CLINICAL PHARMACOLOGY REVIEW

NDA, SDN	210428, 0000
Submission Date	03/30/2017
Submission Type	505(b)(2)
Generic name	Metoprolol succinate
Brand name	METOPROLOL SUCCINATE Extended-Release Capsules
Applicant	Sun Pharmaceutical Industries Ltd.
Dosage form	Extended Release Capsules
Strength	25 mg, 50 mg, 100 mg and 200 mg
Drug Class	Angiotensin II receptor blocker (ARB)
Indications	Hypertension, to lower blood pressure; Angina Pectoris; Heart Failure - for the treatment of stable, (b) (4) heart failure of (b) (4)
Associated IND	127963
OCP Division	Office of Clinical Pharmacology DCP-1
OND Division	Division of Cardiovascular and Renal Products (DCRP)
Primary Reviewer	Snehal Samant, PhD
Secondary Reviewer	Martina Sahre, PhD

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1. EXECUTIVE SUMMARY

Sun Pharmaceutical Industries Limited has submitted a New Drug Application (NDA 210428) for METOPROLOL SUCCINATE Extended-Release (ER) Capsules of strengths 25, 50, 100, and 200 mg under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The application relies on Agency's safety and efficacy findings for the listed drug TOPROL-XL® (metoprolol succinate) Tablet, Extended-Release approved as NDA 019962 in 1992. The applicant has developed the capsule formulation containing metoprolol succinate ER pellets intended to be taken as whole or sprinkled on applesauce, pudding and yogurt; or administered through a nasogastric tube. The applicant is seeking approval for the following indications at the same doses as approved for TOPROL-XL:

- Treatment of hypertension, to lower blood pressure
- Treatment of Angina Pectoris
- Heart Failure - for the treatment of stable, (b) (4) heart failure of (b) (4)

In addition to the above indications, TOPROL-XL, which is a scored tablet formulation available in strengths 25, 50, 100, and 200 mg, is also approved for the treatment of severe heart failure with the recommended starting dose of 12.5 mg once daily. The applicant has not developed 12.5 mg strength ER capsules formulation and therefore is not seeking an indication for the treatment of patients with severe heart failure.

The applicant has submitted two clinical pharmacology studies: 1) One four-period, complete-replicate crossover study comparing the relative bioavailability (BA) of metoprolol succinate ER capsules (200 mg) to the listed drug TOPROL-XL tablet (200 mg); 2) Three-period, crossover food effect study comparing fasted state administration of intact metoprolol succinate ER capsule (200 mg) to fed state administration of intact capsule and fasted state administration by sprinkling the contents on applesauce. The applicant has conducted an in vitro stability study of the drug product in soft foods (applesauce, pudding and yogurt) and an in vitro study to evaluate administration by nasogastric tube. The applicant is relying on the relative BA study for bridging to the efficacy and safety of the listed drug.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1(OCP/DCP1) has reviewed the NDA submission. The results of the relative BA study and food effect study support approval of METOPROLOL SUCCINATE Extended-Release Capsules for the proposed indications at the doses as approved for the listed drug TOPROL-XL. The food effect study results support administration of METOPROLOL SUCCINATE Extended-Release Capsules by sprinkling the contents on soft food and without regards to meal. The clinical pharmacology section of the proposed label was updated to reflect the current Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products.

1.2 Post-Marketing Requirements and Commitments

None

1.3 Summary of important clinical pharmacology and biopharmaceutics findings

The results of the relative BA study show that metoprolol succinate ER capsules (200 mg) and the listed drug, TOPROL-XL tablet (200 mg), are bioequivalent. The results from food effect study indicate that fed state administration of the metoprolol succinate extended release capsules and administration by sprinkling the capsule contents on apple sauce does not have a significant effect on the oral absorption of metoprolol. The results of the relative BA study and food effect study are summarized in Tables 4, 5, and 6.

2. QUESTION BASED REVIEW

This is an abridged version of the question-based review. For review of clinical and clinical pharmacology studies supporting the approval of TOPROL-XL, refer to the reviews associated with original NDA 019962.

2.1 General Attributes of the Drug Product

Metoprolol succinate ER capsules are formulated as hard gelatin capsules with yellow/dark yellow opaque cap and white opaque body containing white to off-white colored extended release pellets. The four dose strengths contain 23.75/ 47.5/ 95/ 190 mg of metoprolol succinate equivalent to 25/ 50/ 100/ 200 mg of Metoprolol tartrate, USP, respectively.

