# CENTER FOR DRUG EVALUATION AND RESEARCH

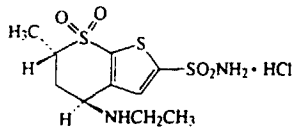
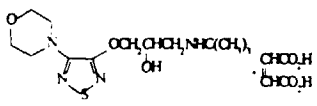
**Application Number** 20-869

## PHARMACOLOGY REVIEW(S)

OCT 2 1997

# DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG PRODUCTS

## PHARMACOLOGY AND TOXICOLOGY REVIEW

| | |
|---|---|
| **NDA** | **20-869** |
| **DRUG:** | COSOPT™ (2.0% Dorzolamide HCl + 0.5% Timolol Maleate Ophthalmic Solution) |
| **EXPERIMENTAL CODE NAME:** | MK-507 and L-671,152 for Dorzolamide HCl |
| **SPONSOR:** | Merck Research Laboratories<br>Sunnytown Pike, P.O. Box 4, BLA-20<br>West Point, PA 19486 |
| **SUBMISSION DATE:** | June 25, 1997 |
| **TYPE OF SUBMISSION:** | Full Original Application |
| **DATE COMPLETED:** | September 30, 1997 |
| **REVIEWER:** | W. C. Josie Yang, Ph.D. |
| **CDER STAMP DATE:** | June 26, 1997 |
| **DATE RECEIVED IN HFD-550:** | June 27, 1997 |
| **DATE ASSIGNED TO REVIEWER:** | July 1, 1997 |
| **DRUG CATEGORY:** | Topical Carbonic Anhydrase (CA) and β Blocker |
| **FORMULA:** | |
| Dorzolamide Hydrochloride: | $C_{10}H_{16}N_2O_4S_3 \cdot HCl$, (4S-trans)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride, MW =360.91  |
| Timolol Maleate: | $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$, (S)-1-[(1,1-dimethylethyl) amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol,(Z)-2-butenedioate (1:1) salt, MW= 432.50  |
| **CAS REGISTRY Nº:** | Dorzolamide HCl,<br>Timolol Maleate, |
| **INDICATION:** | Treatment of Elevated Intraocular Pressure |
| **DOSAGE FORM:** | Sterile Ophthalmic Solution |
| **ROUTE OF ADMINISTRATION:** | Topical (Ocular) |
| **RELATED DRUG/INDs/NDAs/DMFs:** | |

## TABLE OF CONTENTS

# I. PRECLINICAL/LABORATORY STUDIES:

## PHARMACOLOGY

### *PHARMACODYNAMIC OF DORZOLAMIDE HCL AND TIMOLOL*

Both dorzolamide HCl (DZ) and timolol maleate (TM) have been marketed for the indication to lower the intraocular pressure (IOP) in patients with elevated intraocular pressure or glaucoma. Both drugs achieve this function by ↓ the secretion of aqueous humor from the ciliary process. DZ has been shown to lower IOP by decreasing the formation of aqueous humor by inhibition of carbonic anhydrase-II (CA-II) in the ciliary process. TM is a beta-adrenergic blocking agent that lowers IOP by reducing the aqueous humor inflow. COSOPT™ is formulated to contain 2% DZ and 0.5% TM (doses expressed as the free base).

### DISTRIBUTION IN EYE

1. MRL Preclinical Report: Ocular Distribution Studies in the Pigmented Rabbit after Topical Administration of Dorzolamide/Timolol, Dorzolamide or Timolol, MRL, February 19, 1997

This study was conducted in pigmented rabbits to evaluate the penetration of both dorzolamide and timolol into the eye following the acute instillation of the drugs either in combination or individually. A 50 µl drop of either DZ/TM (2%/0.5%, batch number FE-1537), DZ (2%, batch number FE-1486) or TM (0.5%, batch number 1636B) were instilled bilaterally into the conjunctival cul-de-sac of conscious, non-fast, ♂ Dutch belted rabbits (weighing approximately 1.5 to 2.5 kg). Concentrations of DZ and TM in the cornea, aqueous humor, iris-ciliary body, lens, vitreous, retina, choroid and sclera were determined by at 1, 2 and 4 hours after the acute instillation. Results are summarized in the following table.

