8(<0.001) (-10.9, -4.74)	8.23	-24.9 (<0.001) (-32.7, -17.2)
Difference at Week 12: Dorzolamide – Timolol (95% CI)							0.57 (-3.39, 4.54)		4.30 (-5.66, 14.26)

Note: p-Values were based on the ANOVA model with terms of region (US and non-US), patient, and week.
The ITT population consists of all randomized patients that have a baseline value and at least one efficacy measurement subsequent to at least one dose of study therapy during the double-masked phase of the study.

Table 6. Analysis Results of IOP (mm Hg) (Age Cohort ≥2 Years but <6 Years - Monotherapy): ITT and LOCF

Visit	Treatment	N	Baseline outcome		Study outcome		Change		% Change (p-Value)
			Mean	SD	Mean	SD	Mean (p-Value)	SD	
Week 1	Dorzolamide 2%	59	28.49	7.40	21.32	7.95	-7.2 (<0.001)	5.97	-24.8 (<0.001)
	Timolol GS 0.5%	29	30.26	6.76	22.19	7.57	-8.1(<0.001)	7.03	-26.3 (<0.001)
Week 4	Dorzolamide 2%	60	28.22	6.81	20.96	6.31	-7.3(<0.001)	6.26	-24.5 (<0.001)
	Timolol GS 0.5%	30	30.16	6.63	21.97	7.09	-8.2(<0.001)	4.22	-28.0 (<0.001)
Week 12	Dorzolamide 2%	63	28.54	7.49	21.49	6.78	-7.1(<0.001) (-8.72, -5.39)	6.74	-23.3 (<0.001) (-28.9, -17.8)
	Timolol GS 0.5%	34	30.25	6.61	22.85	8.97	-7.4(<0.001) (-9.67, -5.13)	6.74	-25.3 (<0.001) (-33.2, -17.4)
Difference at Week 12: Dorzolamide – Timolol (95% CI)							0.34 (-2.50, 3.19)		1.95 (-7.71, 11.62)

Note: p-Values were based on the ANOVA model with terms of region (US and non-US), patient, and week.
The ITT population consists of all randomized patients that have a baseline value and at least one efficacy measurement subsequent to at least one dose of study therapy during the double-masked phase of the study.

Table 7. Analysis Results of IOP (mm Hg) at Week 12 (Age Cohorts Combined - Monotherapy): ITT and LOCF

Visit	Treatment	N	Baseline outcome		Study outcome		Change		% Change (p-Value)
			Mean	SD	Mean	SD	Mean (p-Value)	SD	
Week 12	Dorzolamide 2%	121	30.49	9.53	23.33	8.32	-7.2(<0.001) (-8.53, -5.79)	7.70	-22.0 (<0.001) (-26.0, -18.1)
	Timolol GS (0.25% or 0.5%)	61	30.08	7.49	22.49	8.22	-7.6(<0.001) (-9.45, -5.75)	7.38	-25.1 (<0.001) (-30.7, -19.6)
Difference at Week 12: Dorzolamide – Timolol (95% CI)							0.44 (-1.92, 2.79)		3.09 (-3.77, 9.95)

Note: p-Values were based on the ANOVA model with terms of region (US and non-US), patient, and week.
The ITT population consists of all randomized patients that have a baseline value and at least one efficacy measurement subsequent to at least one dose of study therapy during the double-masked phase of the study.

3.2 Evaluation of Safety

Safety analyses were based on the All-Patients-as-Treated analysis population, which included all patients who were randomized to double-masked therapy and received at least one dose of study therapy.

3.2.1 Evaluation of Safety (Age Cohort <2 Years Old)

One patient (1.79%, 95% CI [0.05%, 9.55%]) initially randomized to dorzolamide 2% monotherapy discontinued therapy due to a drug-related clinical adverse experience. No patients (0.00%) initially randomized to timolol GS 0.25% monotherapy discontinued therapy due to a drug-related clinical adverse experience.