The inactive ingredients in metoprolol succinate ER capsules include ethyl cellulose (b) (4) (b) (4) (b) (4) Sugar Spheres (b) (4) (b) (4), hypromellose (b) (4) triethyl citrate (b) (4) and talc (b) (4)

2.1.1 What is the potential advantage of developing the extended release capsule formulation?

The applicant has developed an extended release capsule formulation for oral administration by swallowing whole or, when the capsule is opened, sprinkled on soft food (applesauce, pudding and yogurt); or administered through a nasogastric tube. The listed drug, Toprol-XL® is available as a scored tablet dosage form to be taken orally by swallowing.

2.1.2 Are additional instructions for administration of the dosage form required to ensure accurate dosing?

Metoprolol succinate extended-release capsules should be taken as whole (intact capsule). However, for patients unable to swallow an intact capsule or those requiring a nasogastric administration, the product is labelled with the following directions:

The contents of the capsules should be swallowed along a small amount (teaspoonful) of soft food (such as apple sauce, pudding, or and yogurt). (b) (4) The drug/food mixture should be swallowed within 60 minutes and not stored for future use.

Nasogastric tube administration:

(b) (4)

2.1.3 What are the proposed therapeutic indications?

The proposed therapeutic indications for Metoprolol succinate ER capsules are:

- Hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions.
- Angina Pectoris.
- Heart Failure - for the treatment of stable, [redacted] heart failure [redacted]

2.1.4 What are the proposed dose(s)?

The proposed doses are the same as those for the listed drug TORPROL-XL (Table 1).

Table 1. Proposed starting dosing for metoprolol succinate ER capsules

Indication	Dose
Adult Hypertension	25 mg or 100 mg once daily The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. Dosages above 400 mg per day have not been studied.
Pediatric Hypertension (≥ 6 years of age or older)	1 mg/kg once daily (up to 50 mg once daily) Dosage according to blood pressure response. Doses above 2 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients
Angina Pectoris	100 mg once daily Gradually increase the dosage at weekly intervals until optimum clinical response has been obtained or there is an unacceptable bradycardia. Dosages above 400 mg per day have not been studied.
Heart Failure [redacted]	25 mg once [redacted] daily Doubled every two weeks to the highest dose tolerated or up to 200 mg

2.2 Review of relative bioavailability studies

2.2.1 What are the design features of clinical pharmacology studies used to support dosing or label claims?

The applicant submitted two clinical pharmacology studies to support proposed doses and labelling (Table 2). The pivotal relative bioavailability study (MPL_200C_0179_16) compared the bioavailability of metoprolol from the metoprolol succinate ER capsules and TOPROL-XL tablets for the highest approved strength of 200 mg following single oral dose administration. The food effect study (MPL_200C_0180_16) evaluated the effect of high-fat, high-calorie meal on the bioavailability of metoprolol from metoprolol succinate ER capsules. This study also compared the bioavailability of metoprolol when swallowed whole to that when sprinkled on soft food (applesauce).

Table 2. Summary of clinical pharmacology studies

Study	Type	Design	Study participants
MPL_200C_0179_16	Relative Bioavailability study	An open label, randomized, two-treatment, four-period, two-sequence, full replicate crossover, single oral dose comparative bioavailability study in healthy adults under fasted state administration	Enrolled: 36 Completed: 33 (33 males) Age Range: 18-41 years
MPL_200C_0180_16	Food effect study	Open-label, randomized, three-period (fasting versus fed versus sprinkling on soft food), crossover, single-dose food effect study in healthy adults	Enrolled: 36 Completed: 29 (29 males) Age Range: 20-41 years

Source: Clinical Study Reports of Study No. MPL_200C_0179_16 (Version No. 01) and MPL_200C_0180_16 (Version No. 01)

2.2.2 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

The active moiety analyzed was metoprolol. All blood samples were collected in K_3EDTA (Tri-potassium salt of ethylene di-amine tetra acetic acid) vacutainers. High performance liquid chromatography mass spectrometric method was used for the estimation of metoprolol in human plasma using (b) (4) as internal standard. Sample preparation was done by (b) (4). Calibration curve was found to be linear from 0.500 ng/mL to 300.000 ng/mL. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLOQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Greater than two-thirds (67%) of the incurred samples concentration results were within 20% of the original concentration of the respective samples and meeting the acceptance criteria for incurred samples reanalysis. Analytical methods were validated and performed within acceptable limits as shown in Table 3.