| Sample | Concentrations of Dorzolamide | | | | | | Concentrations of Timolol | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 hr | | 2 hr | | 4 hr | | 1 hr | | 2 hr | | 4 hr | |
| | DZ | DZ/TM | DZ | DZ/TM | DZ | DZ/TM | TM | DZ/TM | TM | DZ/TM | TM | DZ/TM |
| Cornea (µg/g) | 73.37 | 38.12* | 42.61 | 23.51* | 14.53 | 15.32 | 21.05 | 15.94 | 8.58 | 10.56 | 6.08 | 3.82 |
| Aqueous Humor (µg/ml) | 10.12 | 6.80* | 6.51 | 6.57 | 2.56 | 4.26 | 1.03 | 1.55 | 0.24 | 0.82* | 0.08 | 0.27 |
| Iris-Ciliary Body (µg/g) | 22.19 | 15.42* | 22.81 | 22.02 | 25.55 | 37.80* | 23.66 | 20.37 | 23.29 | 25.92 | 28.27 | 30.69 |
| Lens (µg/g) | 0.96 | 0.28* | 0.86 | 0.32 | 0.90 | 0.31* | 0.04 | 0.01 | 0.01 | 0.02 | 0.03 | 0.02 |
| Vitreous (µg/ml) | 0.29 | 0.06* | 0.23 | 0.07 | 0.10 | 0.06 | 0.02 | 0.04* | 0.02 | 0.03 | 0.03 | 0.02 |
| Retina (µg/g) | 2.96 | 0.96* | 4.91 | 1.20 | 4.36 | 1.16 | 0.09 | 0.18 | 0.05 | 0.17* | 0.01 | 0.08* |
| Choroid (µg/g) | 23.57 | 11.71* | 26.52 | 16.36 | 12.56 | 9.88 | 4.32 | 11.55* | 4.93 | 14.33* | 3.18 | 13.21 * |
| Sclera (µg/g) | 33.95 | 16.04* | 43.59 | 15.79 | 15.56 | 6.95* | 1.16 | 4.19* | 0.90 | 1.94 | 0.87 | 1.41 |

*Significantly different from values for DZ or TM for p≤0.05 using Student's "t" test.

A higher level of DZ (37.80 µg/g) was noted in the iris-ciliary body at four hours after the topical administration with DZ/TM combination. In contrast, significantly less DZ was present at one hour in the iris-ciliary body after the instillation of DZ/TM. The instillation of DZ/TM resulted in a peak concentration of timolol (30.69 µg/g) in the iris-ciliary body which was very similar to the corresponding concentration of drug present after dosing with TM (28.27 µg/g) at four hours. This study demonstrates that high concentrations of both DZ and TM are present in the iris-ciliary body following the administration of DZ/TM. In addition, the iris-ciliary body content of the two drugs was not markedly and consistently different following the administration of DZ and TM either in combination or individually. Similar TM concentrations were detected in the corneal after the instillation of either DZ/TM or TM. The peak concentrations of DZ in the aqueous humor at one hour after the application of either DZ/TM or DZ were 6.80 µg/ml and 10.12 µg/ml, respectively. Levels declined with time and significant differences between the two treatments were absent at both two and four hours.

## ADME

Two non-GLP *in vitro* metabolism studies with human liver microsomes were included in this NDA:

1. MRL Preclinical Report: Human Liver Microsome Studies With MK-507: Assessment of Isozymes Mediating *N*-Deethylation and Effect of MK-507 on Metabolism of Probe Substrates, April 14, 1994.
2. MRL Preclinical Report: Lack of Effect of Dorzolamide on the Metabolism of Timolol by Human Liver Microsomes, October 11, 1996.

Results from these studies are summarized as followings:

- Metabolism of DZ to *N*-desethyl metabolite (L-706,803) was mediated by Human microsome CYP2C9, CYP2C19 and CYP3A4 isoenzymes.
- DZ at concentrations up to 200 $\mu$M did not interfere the metabolism of TM by human microsomes.

The following information provided by the sponsor based on the data from previous NDA submissions (NDA 18-086: Timolol Maleate; NDA. 20-408: Dorzolamide HCl ).

### ABSORPTION AND PHARMACOKINETICS

In rats and dogs, DZ is systemically available following oral administration with bioavailability values of ≥73%. Disposition kinetics of DZ are species-dependent and data obtained from iv administration are given in the below table. In rats, the pharmacokinetics of dorzolamide are nonlinear at doses greater than 0.5 mg/kg, with the AUC increasing less than proportionally to dose as results of concentration-dependent distribution into erythrocytes and displacement by the active *N*-desethyl metabolite (L-706,803) from CA-II binding sites.

| Species | Clp (ml/hr•kg) | $T_{½}$ (day) |
|---|---|---|
| Dog | 0.028 | 4.2 |
| Rat | 0.70-0.92 | 185 |

TM is well absorbed from oral solutions in rats and dogs. Absorption is nearly 100% in both species. The plasma half-life is 28 min in rats, while it is 48 min in dogs.