3.2.2 Evaluation of Safety (Age Cohort ≥2 Years Old but <6 Years Old)

Three (3) patients discontinued therapy due to a drug-related clinical adverse experience: of these 2 patients (3.03%, 95% CI [0.37%, 10.52%]) initially randomized to dorzolamide 2% and 1 patient (2.86%) was initially randomized to timolol GS 0.5%.

3.2.3 Evaluation of Safety (Age Cohorts Combined)

Three (4) patients discontinued therapy due to a drug-related clinical adverse experience: of these 3 patients (2.46%) initially randomized to dorzolamide 2% and 1 patient (1.61%) was initially randomized to timolol GS 0.25% or 0.5%.

3.2.4 Results and Conclusions

The 95% confidence intervals for the proportion of discontinuation of therapy due to a drug-related adverse experience for dorzolamide group were (0.05%, 9.55%) for age-cohort < 2 years of age and (0.37%, 10.52%) for age-cohort ≥2 years but <6 years of age. Therefore, the safety of dorzolamide in both age-cohorts was shown according to the pre-defined decision rule, which claims the safety if the upper limit is lower than 25%.

The proportions of discontinuation of therapy due to a drug-related clinical adverse experience were calculated for each treatment and tested if they were statistically lower than 25% within dorzolamide group using a confidence interval approach.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Sponsor analyzed data for each of 2 age cohorts: "patients <2 years old" cohort and "patients ≥2 years but <6 years old" cohort.

4.2 Other Special/Subgroup Populations

No further subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

For the efficacy analysis, the sponsor focused on the statistical significance of decrease in IOP 'before and after' dorzolamide treatment without comparing the decrease with that of the active comparator, timolol.

The comparisons in efficacy between dorzolamide and timolol groups were done using a confidence interval method in a post hoc manner instead of a pre-planned statistical hypothesis testing method. While 95% confidence intervals of difference in IOP decrease after treatment between dorzolamide and timolol included zero indicating that the effect of dorzolamide was not statistically different from that of timolol, a clinical judgment is required regarding similarity in efficacy between the two treatments by assessing the width of the confidence interval.

The safety endpoint was not compared between treatment groups, but was evaluated only within dorzolamide group although the clinical trial was controlled with active comparator.

5.1.2 Collective Evidence

Based on our review of the data up to 12 weeks we conclude the following:

1. The 95% confidence intervals for the proportion of discontinuation of therapy due to a drug-related adverse experience for dorzolamide group were (0.05%, 9.55%) for age-cohort < 2 years of age and (0.37%, 10.52%) for age-cohort ≥2 years but <6 years of age. Therefore, the safety of dorzolamide in both age-cohorts was shown according to the pre-defined decision rule, which claims the safety if the upper limit is lower than 25%.

2. At Week 12 for age-cohort <2 years of age, there were statistically significant decreases from baseline in IOP in both treatment groups and the decrease were similar in the dorzolamide and timolol groups with mean change changes from baseline (95% CI) in IOP of -7.30 (-9.51, -5.03) vs. -7.80 (-10.90, -4.74) mm Hg. The

difference between the two treatments and the 95% CI for the difference were 0.57 (-3.39, 4.54) mm Hg, indicating a similar effect for the two treatment groups.

3. At Week 12 for age-cohort ≥2 years but <6 years of age, there were statistically significant decreases from baseline in IOP in both treatment groups and the decrease were similar in the dorzolamide and timolol groups with mean change changes from baseline (95% CI) in IOP of -7.10 (-8.72, -5.39) vs. -7.40 (-9.67, -5.13) mm Hg. The difference between the two treatments and the 95% CI for the difference were 0.34 (-2.50, 3.19) mm Hg, indicating a similar effect for the two treatment groups.

4. At Week 12 for age-cohorts combined, there were statistically significant decreases from baseline in IOP in both treatment groups and the decrease were similar in the dorzolamide and timolol groups with mean change changes from baseline (95% CI) in IOP of -7.20 (-8.53, -5.79) vs. -7.60 (-9.45, -5.75) mm Hg. The difference between the two treatments and the 95% CI for the difference were 0.44 (-1.92, 2.79) mm Hg, indicating a similar effect for the two treatment groups.

