CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-869

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

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Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-869 SUBMISSION DATE: 6/26/97

PRODUCT: Dorzolamide Hydrochloride/
Timolol Maleate Ophthalmic Solution
COSOPT™

SPONSOR: Merck Research Laboratories, West Point, PA

REVIEWER: Veneeta Tandon, Ph.D.

Review of a NDA

Background

COSOPT™ is a combination of timolol (0.5%), a nonselective adrenergic receptor blocking agent, and dorzolamide (2.0%), a potent carbonic anhydrase inhibitor to be used for the treatment of elevated intraocular pressure (IOP). Both reduce aqueous humor secretion, but by different mechanism of action. According to the sponsor a combination therapy would provide a greater IOP-lowering effect, may increase patient compliance, overcome the risk of elimination of the first drop from the cul de sac by the instillation of the second drop.

In this submission the sponsor has requested a waiver to perform bioavailability studies with the combination product, based on the very low systemic exposure (less than 1 ng/mL) to timolol after administration of TIMOPTIC-XE®. The effects on circulating red blood cell of dorzolamide administered as topical ophthalmic solution have also been characterized for TRUSOPT® and were not of clinical importance.

NDA 18-086, NDA 20-330 for timolol maleate (TIMOPTIC®, TIMOPTIC-XE®, TIMOPTIC® in-OCUDOSE®) was approved on August 17, 1978, November 4, 1993 and NDA 20-408 dorzolamide hydrochloride (TRUSOPT®) was approved on December 10, 1995.

Formulation

The proposed market formulation for Dorzolamide hydrochloride and Timolol maleate ophthalmic solution is shown in the Table below. The fixed combination solution was formulated by adding timolol maleate to the dorzolamide hydrochloride formulation, with an appropriate adjustment of the mannitol concentration to retain iso-osmolarity.

Component
Dorzolamide hydrochloride (as base equivalent)
Timolol Maleate (as base equivalent)
Sodium Citrate Dihydrate
Benzalkonium Chloride
Hydroxyethyl Cellulose
Sodium Hydroxide qs
Mannitol
Water for Injection qs

Dosage and Administration

The dose is one drop of COSOPT in the affected eye(s) twice daily.

Pharmacokinetics

A brief overview of the pharamcokinetic properties of the components of this combination product obtained from their respective approved NDAs is as follows:

For Dorzolamide:

Studies conducted in NDA 20-408, demonstrated that 2% dorzolamide when topically applied to the eye, reaches the systemic circulation and that in blood, dorzolamide distributed entirely into RBCs as a result of strong and selective binding to carbonic anhydrase II (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. Plasma concentrations of dorzolamide and metabolite are generally below the assay limit of quantitation (15nM). Dorzolamide moderately binds to plasma proteins (approximately 33%), is excreted unchanged in the urine. The study further showed that dorzolamide was cleared extremely slowly with a mean terminal half life in RBCs of about 114 days. It is eliminated primarily as urinary excretion as unchanged drug. Steady state levels were not reached at the end of this study.

To simulate the systemic exposure after long-term topical ocular administration, dorzolamide was given orally to eight healthy subjects for 20 weeks in an oral dose of 2 mg b.i.d. which closely approximated the amount of drug delivered by topical ocular administration of TRUSOPT 2% t.i.d. Steady state was reached after 4 weeks of dosing and after 13 weeks of dosing for the metabolite. At steady state, dorzolamide was found at concentrations approaching intracellular RBC concentration of CA-II (20-25 μM), while metabolite concentrations remained well below intracellular RBC concentration of CA-I. At steady state plasma levels of both dorzolamide and the metabolite remained below the 5 ng/mL (about 15 nM) limit of quantitation. At steady state whole blood CA II activity was inhibited by 94%-96% and total CA activity was inhibited by 81% to 88%, levels which are below the levels of CA inhibition required to produce systemic effects.

For Timolol maleate:

Human pharmacokinetic properties for timolol maleate have been evaluated under NDA 18-086 following oral and intravenous administration of the drug. In addition blood samples were obtained during one study following intraocular administration of 0.5% timolol maleate. Based on recovery of radioactivity following oral administration of ^{14}C-labeled timolol maleate, timolol is nearly completely absorbed from the gastrointestinal tract. Timolol represented <20% radioactivity in plasma, indicating significant metabolism. Timolol metabolism is mediated primarily by cytochrome P450 2D6. Nearly 20% of an oral dose is recovered in urine as parent drug. Timolol is moderately bound to plasma proteins (<60%).

Following oral administration of 4-20 mg of timolol maleate, timolol is rapidly absorbed, with C_{max} and AUC increasing linearly with dose. Mean C_{max} is in the range of 10-20 ng/ml following a 5 mg dose of timolol maleate. Because of moderate first pass metabolism, oral bioavailability of timolol averages 50-60%.

In a study of plasma concentrations with 6 subjects, where 0.5% timolol (one drop each eye b.i.d.) was administered intraocularly for 8 days. The mean peak plasma concentration following morning dose was 0.46 ng/ml and following afternoon dosing was 0.35 ng/ml. By comparison to plasma concentration following oral doses, it was estimated that timolol was approximately 50% bioavailable systemically following intraocular administration.

The low systemic exposure (less than 1 ng/ml) to timolol after administration of TIMOPTIC-XE has been characterized in NDA 20-330.

Request for Bio-waiver for the combination product

Based on the pharmacokinetic information available from the approved NDAs of dorzolamide hydrochloride and timolol maleate, the acceptability of a waiver request for the requirement to submit human pharmacokinetic and bioavailability data was agreed upon End-of-Phase II meeting held on April 7, 1993 and again during the pre-NDA meeting held on October 21, 1996. The systemic exposure to timolol after administration of TIMOPTIC-XE® was very low (less than 1 ng/mL) and the effects of the circulating red blood cell levels of dorzolamide were not of clinical importance as characterized in NDA 20-408. However, the sponsor was required to demonstrate the clinical superiority of the combination product COSOPT™ as part of this NDA.

Label

The annotated text for the pharmacokinetic/pharmacodynamic section of the label is for the combination product to dorzolamide hydrochloride/timolol maleate is identical to the of the individual marketed drugs (TRUSOPT® and TIMOPTIC-XE®).

Recommendation

Based on the information presented by the sponsor for dorzolamide hydrochloride and timolol maleate from NDAs 20-408 ,18-086 and 20-330, the combination product of dorzolamide 2%/timolol maleate 0.5% (COSOPT™) is acceptable. The formulation of COSOPT™ involves the addition of timolol maleate to the approved formulation of TRUSOPT®. The recommendation of a biowaiver has already been granted by the Division in 1993.

11/19/97

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CC: NDA 20-869

HFD-550/Div File
HFD-550/CSO/Gorski
HFD-880(Bashaw/Tandon)
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