Table 3. Summary of bioanalytical sample analysis and method validation

Analyte	Metoprolol
Method	LC/MS
Matrix/Analyte	Plasma/K_3-EDTA
(b) (4)	(b) (4)
LLOQ (ng/mL)	0.500

CCs	0.502 1.458 12.570 31.424 62.849 125.698 241.727 302.159
QCs	LOQQC – 0.503 LQC – 1.487 MQC – 126.044 HQC – 242.392 D2QC – 514.632 D4QC – 514.632
Accuracy Intra-day Accuracy (% Nominal) Inter-day Accuracy (% Nominal)	 94.89 to 100.96 95.33 to 101.91
Precision Inter-day Precision (%CV) Intra-day precision (%CV)	 1.00 to 5.25 1.61 to 4.52
Recovery%	LQC- 80.39 MQC-88.19 HQC-89.08

CCs: Calibration Curve standards, QCs: Quality Control Samples, LLOQ: Lower Limit of Quantification
Source: Method validation and analytical reports of Study No. MPL_200C_0179_16 (study-mpl-200c-0179-16-mv-report.pdf, study-mpl-200c-0179-16-ar.pdf) and Study No. MPL_200C_0180_16 (study-mpl-200c-0180-16-mv-report.pdf, study-mpl-200c-0180-16-ar.pdf)

2.2.3 What is the relative bioavailability of metoprolol extended release capsules compared to TOPROl-XL? Does it support the proposed dosing and label claims?
The geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for administration of 200 mg metoprolol succinate ER capsule compared to TOPROL-XL are summarized in Table 4.

Table 4. Results from relative bioavailability study

Relative bioavailability study		
Parameter	**Geometric mean ratio of test drug/listed drug (%)**	**90% C. I.**
C_{max}	95.61	91.29 -100.12
AUC_{0-t}	88.25	80.82 - 96.36
$AUC_{0-\infty}$	88.29	80.89 – 96.38

Source: Clinical Study Reports of Study No. MPL_200C_0179_16 (Version No. 01) and MPL_200C_0180_16 (Version No. 01)

The time to reach peak metoprolol plasma concentration is comparable for the ER capsule and TOPROL-XL. The mean T_{max} for metoprolol were 8.94 hours and 10.15 hours for TOPROL-XL for periods I and II, respectively. The mean T_{max} values for metoprolol were 10.11 hours and 9.87 hours for ER capsule for periods I and II, respectively. Metoprolol has an elimination half-life of ~6 h. Intra-subject variability of metoprolol pharmacokinetics (PK) following administration of ER capsules is similar to that following TOPROL -XL (C_{max}:16.36% for ER capsules and 14.15% for TOPROL-XL, AUC_{0-t}: 22.63% for ER capsules and 18.21% for TOPROL-XL).

Based on the results of the relative BA study, metoprolol succinate ER capsules are bioequivalent to TOPROL-XL. The results support labelling of metoprolol succinate ER capsules for the proposed doses as listed in Table 1.

2.2.4 What is the effect of food on the bioavailability of the drug from the drug product?
Taking metoprolol succinate ER capsules with a high-fat, high-calorie meal does not have a significant effect on the systemic exposure (AUC_{0-t}) and peak plasma concentration of metoprolol as compared to fasted state administration. The geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for administration of metoprolol succinate ER capsule with high-fat, high-calorie meal compared to fasted state administration is summarized in the Table 5. The study results support administration of metoprolol succinate ER capsules without regards to meal.

Table 5. Geometric mean ratio (GMR) and 90% confidence interval for Fed/Fasted state administration of metoprolol succinate ER capsules

Comparison of fed and fasted state administration		
Parameter	**Geometric mean ratio of fed/fasted state (%)**	**90% C. I.**
C_{max}	104.34	97.97 – 111.13
AUC_{0-t}	104.41	95.47 – 114.18
$AUC_{0-\infty}$	104.30	95.42 – 114.03

Source: Clinical Study Report of Study No. MPL_200C_0180_16 (Version No. 01)

2.2.5 What is the effect of administering the drug product with soft food?
C_{max} and AUC of metoprolol following sprinkling the capsule contents on apple sauce are within the 80 – 125% bioequivalence limits for the C_{max} and AUC following fasted state administration of intact capsule. The geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for fasted state administration of metoprolol succinate ER capsules by sprinkling on applesauce compared to swallowing of intact capsule is summarized in Table 6. The applicant has conducted in vitro stability study of the drug product with apple sauce, yogurt and pudding. The results from the healthy adult study and the in vitro stability study together support the administration of metoprolol succinate ER capsules by sprinkling the capsule contents on apple sauce, pudding and yogurt.