### METABOLISM

In rats, the major metabolic pathway of DZ is through *N*-deethylation. Urinary excretion of unchanged drug (38.6% of the dose) and *N*-deethylated metabolite (45.0% of the dose), L-706,803, is the major elimination route. In contrast, renal excretion of unchanged drug is the predominant route of elimination in dogs. *In Vitro* incubation of freshly prepared human liver slices with [$^{14}$C]DZ showed that *N*-deethylated compound, L-706,803, was the only one metabolic product. The *in vivo* studies in rats and dogs and *in vitro* studies with human liver slices suggest that formation of *N*-deethylation be the only metabolic pathway of DZ in rats, dogs and humans.

TM is extensively metabolized in rats and dogs. Formation of the lactic acid derivative, 2-hydroxy-3-(4-morpholino-1,2,5-thiadia-zol-3-yloxy)-propionic acid is a major metabolic pathway in dogs. On contrast, this metabolite appears to be minor in rats. Another metabolic pathway in dogs is the formation of an acetic acid derivative. Several other minor metabolites are detected in urine.

### DISTRIBUTION

The distribution of DZ into red blood cells is vast and dose-dependent in the rat, dog and human blood due to the saturation of binding to CA in red blood cells (RBC). The blood concentration of DZ required for nonlinear distribution is consistent with that predicted from the physiological concentration of CA-II. Following iv administration of [$^{14}$C]DZ to rats, radioactivity is distributed widely in tissues. However, higher levels of DZ are detected in the CA containing tissues that include red blood cells, kidneys and choroid plexus. Concentrations of DZ radioequivalents decline with time in all tissues. DZ has moderate affinity for plasma proteins. The unbound fraction of DZ is ~70% in mouse, rat and dog plasma and this binding is not concentration-dependent.

Radioactivity distributes widely in tissues after iv administration of [$^{14}$C]TM to rats. The highest concentrations are found in the liver, small intestine, kidney and lung, while the brain and fat are found to have lowest

radioactivity. Concentrations of TM radioequivalents decline with time in all tissues. TM has low affinity binding for plasma proteins and the unbound fraction is >85% in rat and dog plasma .

EXCRETION

Renal excretion is the major route of elimination of DZ following iv administration of [$^{14}$C]DZ to rats and dogs. In rats, approximately equal amounts of unchanged drug and the *N*-deethylated metabolite, L-706,803 are detected in urine. Contrarily, primarily unchanged drug is found in dog urinary excretions.
Following iv administration of [$^{14}$C]TM to rats and dogs, radioactivity is eliminated primarily via renal excretion, while excretion into feces is moderate.

## TOXICOLOGY

### *ACUTE TOXICITY (SINGLE DOSE) STUDIES*

No new studies were performed with the combination product.

### *SUBCHRONIC (REPEATED DOSE) TOXICITY STUDIES*

The toxic potential of DZ and TM has been assessed after sequential and/or coadministration (dorzolamide/timolol) in ocular irritation studies in monkeys, rabbits, and dogs.

1. MRL Preclinical Report: Timolol/L-671,152: 15-Day Ocular Irritation Study in Monkeys. TT #89-602-0 (Vol. 1.8 p. B-24)

Study Report Nº: TT #89-602-0
Study Aims: To determine the potential of timolol and L-671,152 to cause ocular irritation in rhesus monkeys when administered concomitantly.
Compound: Timolol maleate, batch Nº PX0150, L-671,152-001E, batch Nº 007,

Formulation:

| | Timolol (mg/ml) | | | L-671,152 (mg/g) | |
|---|---|---|---|---|---|
| | Vehicle | 0.5% | | Vehicle | 2% |
| Timolol | | | L-671,152 | | |
| $NaH_2PO_4 \cdot 2H_2O$ | | | Na Citrate$\cdot 2H_2O$ | | |
| $Na_2HPO_4 \cdot 12H_2O$ | | | Benzalkonium Cl | | |
| Benzalkonium Cl* | | | Hydroxyethylcellulose | | |
| NaOH qs | | | Mannitol | | |
| $H_2O$ for injection | | | HCl | | |
| | | | NaOH | | |
| | | | $H_2O$ for injection | | |

* including 10% overage

Dose and Route: topical eye instillation of both timolol and L-671,152 formulations (10 minutes apart) onto the cornea of the left eye and right eye served as a control, 30 $\mu$l/instillation, 3x/day with ~3 hours apart
Dosing Duration: 15 days
Animal Species: Sixteen rhesus monkeys (Macacca mulatta), 8♂ & 8♀, ~ 2 to 2.5 years old, weighing 2.5 to 3.6 kg for ♂ and 2.3 to 3.9 kg for ♀
Testing Site: Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche, Riom, France
Study Date: Initiation: January 16, 1989.
Termination: January 30, 1989.
GLP/AUC Compliance: Yes
Study Design: Animals were randomly distributed into two groups, one receiving TM and DZ formulation vehicles, and the other receiving 0.5% TM and 2% DZ. The following parameters were performed during the study.