5.2 Conclusions and Recommendations

The data from this pediatric study for marketing exclusivity extension demonstrated that dorzolamide ophthalmic solution resulted in significant reduction of intraocular pressure (IOP) 'after treatment' compared with 'before treatment' in pediatric patients with glaucoma of age less than 6. Also, it appears that the proportion of discontinuation of therapy due to a drug-related adverse experience was within prespecified limits.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer:	Yongman Kim, Ph.D. Mathematical Statistician
Date:	February 9, 2004
Concurring Reviewer:	Stan Lin, Ph.D. Statistical Team Leader

cc:

HFD-550/Nancy Halonen
HFD-550/Jennifer Harris, M.D.
HFD-550/William Boyd, M.D.
HFD-725/Yongman Kim, Ph.D.
HFD-725/Stan Lin, Ph.D.
HFD-725/Mohammad Huque, Ph.D.
HFD-700/Charles Anello, Ph.D.

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

/s/

Yongman Kim
2/9/04 03:18:47 PM
BIOMETRICS

Stan Lin
2/9/04 03:30:21 PM
UNKNOWN

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-408 / S-033

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 20-408 TRUSOPT

Patent Information

Item 13

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredient	Dorzolamide Hydrochloride
2. Dosage(s)	2.0%
3. Trade Name	TRUSOPT
4. Dosage Form	Sterile Ophthalmic Solution
Route of Administration	Topical
5. Applicant Firm Name	Merck Research Laboratories
6. NDA Number	20-408
7. Approval Date	December 9, 1994
8. Exclusivity	NCE December 9, 1999 Six-months pediatric market exclusivity
9. Applicable Patent Numbers	U.S. Patent No. 4,797,413 Expiration Date: 4/28/2008* U.S. Patent No. 4,619,939 Expiration Date: 10/28/2003

*Includes 1,233 days of Term Restoration pursuant to 35 U.S.C. Section 156.

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION

Date of Written Request from FDA: 6/24/99, amended 5/19/00 and 2/12/02.
Application Written Request was made to: NDA# 20-408
Timeframe Noted in Written Request for Submission of Studies 6/30/04.
NDA# _20-408____ Supplement #_033 Choose one: SE5
Sponsor _Merck & Co._____
Generic Name dorzolamide HCL_____ Trade Name TRUSOPT ____
Strength__2%__ _____ Dosage Form/Route____Ophthalmic Solution/Topical_____
Date of Submission of Reports of Studies 10/17/03.
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) _1_/_17_/04_. 14

Was a formal Written Request made for the pediatric studies submitted?	Y _X__	N___
Were the studies submitted after the Written Request?	Y __X_	N___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y _X__	N___
Was the timeframe noted in the Written Request for submission of studies met?	Y __X_	N___
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y _X__	N___
Did the studies fairly respond to the Written Request?	Y _X__	N___

SIGNED_____Jennifer Harris_____ DATE__12-15-03____
(Reviewing Medical Officer)

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ✓ **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
20-408/20-869	4797413	4/28/08
20-408/20-869	4619939	10/28/03

SIGNED _____ DATE 1/5/04

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

/s/

Grace Carmouze
1/6/04 10:26:34 AM

NDA 20-408: TRUSOPT™ Ophthalmic Solution (Dorzolamide Hydrochloride)
Item 16 - Debarment Certification

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

Virginia G. Snyder

16-Oct-2003

Virginia G. Snyder
Associate Director
Regulatory Affairs

Date

Jeffrey R. Tucker, M.D.
Director
Regulatory Affairs

DESK COPY

April 9, 2004

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486
Tel 484 344 7788
215 652 5000
Fax 484 344 2516
Email: jeffrey_tucker@merck.com

Wiley Chambers, M.D., Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products