Table 6. Geometric mean ratio (GMR) and 90% confidence interval for sprinkling contents on applesauce/ swallowing intact capsule

Comparison of sprinkling contents on applesauce and swallowing intact capsule		
Parameter	**Geometric mean ratio of sprinkled/intact capsule (%)**	**90% C. I.**
C_{max}	98.52	92.60 – 104.81

AUC_{0-t}	101.74	93.17 – 111.09
$AUC_{0-\infty}$	101.70	93.18 – 111.01

Source: Clinical Study Report of Study No. MPL_200C_0180_16 (Version No. 01)

3. APPENDICES

3.1 Relative bioavailability study report

Study No: MPL_200C_0179_16	**EDR:** \\cdsesub1\evsprod\nda210428\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-mpl-200c-0179-16\study-mpl-200c-0179-16-body.pdf
Study Date: 15-Jul-2016 to 11-Aug-2016	
Title of Study: Single dose, crossover, two-treatment, two-sequence, four-period fully replicate bioequivalence study on Metoprolol succinate extended release capsules 200 mg in healthy adult human subject under fasting condition.	
Investigational Products **Test (T):** Metoprolol Succinate ER Capsules 200 mg. Manufactured by: Ohm Laboratories Inc. NJ **Reference (R):** TOPROL-XL® (Metoprolol succinate) extended release tablets 200 mg. Manufactured by: AstraZeneca AB, S-151 85 Sodertalje, Sweden.	
Study: • **Design:** Open label, balanced, randomized, two-treatment, two-sequence, four-period, single dose fully replicate crossover bioequivalence study. • **Washout:** Washout period between (period I and II) and (period III and period IV) was seven days and the same was nine days between period II and Period III. • **Study participants:** 36 healthy adults, 18-45 years of age. • **Administration:** A single oral dose of either of test or reference product was administered with 240 mL of drinking water after an overnight fast of at least 10 hours. Fasting state was continued until 4 hours post-dose. Drinking water was not allowed from 1 hour before dosing and up to 2 hours after drug administration. • **Sampling times (h):** pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9,10,11,12,1,3,14,1,5,16,18, 20, 22, 24, 26, 30, 48 and 72 h post-dose. • **Pharmacokinetic parameters calculated:** AUC_{0-t}, $AUC_{0-\infty}$, AUC% Extrap, C_{max}, T_{max}, Kel and $T_{1/2}$ **Analytical Method:** • A validated LC-MS method for the estimation of metoprolol in human K_3EDTA plasma using [redacted] (b) (4) as Internal Standard was used. • Detailed analytical method is described in SOP No. OP011996, Version 1.0. [High performance liquid chromatography tandem mass spectrometric method for the estimation of Metoprolol in human K_3EDTA plasma using [redacted] (b) (4) as an internal standard]. • The analytical range for metoprolol in plasma was 0.503 ng/mL - 301.691 ng/mL *Reviewer comment: The performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.* **Statistical Methods:**	

- The log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were analyzed using an ANOVA model on individual difference of test product and reference product, respectively, of each subject using Type III sum of squares, with the main effect of sequence as fixed effect. The log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were analyzed using a mixed effects ANOVA model using Type III sum of squares with the main effects of sequence, period and formulation as fixed effect.
- A 5% level of significance was used for within-subject comparison (i.e., period, 'treatment condition') and 10% level of significance was used for between-subject comparison (i.e., sequence). Within-subject variance estimates for Test formulation (σ^2T) and Reference formulation (σ^2R) was calculated.

Results:

33 subjects completed the study. A total of 3835 blood samples were collected for the estimation of drug in plasma.

Table 1. Demographics

Age range	18-41 years
Males	33 (100 %)
Weight	44.3 -75.9 kg

Source: Clinical Study Report Study No. MPL_200C_0179_16 (Version No. 01)

Table 2. Statistical Summary of Relative BA Data

Parameter	Geometric Least Squares Mean (%CV)		T/R Ratio (%)	90% C. I.	Intrasubject variability %CV		Upper Limit of the 90% Confidence Interval for σWT/σWR
	T	R			T	R	
C_{max} (ng/mL)	89.61	93.47	95.61	91.29 - 100.12	16.36	14.15	1.55
AUC_{0-t} (ng.hr/mL)	1612.88	1822.05	88.25	80.82 - 96.36	22.63	18.21	1.67
$AUC_{0-\infty}$ (ng.hr/mL)	1625.22	1835.04	88.29	80.89 – 96.38	22.56	18.12	1.67

σWT (within-test standard deviation)/σWR (within-reference standard deviation).