- Physical Examinations and Food Consumption - 1x/day
- Body Weights - pretest on Days 1 and 15
- Ophthalmologic Examination - General eye survey was performed each day after instillation of the drug. Scoring of ocular reactions was done twice a week, before and after the 1st daily instillation of TM and DZ formulations or vehicles on all monkeys. Ocular reactions were graded based on the Draize[1] scoring system.
- Ophthalmoscopic and Biomicroscopic Examination - Day 15 after the last instillation using an indirect ophthalmoscope and a slit lamp to examine the different portions of the eyes.

**Results:** The monkeys were not sacrificed and necropsied. No deaths occurred. No treatment-related physical signs or differences in body weight or food consumption were observed. Transient ocular reactions were seen in eyes receiving vehicle or drug (0.5% TM or 2% DZ solution) treatments. When 0.5% TM solution was given, very slight to moderate blinking, generally persisting about 20 seconds, was observed sporadically throughout the study and was occasionally associated with very slight clear lacrimation. In contrast, when its vehicle was given, only very slight to slight blinking was observed. Similarly, treatment with the DZ vehicle or the 2% DZ solution resulted in very slight to moderate blinking which persisted for about 20 seconds. Very slight lacrimation was also occasionally observed in both of these groups. There were no treatment-related changes seen on ophthalmoscopic or slit lamp examination.
In Conclusion, concomitant use of 0.5% TM and 2% DZ three times a day, 10 minutes apart for two weeks did not caused any significant reactions in monkey eyes.

2. MRL Preclinical Report: MK-0507: three-day Exploratory Ocular Interaction Study in Rabbits. TT #90-69-33 (Vol. 1.8, p. B-147)

| | |
|---|---|
| Study Report Nº: | TT #90-69-33 |
| Study Aims: | To determine the ocular tolerance of a 3% dorzolamide ocular formulation associated with four reference drugs (pilocarpine, betaxolol, timolol, or dipivephrin) when dosed sequentially for three days. |
| Compound: | 3% MK-0507, |
| Dose and Route: | topical eye instillation of 3% dorzolamide solution followed in 10 minutes by the reference drugs onto the cornea of the left eye and right eye served as a control, 30 $\mu$l/instillation, 3x/day with ~4 hours apart |
| Dosing Duration: | 3 days |
| Animal Species: | Sixteen HY/CR albino rabbits, 8♂ & 8♀, ~ 3 months of age, weighing 2.85 and 3.60 kg |
| Testing Site: | Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche, Riom, France |
| Study Date: | Not Available |
| GLP/AUC Compliance: | No |
| Study Design: | Animals were randomly distributed in four groups of 2 males and 2 females. DZ solution (3%) was applied onto the cornea of the left eye followed in 10 minutes by the reference drugs and right eye served as a control. General eye survey was performed each day after instillation of the drug. A detailed examination of the eyes was done on Days 1 and 3. Ocular reactions were graded based on the Draize scoring system. |

**Results:**
- 3%DZ + 4% pilocarpine caused very slight blinking, slight redness, occasional lacrimation, and miosis.
- 3%DZ + 0.5% betaxolol caused very slight redness and/or occasional lacrimation.
- 3%DZ + 0.5% timolol caused very slight blinking, very slight redness and/or slight lacrimation in ¾ rabbits.

---

[1] Draize, J.H.; Woodard, G.; Calvery, H.O.: Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes. J. Pharmacol. Exp. Ther. 82: 377-390, 1944.

- 3% DZ + 0.1% dipivephrin - A very slight to slight redness on the bulbar conjunctiva and/or nictitating membrane and/or palpebral conjunctiva was noted in ¾ rabbits.

The Draize score was zero for all eyes of all groups indicating that the sequential administration of both compounds for three days was not irritating.

In summary, although minor reactions were observed after dosing, the coadministration to rabbits with 3% DZ and four reference compounds did not induce irritation of the treated eyes.

3. MRL Preclinical Report: MK-0507: 28-Day Ocular Interaction Study in Rabbits. TT #90-611-0 (Vol. 1.8 p. B-155)

Study Report Nº: TT #90-611-0

Study Aims: To evaluate the one-month ocular tolerance of 2% dorzolamide instilled sequentially with 4% pilocarpine, 0.5% betaxolol, 0.5% timolol, or 0.1% dipivephrin in albino HY/CR rabbits.

