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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-516

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-516 (000)
Drug Substance	Timolol Maleate
Drug Product	Timolol Maleate 0.5% Opthalmic Solution
Strengths	0.5%
Route of Administration	Topical Ocular
Sponsor	Senju Pharmaceuticals, Co., Ltd., Osaka Japan
Type of submission	3-S
Date of submission	09/25/02
OCPB Division	DPE-III
Clinical Division	Analgesic, anti-inflammatory, and Opthalmic Drug Products (HFD-550)
Reviewer	Shinja R. Kim, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm. D.

1. EXECUTIVE SUMMARY

The sponsor has submitted NDA 21-516 for Timolol Maleate 0.5% Opthalmic Solution as a 505(b)(2) submission. Currently, opthalmic timolol maleate and timolol hemihydrate solutions are on the market for bid use and timolol maleate gellan gum (Timolol GFS, Timoptic-XE) for once daily use. Also, timolol is available as tablet formulations (not for ophthalmic indications). This class of drugs has been studied extensively in the adult population.

The sponsor has developed proprietary technology in formulating timolol maleate with sorbate in order to enhance ocular bioavailability of timolol instilled. The proposed product, named Timolol-LA, is a preserved multi-dose solution of timolol maleate (2.5 mL [ ] bottle and 5 mL fill/10 mL bottle). It is indicated for the chronic treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma with a once daily dosing regimen.

To support the Human Pharmacokinetics and Bioavailability section of this NDA, the sponsor provided the results of a multiple dose study (#TIMA-101). In this study, the systemic exposure to timolol was determined following twice daily administration of Timolol-LA 0.5% and commercially available eye-drops (timolol maleate ophthalmic solution 0.5% by [ ] for eight days in 12 healthy subjects. Following Timolol-LA 0.5% and timolol maleate ophthalmic solution 0.5%, mean (±SD) plasma concentrations of timolol (presumably C_{max}) measured at two hours after (presumably T_{max}) the first dose were 0.68 (±0.53) and 0.60 (±0.42) ng/mL, respectively. These values at steady state (i.e., on Day 8) were 0.88 (±0.69) ng/mL following Timolol-LA 0.5% and 0.89 (±0.48) ng/mL following timolol maleate ophthalmic solution 0.5%. Steady state mean (±SD) plasma concentrations of timolol measured at 15 minutes pre-dose (presumably $C_{min,ss}$) were 0.09 (±0.1) and 0.2 (±0.22) ng/mL after Timolol-LA 0.5% and timolol maleate ophthalmic solution, respectively. Although timolol plasma concentration areas under the curve (AUC) have not been obtained, this data suggested that systemic bioavailability after Timolol-LA 0.5% was similar to that of timolol maleate ophthalmic solution 0.5%.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Human Pharmacokinetics and Bioavailability section and found that NDA 21-516 is acceptable provided the sponsor accepts the minor labeling recommendation (page 7).

/S/

Shinja R. Kim, Ph.D., DPE II

RD/FT_____ E. Dennis Bashaw, Pharm. D., Team Leader

2. Table of Contents

3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The proposed product, Timolol-LA, is formulated timolol maleate with sorbate to enhance ocular bioavailability of timolol instilled. Timolol-LA is a preserved, multi-dose solution of timolol maleate.

To support the Human Pharmacokinetics and Bioavailability section of this NDA, the sponsor conducted a multiple dose study (#TIMA-101). In this study, the systemic exposure (samples taken at 2 time-points) was compared between Timolol-LA 0.5% and the approved eye-drops (timolol maleate ophthalmic solution by [ ]) in 12 healthy subjects. All medications were administered as a single drop in both eyes twice daily for 7 days plus one AM dose on Day 8. The results of this study are summarized as follows: (1) Mean plasma concentrations of timolol measured at 2 hrs after the first dose of timolol were 0.68 ng/mL with TLA and 0.60 ng/mL with TIM (p=0.507). On an individual basis, the highest concentration for TLA and TIM were [ ] ng/mL, respectively in different patient. Detectable timolol concentrations were found in 10 of 12 subjects treated with TLA, and with all 12 subjects treated with TIM. (2) Two hours after dosing on Day 8, mean plasma concentrations of timolol were 0.88 ng/mL with

