CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-963

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-963 SUBMISSION DATE: 2/18/98

PRODUCT: Timolol Maleate Ophthamic Gel Forming Solution (0.25% ad 0.5%)

SPONSOR: Alcon Laboratories Fort Worth, TX.

REVIEWER: Veneeta Tandon, Ph.D.

Review of a NDA

Background

Timolol maleate is a beta1 and beta 2 (non selective) adrenergic receptor blocking agent. Beta-blockers reduce intraocular pressure by reducing the rate of formation of aqueous humor by blocking the beta adrenoreceptors in the ciliary body. Timolol maleate Solution (Timoptic™, 0.25% and 0.5%, Merck) was approved in 1978 under NDA 18-086. Timoptic™-XE (0.25% and 0.5%, Merck) was approved in 1993 under NDA 20-330. Oral Timolol tablets (Blocarden, 5, 10, 20 mg, Merck) was approved in 1981). Timolol maleate solution, 0.25% and 0.5%, Alcon, has been approved in 1995 under ANDA 74-261 and 74-262.

Alcon, now submits an NDA for Timolol maleate gel forming solution, 0.25% and 0.5% under provisions of Section 505(b)2 of the Federal Food, Drug and Cosmetics Act and 21CFR 314.54.

Timoptic™-XE (0.25% and 0.5%, Merck) was formulated in gellan gum, which forms a gel, when applied to the ocular surface. The gellan gum formulation, administered once daily was shown to be as efficacious in reducing intraocular pressure as timolol solution administered twice daily, while resulting in measurably less systemic absorption.

The timolol gel forming solution (0.25% and 0.5%, Alcon) in this NDA utilizes xanthan gum Xanthan gum is a high molecular weight, water soluble, anionic ploysaccaride gum. Xanthan gum formulation like gellan gum formulation is provide action.

Pharmacokinetic literature survey

Oral Administration

Following oral administration of a 0.1 mg/kg (base equivalent) timolol maleate solution to normal volunteers, peak plasma concentrations of approximately 26 ng/ml were achieved between 1 and 2 hours. The apparent volume of distribution ranged from

and the elimination half-life was approximately 2.5 hours. Oral bioavailability in man is about 50%. Linear pharmacokinetics was demonstrated over the 0.05mg/kg-0.4 mg/kg base equivalent dose range[1].

In man, timolol is primarily metabolized by two pathways involving ring-opening oxidation of the morpholine moiety. One route yields an ethanolamine side chain on the thiadiazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with carbonyl adjacent to the nitrogen. Together, these two metabolites accounted for about 40% of urinary radioactivity from an oral 14C-timolol dose. Trace amounts (about 3% of urinary radioactivity) of a metabolite formed by hydroxylation of terminal group were also formed. About 20% of an oral dose in man is excreted as unchanged drug[2].

Systemic side effects include severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure have been reported following systemic or ophthalmic administration of timolol maleate.

Topical Administration

Ocular and systemic exposure to timolol following topical ocular dosing has been studied in rabbits and humans. Following single, bilateral topical ocular doses of 50 ml of 0.5% timolol maleate solutions to rabbits, the drug was absorbed into the anterior chamber. Mean peak concentrations of 2.47 mg/ml and 0.188 mg/ml in aqueous humor and plasma, respectively, were achieved in 30 minutes after dosing. At 2 hours postdose, mean aqueous humor and plasma levels had declined to 0.85 mg/ml and 0.042 mg/ml, respectively[3].

Plasma concentrations of timolol in healthy volunteers were measured following topical ocular doses of two drops per eye of 0.5% timolol maleate solution. Timolol was consistently present in the urine, but not detected in most plasma samples (LOQ 5ng/ml)[4]. However, this data is from a literature report published in 1980.

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following once daily administration of Timoptic-XE 0.5% in the morning and was compared to Timoptic solution 0.5% (Merck). The mean peak plasma concentration following the morning dose of Timoptic-XE was 0.28 ng/ml[5] and the mean peak plasma concentrations following the morning and afternoon dose of Timoptic solution averaged 0.46 and 0.35 ng/ml.