Compound: 2% MK-0507,

Formulation:

| 2% L-671,152 (mg/g) | |
|---|---|
| MK-0507 (L-671,152-001E010) | |
| Na Citrate•2$H_2O$ (USP) | |
| Benzalkonium Cl (NF) | |
| Hydroxyethylcellulose | |
| Mannitol (USP) | |
| NaOH (NF) | qs |
| $H_2O$ for injection (USP) | qs |

*Equivalent to 20.00 mg base.

Dose and Route: topical eye instillation of 2% dorzolamide solution followed in 10 minutes by the reference drugs (commercial preparations of 4% pilocarpine, 0.5% betaxolol, 0.5% timolol, or 0.1% dipivephrin) onto the cornea of the left eye and right eye served as a control, 30 $\mu$l/instillation, 3x/day with ~3 hours apart

Dosing Duration: 28 days

Animal Species: HY/CR albino rabbits, ~14 to 18 weeks old , weighing 2.58 to 4.05 kg, 3/sex/group

Testing Site: Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche, Riom, France

Study Date: 4/17/90 - 5/14/90

GLP/AUC Compliance: Yes

Study Design: DZ solution (2%) was applied onto the cornea of the left eye of 3/sex/group rabbits followed by the reference drugs in 10 minutes part and the right eye served as a control. Animals were dosed 3x a day with ~3hr apart for 28 days. The following parameters were monitored.

- Physical Signs and Mortality - 1x/day.
- Body Weights - pretest and 1x/week.
- General Eye Survey - 1x/day.
- Score Ocular Reactions - pretreatment and 2x/week.
- Indirect Ophthalmoscopic and Slit Lamp Examination - Weeks 2 and 4.
- Necropsy - Not performed.

**Results:**

- Clinical Observation and Mortality - Two rabbits (1 in the 0.5% timolol group and the other in the 0.5% betaxolol group 1) died as a result of intercurrent pleuropneumonia. No remarkable clinical signs were noted.
- Body Weights - No treatment-caused changes in body weights and weight gains.
- Ocular Reactions -
  - ▲ 2% DZ + 4% pilocarpine caused a slight ↑ in lacrimation in comparison with 4% pilocarpine alone or dorzolamide alone.
  - ▲ 2% DZ + 0.5% betaxolol induced slight ↑ in lacrimation and blinking.

- ▲ 2% DZ + 0.5% timolol caused a very slight ↑ in lacrimation.
- ▲ 2% DZ + 0.1% dipivephrin caused slight ↑ in lacrimation, blinking and redness.

- Draize Scores - Individual Draize scores were either zero or very low for all animals.
- Ophthalmoscopic and Biomicroscopic Examination - No drug-related changes were seen.

In summary, topical application of 2%DZ plus 4% pilocarpine, 0.5% betaxolol, 0.5% timolol, or 0.1% dipivephrin to rabbits eyes caused slight increases in lacrimation, blinking incidence, and redness. Scores for ocular irritation (Draize) were very low.

4. MRL Preclinical Report: MK-0507/Timolol: 29-Day Ocular Irritation Study in Rabbits. TT #90-632-0 (Vol. 1.8, p. B-42)

Study Report Nº: TT #90-632-0
Study Aims: To evaluate ocular irritation of a combination of 2% and 0.5% timolol in albino HY/CR rabbits for one month.
Compound: 2% MK-0507, L-671,152-001E, batch Nº 013 and 014; Timolol maleate, batch Nº PX0346 and RX0179.
Formulation:

| Ingredient | Vehicle | 0.5% Timolol (mg/ml) | 2% MK-0507 (mg/g) | 2% MK-0507 + 0.5% Timolol (mg/g) |
|---|---|---|---|---|
| MK-0507 (L-671,152-001E) | | | | |
| Timolol Maleate | | | | |
| $NaH_2PO_4 \cdot 2H_2O$ | | | | |
| $Na_2HPO_4 \cdot 12H_2O$ | | | | |
| Na Citrate$\cdot 2H_2O$ | | | | |
| Benzalkonium Cl* | | | | |
| Hydroxyethylcellulose | | | | |
| NaOH qs | | | | |
| Mannitol | | | | |
| HCl qs | | | | |
| $H_2O$ for injection qs | | | | |

Dose and Route: conjunctival sac of left eye (the right eye was not treated), 30 µl/instillation, 3x/day with ~ 3 hr apart
Dosing Duration: 28 days
Animal Species: HY/CR albino rabbits, ~16 weeks old , weighing 2.60 to 3.10 kg, 4/sex/group
Testing Site: Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche, Riom, France
Study Date: 11/05/90 - 12/3/90
GLP/AUC Compliance: Yes
Study Design: Vehicle, 2% DZ, 0.5% TM, or 2%DZ + 0.5% TM in 30 µl was applied to the rabbit (4/sex/group) left eye 3x a day with ~ 3 hr apart for 28 days. The right eye served as a control The following parameters were monitored.