TLA and 0.89 ng/mL with TIM (p=0.960). On an individual basis, the highest concentration for TLA and TIM were [redacted] ng/mL, respectively. Detectable timolol concentrations were found in all subjects in both treatment groups. (3) Morning pre-dose values measured after 8 days of dosing of timolol were 0.09 ng/mL with TLA and 0.20 ng/mL with TIM (p=0.034). On an individual basis, the highest trough concentration for TLA was [redacted] ng/mL, and for TIM was [redacted] ng/mL. Detectable timolol concentrations were found in 6 of 12 subjects treated with TLA, and with 7 of 12 subjects treated with TIM. In conclusion, although systemic exposures (AUC) have not been obtained, this data suggested that systemic bioavailability after Timolol-LA 0.5% was similar to that of timolol maleate ophthalmic solution 0.5%.

Timolol levels in plasma were quantified by the validated [redacted] methods. The assay method was acceptable in regards to sensitivity and selectivity.

4. QUESTION BASED REVIEW

4.1 General Attributes

4.1.1 What is known about Timolol maleate (backgound)?

Timolol is a nonselective β-adrenergic antagonist without demonstrable local anesthetic properties; it has a minimal intrinsic sympathomimetic activity. β-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. β-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Therefore, such an effect in patients with asthma or other bronchospastic conditions, or in patients with severe impairment of myocardial infarction is potentially dangerous.

Although timolol is well absorbed when given orally, it undergoes considerable first-pass hepatic metabolism. Timolol (and its metabolites) are excreted in the urine rapidly, and the clearance, volume of distribution, and plasma half-life are 7.3 ± 3.3 mL/min/kg, 2.1 ± 0.8 L/kg, and 4.1 ± 1.1 hr, respectively. Effective concentration of timolol is reported to be 15 ng/mL (50% decrease in exercise-induced cardioacceleration). Timolol maleate, applied topically to the eye(s) as a solution, is well known for its ocular hypotensive efficacy.

4.1.2 What is the therapeutic indication? What is the proposed dosage and route of administration? What are the highlights of the formulation of the drug product?

Indication: Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Dosage and administration: The starting dose is one drop of 0.5% Timoptic-LA in the affected eye(s) once a day. If the patients intraocular pressure is not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Formulation: The applicant has developed proprietary technology in formulating timolol maleate with sorbate. According to the sponsor sorbate enhance ocular bioavailability of timolol instilled. The proposed product, Timolol-LA, is to be supplied as a preserved multi-dose solution of timolol maleate. Timolol maleate (molecular weight of 432.49) is a white, odorless, crystalline powder, which is soluble in water and ethanol, sparingly soluble in chloroform, practically

insoluble in isooctane ether. The quantitative formulation for the product is provided in the table below:

Timolol-LA 0.5% Ophthalmic Solution

Ingredients	Actual	Label Claim
Timolol Maleate, USP	6.8 mg/mL	0.5% as Timolol
Potassium Sorbate, NF	4.7 mg/mL	
Sodium Chloride, USP	[ ]	
Sodium Phosphate, Monobasic (Monohydrate), USP		
Benzalkonium Chloride, NF	0.05 mg/mL	
[ ]		

4.2. General Clinical Pharmacology

4.2.1 What is the basis for selecting the clinical-response endpoints (i.e., clinical or surrogate endpoints or biomarkers) and how are they measured in clinical study?

Efficacy variables: Since timolol is (nonselective) β-adrenergic blocker, the primary efficacy endpoint was the change in mean intraocular pressure (IOP) at each visit at each time point (peak and trough) compared to the baseline IOP. In addition, the tested drugs should lower IOP by 25% at peak and 20% at trough testing times when compared to baseline. Other efficacy measures used in support of the IOP findings include change from baseline mean deviation score on perimetry and cup-to-disc ratio.