MERCK
Research Laboratories

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED
APR 12 2004
MEGA / CDER

Dear Dr. Chambers:

NDA 20-408/S-033: TRUSOPT™ Ophthalmic Solution
(Dorzolamide Hydrochloride)

Amendment to Pending Drug Application

Reference is made to the supplemental New Drug Application cited above for TRUSOPT™, submitted as an electronic archive on October 16, 2003, providing pediatric use information. Reference is also made to an electronic-mail received on April 2, 2004, from Ms. Nancy Halonen, FDA, to Dr. Jeffrey Tucker, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., that contained the proposed labeling for this supplement. Reference is also made to several telephone conversations between Ms. Halonen and Dr. Tucker on April 6 and 7, 2003, regarding the proposed labeling. Further reference is made to an electronic-mail received on April 7, 2004, from Ms. Halonen to Dr. Tucker requesting that MRL formally submit the labeling agreed to in the referenced conversations.

As indicated on the attached Form FDA 356h, this amendment provides for changes in the labeling section of the approved New Drug Application for TRUSOPT™. With this amendment we are accepting the labeling revisions requested by the Agency in the above cited telephone conversations. The Statement of Organization following this letter describes the sections contained in this application.

With this submission are the following item:

Labeling

- Proposed labeling text

This amendment is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED.DOC within the labeling folder on the Compact Disk (CD) provided.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Nancy M. Halonen, Regulatory Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.

We consider the filing of this amendment to be a confidential matter, and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Jeffrey R. Tucker, M.D. (484-344-7788) or, in my absence, to Michelle W. Kloss, Ph.D. (484-344-2905).

Sincerely,

Jeffrey R. Tucker, M.D.
Director, Regulatory Affairs

Enclosure: CD

Federal Express #1

Desk Copies: Ms. Nancy M. Halonen, Regulatory Project Manager (cover letter)
HFD-550, Room N313
Federal Express #2

Q:\Dubs\TRUSOPT Peds filing\pedsamend_labeling.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-408/S-033

Merck & Co., Inc.
Attention: Jeffrey Tucker
Director, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tucker:

Please refer to your new drug application (NDA) submitted October 16, 2003, and received October 17, 2003, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRUSOPT (dorzolamide hydrochloride ophthalmic solution) 2%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 16, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Nancy Halonen, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Nancy Halonen
12/16/03 12:15:14 PM
Nancy Halonen has signed for Carmen DeBellas

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: November 10, 2003

From: Sonny Saini, Pharm.D. - DDMAC

To: Nancy Halonen

Re: Trusopt (dorzolamide hydrochloride ophthalmic solution) Sterile Ophthalmic Solution 2%
NDA 20-408

Clinical Studies - Pediatric Patients

- In the Pediatric Patients Clinical Studies section of the proposed product label (PI) we recommend deleting the phrase " [redacted] because it is misleading. This claim is promotional in tone and minimizes the risks associated with Trusopt treatment. For example, the Pediatric patients – Adverse Reactions section of the proposed PI states that 12.1% of pediatric patients under 2 years of age experienced burning/stinging in the eye. Therefore, due to the incidence of burning/stinging in the eye, we would not consider this product to be " [redacted]

- If the consensus is to keep the claim " [redacted] in the PI, it seems more appropriate to have this located in the Adverse Reactions section instead of the Clinical Studies section.

- In the Pediatric Patients Clinical Studies section of the proposed PI the age group in the first age cohort (less than 2 years of age) is not specified. Should the age cohort be specified by stating the youngest age of the patients in the study?

Precautions – Pediatric Use

- Should the age range of the pediatric patients be stated here instead of broadly stating "pediatric patients

Adverse Reactions – Pediatric patients

- The age group in cohort (less than 2 years of age) is not specified. Should the age cohort be specified by stating the youngest age of the patients in the study?