- Physical Signs and Mortality - 1x/day.
- Body Weights - pretest and 1x/week.
- General Eye Survey - 1x/day.
- Score Ocular Reactions - pretreatment and 2x/week.
- Indirect Ophthalmoscopic and Slit Lamp Examination - pretreatment and Weeks 2 and 4.
- Cornea Thickness Determination - pretreatment and Weeks 2 and 4.
- Necropsy - Day 29. Necropsy was limited to eyes and ocular adnexa. The eyes, lacrimal and harderian glands, upper and lower eyelids, and nictitating membrane of each eye of all rabbits were examined histologically.

**Results:**

- Physical Signs and Mortality - No deaths occurred. No remarkable clinical signs were observed.
- Body Weights - No drug-related changes were noted.

- General Eye Survey and Score of Ocular Reactions - Slight blinking was observed after instillation in vehicle control and drug-treated animals. Slight transient redness of the bulbar conjunctiva was seen drug-treated groups. The value for the Draize scores were zero for all groups.
- Indirect Ophthalmoscopic and Slit Lamp Examination - No drug-related changes were noted.
- Cornea Thickness Determination - No drug-related changes in corneal thickness were noted.
- Histopathology - No remarkable histopathological changes contributable to treatment were noted in all examined eye tissues.

In conclusion, the formulation containing 2% dorzolamide and 0.5% timolol was well tolerated by rabbits when applied topically in the eye 3x a day for 28 days.

5. MRL Preclinical Report: MK-0507/Timolol: 14-Week Ocular Irritation Study in Rabbits. TT #91-602-0 (Vol. 1.8, p. B-71)

Study Report Nº: TT #90-602-00

Study Aims: To evaluate ocular irritation of a combination of 2% and 0.5% timolol in albino HY/CR rabbits for three months.

Compound: 2% MK-0507, L-671,152-001E, batch Nº 017; Timolol maleate, batch Nº RX0179; Vehicle, batch Nº FE-1141; 2% MK-0507 + 0.5% Timolol, batch Nº MCPRL: 14618801.

Formulation:

| Ingredient | Vehicle (mg/g) | 2% MK-0507 + 0.5% Timolol (mg/g) |
|---|---|---|
| MK-0507 (L-671,152-001E) | | |
| Timolol Maleate | | |
| Na Citrate•2$H_2O$ | | |
| Benzalkonium Cl* | | |
| Hydroxyethylcellulose | | |
| NaOH | qs | |
| Mannitol | | |
| HCl | qs | |
| $H_2O$ for injection | qs | |

Dose and Route: conjunctival sac of left eye (the right eye was not treated), 30 $\mu$l/instillation, 3x/day with ~ 3 hr apart

Dosing Duration: 91 days

Animal Species: HY/CR albino rabbits, ~16 weeks old , weighing 2.65 to 3.25 kg, 4/sex/group

Testing Site: Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche, Riom, France

Study Date: 1/14/91 - 4/15/91

GLP/AUC Compliance: Yes

Study Design: Vehicle, 2% DZ, 0.5% TM, or 2%DZ + 0.5% TM in 30 $\mu$l was applied to the rabbit (4/sex/group) left eye 3x a day with ~ 3 hr apart for 91 days. The right eye served as a control The following parameters were monitored.

- Physical Signs and Mortality - 1x/day.
- Body Weights - pretest and 1x/week.
- General Eye Survey - 1x/day.
- Score Ocular Reactions - pretreatment and 2x/week.
- Indirect Ophthalmoscopic and Slit Lamp Examination - pretreatment and Weeks 4, 8, and 13.
- Cornea Thickness Determination - pretreatment and Weeks 4, 8, and 13.
- Necropsy - Day 92. Necropsy was limited to eyes and ocular adnexa. The eyes, lacrimal and harderian glands, upper and lower eyelids, and nictitating membrane of each eye of all rabbits were examined histologically.

**Results:**

- Physical Signs and Mortality - No deaths occurred. No remarkable clinical signs were observed.
- Body Weights - No drug-related changes were noted.

- General Eye Survey and Score of Ocular Reactions - Very slight blinking and transient redness of the bulbar conjunctiva was observed after instillation in vehicle control and drug-treated animals. The value for the Draize scores were 0 -0.2 for all groups.
- Indirect Ophthalmoscopic and Slit Lamp Examination - No drug-related changes were noted.
- Cornea Thickness Determination - No drug-related changes in corneal thickness were noted.
- Histopathology - No drug related gross and histopathological changes were noted in all examined eye tissues.