Safety Measures: Ocular signs and symptoms, visual acuity, ophthalmoscopy, IOP measurement, heart rate, blood pressure, and the incidence of adverse events.

4.2.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

As this application is a 505(b)(2), no (Phase 2) dose-response studies were undertaken. One Phase 3 study (TIMLA-301) was conducted, and the objective of this trial was to demonstrate that Timolol-LA once daily (q.d.) is equivalent in efficacy to currently marketed timolol maleate ophthalmic solution twice-daily (b.i.d). The sponsor concluded that Timolol-LA once daily was found equivalent in ocular hypotensive efficacy to timolol maleate ophthalmic solution b.i.d dose.

In the PK study (TIMLA-101), efficacy was not evaluated since the subjects were healthy normal, but safety profiles were obtained. Heart rate measured 2 hrs Post dose was generally slightly lower (~2-5 bpm) compared to that of the Pre-dose, and similar effect was seen with systolic blood pressure (e.g., decrease of ~5 mm Hg at 2hr-post dose on Day 8). However, these differences were not clinically significant. A greater incidence of burning/stinging, tearing, and light sensitivity associated with Timolol-LA 0.5% (90-100%) than with commercially available timolol maleate ophthalmic solution (50-100%). It was noted that laboratory values (including hematology) were assessed only at study entry, thus, there was no measure of the laboratory values over time.

4.2.3 What are the systemic exposures to timolol after topical ocular administration?

Systemic exposure of Timolol-LA 0.5% (TLA) was compared to commercially available eye-drops timolol maleate ophthalmic solution (TIM) in 12 healthy subjects (Protocol #TIMLA-101). Each subject received TLA or TIM (randomized, crossover study), and all medications were administered as a single drop, O.U., bid for 7 days, plus one morning instillation on day 8. TLA was dosed bid in order to maximize the probability of having detectable blood levels. It also mimics the situation where patient inadvertently administers the LA product as an immediate release product. Drug levels at 15 min before the dose (Pre) and 2 hrs after the dose (Post) on Day 1 and 8 are shown in Table 1.

Table 1. Mean timolol plasma concentrations (ng/mL)

Day	*Time*	*Treatment*	*N*	*Mean*	*Min*	*Max*	*SD*	*SE*
1	Pre	TLA	12	0.00			---	---
		TIM	12	0.00			---	---
		Δ	12	0.00			---	---
	Post	TLA	12	0.68			0.53	0.15
		TIM	12	0.60			0.42	0.12
		Δ	12	0.09			0.50	0.14
8	Pre	TLA	12	0.09			0.10	0.03
		TIM	12	0.20			0.22	0.06
		Δ	12	-0.11			0.17	0.05
	Post	TLA	12	0.88			0.69	0.20
		TIM	12	0.89			0.48	0.14
		Δ	12	-0.01			0.52	0.15

Δ = TLA – TIM: A positive number indicates a higher concentration in the TLA group.

The mean plasma concentrations at 2-hrs after the first dose were 0.68 and 0.60 ng/mL following TLA and TIM, respectively. The steady state (i.e., Day 8) pre-dose and 2-hrs post dose (values) following TLA and TIM were 0.09 and 0.88 ng/mL and 0.2 and 0.89 ng/mL, respectively in all subjects (i.e., detectable and LOQ). These concentration levels are much less than the plasma level associated with systemic cardiovascular effects (half maximum inhibition at concentrations of ~ ~ ng/ml and maximum inhibition above ~ ng/ml). The single largest value observed was ~ and ~ ng/mL, respectively, for TLA and TIM.

In conclusion, the data suggested that a systemic bioavailability after Timolol-LA 0.5% was similar to that of timolol maleate ophthalmic solution 0.5%.

4.3 Intrinsic Factors

4.3.1 Are there any effects of intrinsic factors (such as gender, renal impairment, hepatic impairment and ethnicity) or extrinsic factors (such as drugs, herbal products, diet, smoking, and alcohol) influence exposure and/or response of timolol after topical ocular administration? What are the relevant covariates that influence the pharmacokinetic variability of timolol?