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[1] P. Vermeji et.al., J. Pharm. Pharmacol., 1978, 30, 53-55
[2] D.J. Tocco, et.al. Drug Metab. Disp., 1975, 3, 361-370.
[3] P. Vareilles, et.al., Invest. Opthalm. Vis. Sci., 1977, 16, 987-996
[4] M.B. Affrime, et.al, "Dynamics and kinetics of ophthalmic timolol", Clin. Pharmacol. Ther., 1980,27,471-477.
[5] NDA 20-330 review by Dr. Angelica Dorantes, FDA

The reviewer in concurrence with the division recommends a similar study along the lines of Timoptic-XE (NDA 20-330) be conducted with the Timolol maleate gel forming solution (Alcon). Recommendations have been made at the end of this review.

Ocular vs systemic absorption

In order to reduce the intraocular pressure the antiglaucoma drugs must penetrate into the inner eye. Ocular bioavailability is determined by the ability of the drug to penetrate through the cornea and conjunctiva/sclera, and on the other hand, by its elimination from the conjunctival sac. Major part of the elimination is by systemic drug absorption via conjunctiva. Typically conjunctival systemic absorption of a drug is an order of magnitude greater than their ocular absorption. In addition substantial absorption of ophthalmic drugs takes place via nasal mucosa. Systemic absorption of antiglaucoma drugs like beta blocking agents may cause systemic side effects. Increasing the ocular/systemic ratio of drug absorption may decrease the risk of systemic effects.

It has been shown that ocular absorption of timolol increases but systemic absorption decreases with an increase in viscosity of drug in solution in rabbits[6]. These effects are dependent on the drug concentration and the viscosity of the polymer solution. Systemic absorption can decrease due to high viscosity because viscous solutions reach the nasal mucosa slower than non-viscous solutions. High viscosity may also decrease spreading of solutions in nasal mucosa and hence decrease absorptive area. However, on the other hand, high viscosity may increase the contact time of the drug to the nasal mucosa, by reducing the mucociliary clearance of the formulations from the nose[7].

Keeping all these facts in mind the difference in systemic exposure from different gelling agents (gellan gum vs xanthan gum) cannot be outlined clearly. It is also know that timolol maleate has severe respiratory and cardiac side effects upon both oral and topical administration.

Recommendation and Comments to the Sponsor

The applicant's request of a waiver from the requirements for submission of ocular bioavailability data according to the criteria set forth in 21CFR 320.22 (b)(1) cannot be accepted as such. The CFR provisions to grant such a waiver is not applicable in this case, since the inactive ingredients are not the same as the approved full NDA. There is a difference in the gel used to formulate the approved NDA (Timoptic-XE, Merck) and the applicants' product. The agency has no expectations of conducting the bioavailability in ocular samples. However, the agency would like to see a systemic bioavailability study conducted in healthy volunteers comparing their Timolol maleate gel forming solution 0.5% to the Timoptic solution 0.5% (Merck).

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[6] S.R. Podder, et.al, "Improving the safety of topically applied timolol in pigmental rabbit through manipulation of formulation composition", Exp. Eye Res., 1992, 54, 747.

[7] J.G. Hardy, et.al., "Intranasal drug delivery by spry and drops", J.Pharm, 1985, 37, 294.

The study design should be a 2-period crossover, multiple dose plasma-drug concentration study of Timolol maleate gel forming solution 0.5% (Alcon) q.d and Timoptic solution 0.5% (Merck) b.i.d. for 8 days in 6-8 normal volunteers. Timolol concentrations in plasma should be measured after 8 days of dosing.

The Division of Pharmaceutical Evaluation III would normally require that this study be conducted pre-approval. As the sponsor has shown clinically that Timolol maleate gel forming solution (Alcon) is equally efficacious and safe to the Timoptic solution (Merck), the study can be deferred to a Phase IV study.

The pharmacokinetics section of the label should be changed to read as follows:

"Pharmacokinetic studies in humans using the gel forming solution were not performed. Following topical ocular administration of timolol maleate solution to humans, low concentrations of drug are found in plasma. After bilateral administration of a 0.5% timolol maleate solution to healthy volunteers, maximum plasma concentrations were below 5 ng/mL."

The last sentence in the "pharmacokinetics" section of the label as been cut because the statement is made on mere speculation (see review).

Veneeta Tandon 8/28/98

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. EW for Bashaw 8/28/98

CC: NDA 20-963
HFD-550/Div File
HFD-550/CSO/Gorski
HFD-880(Bashaw/Tandon)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

APPEARS THIS WAY
ON ORIGINAL