Based on above information, the formulation containing 2% dorzolamide and 0.5% timolol was well tolerated by rabbits when applied topically in the eye three times a day for 182 days.

6. Preclinical Report: MK-0507/Timolol: 27-Week Ocular Irritation Study in Dogs. TT #91-614-0 (Vol. 1.8, p. B-101)

Study Report Nº: TT #91-614-0
Study Aims: To evaluate ocular irritation of a combination of 2% and 0.5% timolol in dogs.
Compound: 2% MK-0507, L-671,152-001E, batch Nº 017; Timolol maleate, batch Nº RX0278; Vehicle, batch Nº MCPRL 146 246 01; 2% MK-0507 + 0.5% Timolol, batch Nº MCPRL: 146 245 01.

Formulation:

| Ingredient | Vehicle (mg/g) | 2% MK-0507 + 0.5% Timolol (mg/g) |
|---|---|---|
| MK-0507 (L-671,152-001E) | | |
| Timolol Maleate | | |
| Na Citrate•2$H_2O$ | | |
| Benzalkonium Cl* | | |
| Hydroxyethylcellulose | | |
| NaOH qs | | |
| Mannitol | | |
| HCl qs | | |
| $H_2O$ for injection qs | | |

Dose and Route: conjunctival sac of left eye (the right eye was not treated), 30 µl/instillation, 3x/day with ~ 3 hr apart
Dosing Duration: 91 days
Animal Species: Beagle dogs, ~12 to 21 months old , weighing 7.0-11.2 kg, 4/sex/group
Testing Site: Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche, Riom, France
Study Date: 3/11/91 - 9/9/91
GLP/AUC Compliance: Yes
Study Design: Vehicle, 2% DZ, 0.5% TM, or 2%DZ + 0.5% TM in 30 µl was applied to the dog (4/sex/group) left eye 3x a day with ~ 3 hr apart for 182 days. The right eye served as a control The following parameters were monitored.

- Physical Signs and Mortality - 1x/day.
- Body Weights - pretest and 1x/week.
- Food Consumption - weekly from Weeks 1-14 and 4-day consumption basis for Weeks 17, 21, and 25
- General Eye Survey - 1x/day.
- Detailed Ocular Examinations - pretreatment and 1x/week.
- Indirect Ophthalmoscopic and Slit Lamp Examination - pretreatment and Weeks 4, 8,12, and 26.
- Necropsy - Day 183. Necropsy was limited to eyes and ocular adnexa. The eyes, lacrimal and harderian glands, upper and lower eyelids, and nictitating membrane of all dogs were examined histologically.

**Results:**

- Physical Signs and Mortality - No deaths occurred. No remarkable clinical signs were observed.
- Body Weights - No drug-related changes were noted.
- General Eye Survey and Score of Ocular Reactions - Very slight to slight ocular reactions (blinking and/or lacrimation) just after dosing in dogs of both groups were noted. However, these signs were slightly more

prominent in dogs given 2% dorzolamide/0.5% timolol. The value for the Draize scores were 0 - 1.2 for both groups.

- Indirect Ophthalmoscopic and Slit Lamp Examination - No drug-related changes were noted.
- Histopathology - No drug related gross and histopathological changes were noted in all examined eye tissues.

Based on above information, the formulation containing 2% dorzolamide and 0.5% timolol was well tolerated by rabbits when applied topically in the eye three times a day for 91 days.

It could be concluded that three daily ocular doses of 2% dorzola-mide/0.5% timolol ophthalmic solution for six months did not cause significant eye irritation in dogs.

## REPRODUCTIVE TOXICOLOGY STUDIES

There were no new reproductive toxicity studies conducted with the combination product submitted in the present NDA. Studies performed using the individual components were included in the previously approved applications timolol maleate (NDA 18-086) and dorzolamide HCl (NDA. 20-408).

## GENETIC TOXICOLOGY STUDIES

There were no new genetic toxicity/mutagenic potential studies conducted with the combination product submitted. Studies performed using the individual components were included in the previously approved applications for timolol maleate (NDA 18-086) and dorzolamide HCl (NDA 20-408).

## CARCINOGENICITY STUDIES

Carcinogenic potential studies with the combination of TM and DZ were not performed. Studies performed using the individual components were included in the previously approved applications for timolol maleate (NDA 18-086) and dorzolamide HCl (NDA. 20-408).

## SPECIAL TOXICITY STUDIES

There have been no new special toxicity and local tolerance studies conducted with the combination product. Studies performed using the individual components were included in the previously approved applications for timolol maleate (NDA 18-086) and dorzolamide HCl (NDA. 20-408).