Gender: The mean (±SD) values of timolol plasma concentrations at two time points (15 min pre-dose and 2-hrs post dose) on Day 8 from the Study TIMLA-101 are shown in the table below;

	TLA		TIM	
	Pre	Post	Pre	Post
Males (n=4)	0.05 ± 0.09[a]	0.52 ± 0.62	0.14 ± 0.19	0.72 ± 0.37
Females (n=8)	0.11 ± 0.11	1.1 ± 0.69	0.23 ± 0.24	0.97 ± 0.54

[a]3 subjects had LOQ levels (i.e., considered as zero concentrations)

As shown in the table, timolol plasma concentrations in males were consistently numerically smaller compared to those in females; it could be due to difference in weights between gender but also it could be due to the extremely high inter individual variability. Anyhow, this gender effect can not be confirmed/generalized since this finding was based on 8 females and 4 males.

Renal impairment, hepatic impairment, ethnicity and extrinsic factors: Timolol PK in renal impairment or hepatic impairment was not undertaken, nor effects of above mentioned extrinsic factors on timolol PK and/or PD were not evaluated. There were 2 blacks and 10 Caucasians in Study TIMLA-101, therefore, the effect of ethnicity on timolol PK is not evaluated.

Effect of Age: Pharmacokinetics of timolol in elderly was not evaluated (the oldest subject in TIMLA-101 was 44 years old). The sponsor plans to conduct a clinical study in pediatrics (TIMLA-302).

In conclusion, effects of intrinsic, extrinsic factors or relevant covariates that influence exposure and/or response of timolol after topical ocular administration has not been evaluated. However, considering the fact that this application is a 505(b)(2) submission plus this product is for ophthalmic route of administration, the evaluation of above factors on PK of timolol could be waived.

4.4 General Biopharmaceutics

4.4.1 Has the proposed commercial formulation been adequately linked to the Phase III clinical trial formulation?

Clinical pharmacology study (TIMLA-101) and the pivotal Phase 3 study (TIMLA-301) used different batch (to-be-marketed formulation). However, since the proposed product is formulated as a solution, using different batches (same formulation) do not cause any significance in clinical outcomes.

4.5 Analytical

4.5.1 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Timolol concentrations in plasma were quantified by the validated [ ] assay method.

[ ] The linear range of the assay was [ ] ng/mL with limit of quantification at — ng/mL. The performance of the assay during study sample analysis was acceptable as evidenced by QC samples precision and accuracy within ±15%.

5 LABELING RECOMMENDATIONS

The following is the sponsor's proposed labeling for Pharmacokinetics (under Clinical Pharmacology) section. It is appropriate, except that it is recommended that the sponsor add the word 'healthy' (underlined as shown below) to the proposed the labeling:

CLINICAL PHARMACOLOGY

Pharmacokinetics

In a study of plasma drug concentration in 12 healthy subjects, the systemic exposure to timolol was determined following twice daily administration of BRANDNAME (exaggerated regimen) or timolol maleate ophthalmic solution 0.5% (standard regimen) for eight days. With BRANDNAME, mean plasma concentrations of timolol were 0.68 ng/mL and 0.88 ng/mL two hours after the first dose and the dose on the eighth day, respectively. With timolol maleate ophthalmic solution 0.5%, mean plasma concentrations of timolol were 0.60 ng/mL and 0.89 ng/mL at the same timepoints.

APPENDICE

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Protocol TIMLA-101

Title of Study: A double-masked, active-controlled, randomized, crossover, comfort, ocular safety, and systemic bioavailability study of Timolol-LA 0.5%- in healthy volunteers.

Principal Investigator: [redacted]

Objectives: To evaluate the comfort, ocular safety, and systemic bioavailability of Timolol-LA 0.5% compared to commercially available eye-drops (timolol maleate ophthalmic solution).