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

/s/

Sonny Saini
11/12/03 10:41:28 AM
DDMAC REVIEWER

Virginia G. Snyder
Associate Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486
Tel 484 344 7984
215 652 5000
Fax 484 344 2516

November 3, 2003

MERCK
Research Laboratories

Wiley Chambers, M.D., Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Chambers:

NDA 20-408: TRUSOPT™ Ophthalmic Solution
(dorzolamide hydrochloride ophthalmic solution)

Response to FDA Request For Information

Reference is made to the New Drug Application cited above and to the submission of a pediatric study report on October 16, 2003, requesting pediatric exclusivity for TRUSOPT™ Ophthalmic Solution. Reference is also made to an October 29, 2003 telephone conversation between Mr. Raphael Rodriguez, FDA, and Ms. Virginia Snyder, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., in which Mr. Rodriguez requested additional review copies of the administrative items, labeling information (Item 2), annotated labeling and Executive Summary (Item 3), and pediatric use information (Item 20) provided in the pediatric supplement. Mr. Rodriguez also requested that the review copies be sent to Ms. Nancy Halonen, who was assuming the responsibilities of FDA Regulatory Project Manager.

By copy of this letter, MRL is providing Ms. Halonen with fifteen (15) desk copies containing the administrative items and Items 2, 3, and 20, as requested.

We hope that the materials provided in this submission have adequately addressed the Agency's request.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Nancy M. Halonen, Regulatory Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Virginia G. Snyder (484-344-7984) or, in my absence, to Michael C. Elia, Ph.D., DABT (484-344-3180).

Sincerely,

Virginia G. Snyder
Associate Director, Regulatory Affairs

Enclosure: CD

Federal Express #1

Desk Copies: Ms. Nancy M. Halonen, Regulatory Project Manager
(cover letter + 15 Review Copies of Volume 1 containing
Administrative Items & Items 2, 3, 20)
HFD-550, Room N-313
Federal Express #2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-408/S-033

Merck & Co., Inc.
Attention: Virginia G. Snyder
Associate Director, Regulatory Affairs
BLA-20
P.O. Box 4
West Point PA 19486

Dear Ms. Snyder:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	TRUSOPT (dorzolamide hydrochloride) 2% Ophthalmic Solution
NDA Number:	20-408
Supplement number:	S-033
Review Priority Classification:	Priority (P)
Date of supplement:	October 16, 2003
Date of receipt:	October 17, 2003

This supplemental application proposes revisions in the label to reflect the safe and effective use of TRUSOPT in pediatric patients with elevated intraocular pressure or glaucoma.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 6, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 17, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Attention: Document Room, N115
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Attention: Document Room, N115
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any question, call name, Nancy Halonen, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Carmen DeBellas
10/27/03 10:14:35 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-408

Merck & Co., Inc.
Attention: Virginia G. Snyder
Manager, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Ms. Snyder:

Please refer to the Written Request, originally issued on June 24, 1999, that you received from the Center for Drug Evaluation and Research. This Written Request was issued under Section 505A of the Federal Food, Drug, and Cosmetic Act to conduct pediatric studies using dorzolamide. As you know, on January 4, 2002, the President signed into law the "Best Pharmaceuticals for Children Act," (BPCA) which both extended the pediatric exclusivity program established in the 1997 FDA Modernization Act (FDAMA) and provided new mechanisms for studying pediatric uses for drugs. The BPCA also contains new provisions of which you should be aware related to user fees, priority review, drug labeling, and disclosure of pediatric study results. FDA is revising its Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act to provide additional information on the pediatric drugs study provisions of the BPCA.

FDA has received questions about whether sponsors who were issued Written Requests to conduct pediatric studies prior to passage of the BPCA, but who had not as yet submitted the reports of the studies as of January 4, 2002, would be governed by the provisions of FDAMA or the BPCA. In order to maximize the benefit to be derived from the BPCA and to minimize uncertainty and delay in implementing the pediatric exclusivity program, FDA has decided to reissue those Written Requests originally issued prior to passage of the BPCA for which studies have not already been submitted.

This letter is your notification that the Written Request (and any subsequent amendments) described above is considered to be reissued as of the date of this letter. The terms of the Written Request are not otherwise altered by this letter. If you believe that the Written Request should be amended, please contact the division directly.