## LABELING REVIEW

*Carcinogenesis, Mutagenesis, Impairment of Fertility*

[redacted]

*Dorzolamide Hydrochloride*

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.

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.

*Timolol Maleate*

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended
human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested in vivo (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 mg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mg/plate, were associated with statistically significant elevations of revertants observed
but not in the remaining three strains. In the assays with tester strain no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

*Pregnancy*

Teratogenic Effects. Pregnancy Category C. [redacted] There are no adequate and well-controlled studies in pregnant women. COSOPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Dorzolamide Hydrochloride*

Developmental toxicity studies with dorzolamide hydrochloride in rabbits at oral doses of 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 were no treatment-related fetal malformations in developmental toxicity studies with dorzolamide hydrochloride in rats at oral doses up to 10 mg/kg/day (125 times the recommended human ophthalmic dose).

*Timolol Maleate*

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

## II. SUMMARY AND EVALUATION:

The $LD_{50}$ for dorzolamide HCl (DZ) and timolol maleate (TM) are listed in the following table.

| Species | Route | DZ (mg/kg) | TM (mg/kg) |
|---|---|---|---|
| Rat | Oral | 1927 | 1028 |
| | SC | >2000 | 881 |
| | IV | 726 | - |
| | IP | - | 381 |
| Mouse | Oral | 1320 | 1137 |
| | SC | >2000 | 805 |
| | IV | 469 | - |
| | IP | - | 805 |
| Dog | PO | >250 | - |

Summaries of Dorzolamide/Timolol (DZ/TM) Repeated Dose Toxicity Studies are presented in the following table.

| Study N° | Species/Sex | Study Type/Dose | Route | Duration | Results |
|---|---|---|---|---|---|
| TT #89-602-0 GLP | Monkeys, ♂ & ♀ | Ocular irritation: 2% DZ/0.5% TM TID | Ocular | 15 days | Transient ocular reaction - slight to moderate blinking which persisted for ~20 sec. |
| TT #90-69-33 Non-GLP | Rabbits, ♂ & ♀ | exploratory interaction: 3% DZ / 0.5% TM, 3% DZ/ 0.5% Betaxolol, 3% DZ/0.1% Dipivephrin, 3% DZ/ 4.0% Pilocarpine, TID | Ocular | 3 days | Very slight blinking, slight redness, occasional lacrimation were observed. |
| TT #90-611-0 GLP | Rabbits, ♂ & ♀ | Ocular interaction: 2% DZ, 2% DZ/0.5% TM, 2% DZ/0.5% Betaxolol, 2% DZ/0.1% Dipivephrin, 2% DZ/ 4.0% Pilocarpine, TID | Ocular | 28 days | Minor ocular reactions including slight ↑ in lacrimation , blinking incidence, and redness were seen. |
| TT #96-632-0 GLP | Rabbits, ♂ & ♀ | Ocular irritation: 2% DZ/0.5% TM TID | Ocular | 29 days | Slight blinking and slight transient redness of the bulbar conjunctiva were noted following treatment. |
| TT #91-602-0 GLP | Rabbits, ♂ & ♀ | Ocular irritation: 2% DZ/0.5% TM TID | Ocular | 14 wk | Slight blinking and slight transient redness of the bulbar conjunctiva were noted following treatment. |
| TT #91-614-0 GLP | Dogs, ♂ & ♀ | Ocular irritation: 2% DZ/0.5% TM TID | Ocular | 27 wk | Slight ocular reactions (↑ blinking and/or lacrimation) immediately after dosing were seen in both groups. |

## III. CONCLUSION AND RECOMMENDATION:

COSOPT™ is formulated to contain 2% dorzolamide hydrochloride and 0.5% timolol maleate (doses expressed as the free base). Both 0.5% timolol maleate (a beta-adrenergic receptor antagonist) and 2% dorzolamide hydrochloride (an inhibitor of carbonic anhydrase) have been marketed for the treatment of glaucoma or lowering intraocular pressure in the U.S. since 1993 and 1994, respectively. Data from repeated dose ocular toxicity study showed that concomitant application of 2% dorzolamide hydrochloride and 0.5% timolol maleate caused very slight ocular reactions including slight ↑ in blinking and slight transient redness of the bulbar conjunctiva in rabbits and ↑ blinking and/or lacrimation in dogs.

The approval of this NDA 20-869, COSOPT™, is recommended by the pharmacologist.

9/30/97
/W.C. Josie Yang, Ph.D.

Concur by team leader: Yes ☒ No ☐

10-2-97
Conrad Chen, Ph.D.

cc:
**NDA 20-869**
HFD-550/Division File
/JYang
/WCambers
/BHo
/LGorski
HFD-345
HFD-024
F/T by JYang, September 30, 1997