Study Design: This study was a randomized, double-masked, active-controlled, crossover study (7-14 days washout period) in 12 healthy subjects. Each subject received Timolol-LA (TLA) 0.5% ophthalmic solution (batch No. 91089) or Timolol maleate (TIM) by [redacted] (batch No. 91389) as reference drug. All medications were administered as a single drop, O.U., bid for 7 days, plus one morning instillation on day 8. Blood samples were collected on Days 1 and 8 per period at 15 min before the dose (pre-dose) and 2 hrs after the dose.

Subjects: The subjects mean age was 32.1 years with range of 19-44 years. There were 8 females and 4 males, and 2 Black females and rest of 10 subjects were Caucasians.

Criteria for Evaluation:
Pharmacokinetics: Plasma concentrations of timolol.
Safety: Assessment of ocular and systemic adverse events, cardiovascular parameters, visual acuity, laboratory values and general physical examination findings.

Analytical Methodology
Assay Method: [redacted]
Assay Sensitivity: Limits of quantification was [redacted] ng/mL with linear range [redacted] ng/mL.
Accuracy and Precision: Precision and accuracy of QC samples of timolol for interday and intraday were [redacted] respectively.

Statistical Methods: Descriptive statistics and analysis of variance for timolol concentrations.

Results: Pharmacokinetics of timolol is summarized in tables below and displayed in the Figure 1.

Table 1. Mean timolol plasma concentrations (ng/mL)

Day	*Time*	*Treatment*	*N*	*Mean*	*Min*	*Max*	*SD*	*SE*
1	Pre	TLA	12	0.00	[redacted]		—	—
		TIM	12	0.00			—	—
		Δ	12	0.00			—	—
	Post	TLA	12	0.68			0.53	0.15
		TIM	12	0.60			0.42	0.12
		Δ	12	0.09			0.50	0.14
8	Pre	TLA	12	0.09			0.10	0.03
		TIM	12	0.20			0.22	0.06
		Δ	12	-0.11			0.17	0.05
	Post	TLA	12	0.88			0.69	0.20
		TIM	12	0.89		[redacted]	0.48	0.14
		Δ	12	-0.01			0.52	0.15

Δ = TLA – TIM: A positive number indicates a higher concentration in the TLA group.

Table 2. Timolol plasma concentrations (ng/mL): Statistical analyses

Day	*Time*	*Source*	*df*	*pr>F*	*Estimated Mean Δ** *(ng/mL)*	*95 % Confidence Interval (ng/mL)*
1	Post	Sequence	1	0.485	0.17	-0.36, 0.71
		Period	1	0.071	0.26	-0.03, 0.54
		Treatment	1	0.507	0.09	-0.20, 0.37
8	Pre	Sequence	1	0.042	0.17	0.01, 0.33
		Period	1	0.167	-0.07	-0.17, 0.03
		Treatment	1	0.034	-0.11	-0.22, -0.01
8	Post	Sequence	1	0.480	0.23	-0.47, 0.94
		Period	1	0.119	0.24	-0.07, 0.55
		Treatment	1	0.960	-0.01	-0.32, 0.30

***Estimated differences are based upon Sequence TLA:TIM minus TIM:TLA; Period 2 minus 1; and Treatment TLA minus TIM.**

Figure 1. Timolol plasma concentrations (ng/mL)