Please note that if the original Written Request was issued under Section 505A(a), it will now be considered to be issued under Section 505A(b), due to the reordering of the sections, as described in Section 19 of the BPCA. If the original Written Request was issued under Section 505A(c), it will still be considered to be issued under Section 505A(c).

An important change to note is that, if the drug for which FDA issued the Written Request under 505A(c) has listed patent or exclusivity protection, new section 505(d)(4)(A) states that within 180 days of receipt of this "reissued" Written Request, you must notify FDA when the pediatric studies will be initiated, or that you do not agree to conduct the requested studies. New provisions at Section 505(d)(4)(B)-(F) describe alternative methods for obtaining these pediatric studies.

If you have questions regarding the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. As noted above, requests to amend your Written Request should be directed to the review division.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

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

/s/

Dianne Murphy
7/2/02 07:51:25 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-408

Merck & Co., Inc.
Attention: Virginia G. Snyder
Manager, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Ms. Snyder:

Reference is made to your correspondence dated December 21, 2001, requesting changes to FDA's June 24, 1999, Written Request for pediatric studies for dorzolamide.

We have reviewed your proposed changes and are amending the below listed section of the Written Request. All other terms stated in our Written Request issued on June 24, 1999, as amended May 19, 2000 remain the same.

Timeframe
The report of the study that meets the terms of the Written Request dated June 24, 1999, as amended May 19, 2000 and by this letter must be submitted to the Agency on or before June 30, 2004, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

The report of the study should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bold type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

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

/s/

Jonca Bull
2/12/02 12:55:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-408

Merck Research Laboratories
Attention: Dennis M. Erb, Ph.D.
Senior Director, Regulatory Affairs
P.O. Box 4, BLA-20
Sumneytown Pike
West Point, Pennsylvania 19486

MAY 19 2000

Dear Dr. Erb:

Reference is made to your correspondence dated February 18, 2000, requesting changes to FDA's June 24, 1999, Written Request for pediatric studies for Trusopt (dorzolamide hydrochloride ophthalmic solution) Sterile Ophthalmic Solution, 2%. We also refer to our letter dated November 28, 1999.

We have reviewed your proposed changes and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on June 24, 1999, remain the same.

Age Groups:
A minimum of 50 patients less than 2 years of age and a minimum of 50 patients from 2 through 5 years of age inclusive should be enrolled to receive dorzolamide hydrochloride monotherapy.

Drug Information:
Dorzolamide hydrochloride ophthalmic solution, 2% should be compared to timolol maleate ophthalmic gel forming solution.

The report of the study that meets the terms of the Written Request dated June 24, 1999, as amended by this letter, must be submitted to the Agency on or before March 31, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Please submit the protocol for the above study to an investigational new drug application (IND) and clearly mark your submission, "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-408

Merck Research Laboratories
Attention: Jeffery R. White, M.D.
Director, Regulatory Affairs
P.O. Box 4 (BLA-20)
Sumneytown Pike
West Point, Pennsylvania 19486

JUN 24 1999

Dear Dr. White:

Reference is made to your Proposed Pediatric Study Request submitted on February 16, 1999, for Trusopt (dorzolamide hydrochloride ophthalmic solution) Sterile Ophthalmic Solution, 2% to NDA 20-408.

To obtain needed pediatric information on dorzolamide hydrochloride for the treatment of elevated intraocular pressure, the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. FDA requests that you submit information from the following study:

Type of Study:
The study should be a randomized, double-masked, parallel comparison trial.

Indication/Objective:
The primary objective of the study should be to evaluate the safety and the clinical response on elevated intraocular pressure between treatment groups. Enrolled patients should include male and female pediatric patients with a clinical diagnosis of glaucoma or elevated intraocular pressure.

Drug Information:

REGULATORY AFFAIRS
JUL 16 1999
D M. ERB

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your applications. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact Joanne Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

Robert J DeLap

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research