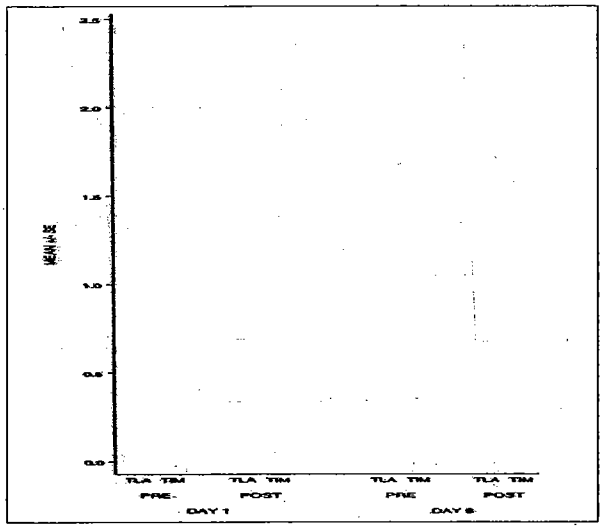

Table 3. Mean timolol plasma concentrations (ng/mL) by gender

TLA								
Day	Time	Gender	N	Mean	Max	Min	SD	s.e.m
1	Post	Female	8	0.80			0.45	0.13
		male	4	0.46	\	\	0.68	0.68
8	Pre	Female	8	0.11			0.11	0.03
		male	4	0.05			0.09	0.03
	Post	Female	8	1.1			0.69	0.2
		male	4	0.52			0.62	0.18
TIM								
Day	Time	Gender	N	Mean			SD	SE
1	Post	Female	8	0.73			0.43	0.12
		male	4	0.33			0.27	0.08
8	Pre	Female	8	0.24			0.24	0.07
		male	4	0.14			0.19	0.05
	Post	Female	8	0.97			0.54	0.15
		male	4	0.72			0.37	0.11

s.e.m = standard error mean

Summary:

Morning pre-dose:

- The timolol concentration from all pre-instillation samples on Day 1 was below the limit of detection.
- After 8 days of dosing, morning pre-dose values for TLA, 0.09 ng/mL, were 0.11 ng/mL less than with TIM, 0.20 ng/mL (p=0.034). On an individual basis, the highest concentration for TLA was [redacted] ng/mL, and for TIM was [redacted] ng/mL. Detectable timolol concentrations were found in 6 of 12 subjects treated with TLA, and with 7 of 12 subjects treated with TIM.
- After 8 days of dosing, a statistically significant sequence effect (p=0.042) was observed with mean timolol concentrations of 0.23 ng/mL and 0.06 ng/mL for the TLA:TIM and TIM:TLA sequences, respectively. In other-words, subjects who received TLA first tended to have higher plasma concentrations in both periods than those who received TIM first. The magnitude of this difference was relatively small, approximately 0.17 ng/mL (Table 2).

Two hours post-dose:

- Two hours after the first dose of timolol, mean plasma concentrations of timolol were 0.68 ng/mL with TLA and 0.60 ng/mL with TIM (p=0.507). On an individual basis, the highest concentration for TLA and TIM were [redacted] ng/mL, respectively. Detectable timolol concentrations were found in 10 of 12 subjects treated with TLA, and with all 12 subjects treated with TIM.
- Two hours after dosing on Day 8, mean plasma concentrations of timolol were 0.88 ng/mL with TLA and 0.89 ng/mL with TIM (p=0.960). On an individual basis, the highest concentration for TLA and TIM were [redacted] ng/mL, respectively. Detectable timolol concentrations were found in all subjects in both treatment groups.
- Timolol plasma concentrations were numerically smaller in males compared to that in females (Table 3).

Safety: Heart rate of 2 hrs Post dose was slightly lower (~2-5 bpm) compared to the Pre-dose, and similar effect was seen with systolic blood pressure (e.g., decrease of ~5 mm Hg on Day 8) following TLA or TIM administration. The sponsor reported that there was a greater incidence of burning/stinging, tearing, and light sensitivity associated with TLA (90-100%) than with TIM (50-100%). A greater proportion of subjects with discordant experience (experiencing a symptom with the use of one study medication but not with the other) reported the symptom during TLA use than with TIM use. Note that laboratory values (including hematology) were assessed only at study entry, thus, there was no measure of the laboratory values over time.

Conclusion: The results suggested that systemic bioavailability after Timolol-LA 0.5% was similar to that of timolol maleate ophthalmic solution 0.5%. Timolol plasma concentrations were consistently numerically smaller in males compared to that in females, however, this gender effect can not be confirmed/generalized since this finding is based on small number of subjects. A greater incidence of burning/stinging, tearing, and light sensitivity associated with TLA than with TIM and safety profile (heart rate and blood pressure) of Timolol-LA 0.5% was similar to that of TIM.

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