Source: Clinical Study Report Study No. MPL_200C_0179_16 (Version No. 01)

Table 3. Summary of Pharmacokinetic Parameters for metoprolol by treatment and period

Parameter	T1 Arithmetic Mean (%CV)	T2 Arithmetic Mean (%CV)	R1 Arithmetic Mean (%CV)	R2 Arithmetic Mean (SD)
C_{max} (ng/mL)	100.60 (50.89)	101.38 (48.99)	104.70 (46.44)	103.03 (45.42)
AUC_{0-t} (ng.hr/mL)	2035.90 (71.09)	1957.94 (66.10)	2184.22 (64.06)	2168.31 (64.01)
$AUC_{0-\infty}$ (ng.hr/mL)	2050.99 (71.30)	1972.79 (66.31)	2200.15 (64.24)	2183.22 (64.43)
T_{max} (hr)*	10.11 (34.56)	9.87 (33.93)	8.94 (46.81)	10.15 (43.99)

$t_{1/2}$ (hr)	6.39 (26.30)	6.85 (26.33)	6.44 (24.11)	6.59 (27.73)

* Median (minimum-maximum), SD standard deviation

Source: Clinical Study Report Study No. MPL_200C_0179_16 (Version No. 01)

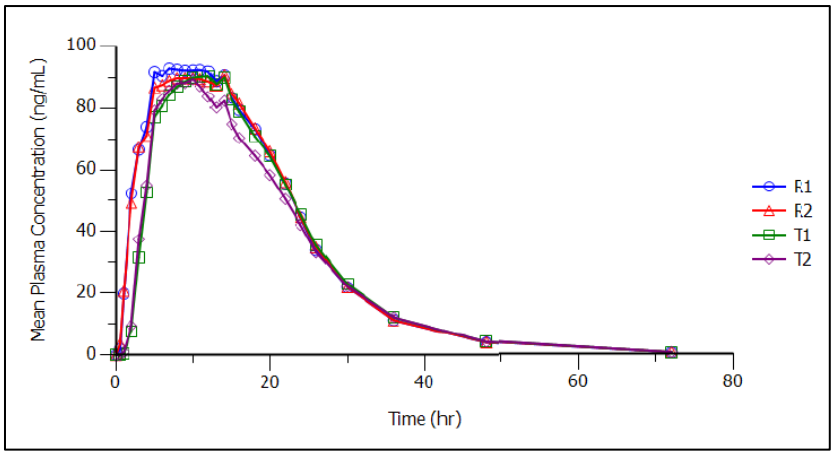

Figure 1. Linear scale plot of mean plasma concentration vs time profiles of metoprolol – by treatment

Source: Clinical Study Report Study No. MPL_200C_0179_16 (Version No. 01)

T1: Test product in period 1
T2: Test product in period 2
R1: Reference product in period 1
R2: Reference product in period 2

Conclusions:
Metoprolol succinate extended release capsules were bioequivalent to TOPROL-XL. The within-subject variability of the extended release capsule formulation was similar to that of TOPROL-XL.

3.2 Food effect study report

Study No: MPL_200C_0180_16	EDR: \\cdsesub1\evsprod\nda210428\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-mpl-200c-0180-16\study-mpl-200c-0180-16-body.pdf
Study Date: 20-Sep-2016 08-Oct-2016	
Title of Study: Single dose, crossover, three-treatment, three-sequence, three-period, bioavailability study to investigate the impact of food and applesauce on Metoprolol Succinate Extended Release Capsules 200 mg in healthy, adult, human subjects.	
Investigational Product: Metoprolol Succinate ER Capsules 200 mg. Manufactured by: Ohm Laboratories Inc. NJ	

Study:

- **Design:** Open label, balanced, randomized, three-treatment, three-sequence, three-period, single dose crossover study
- **Washout:** All periods were separated by washout period of 07 days.
- **Study participants:** 36 healthy adults, 18-45 years of age.
- **Treatments Administered**
  Test product (Treatment A):
  A single oral dose of test product was administered with 240 mL (milliliter) of drinking water, at an ambient temperature after an overnight fasting of at least 10 hours
  Test product (Treatment B):
  A single oral dose of test product was administered with 240 mL (milliliter) of drinking water, at an ambient temperature, 30 minutes after the start of high-fat high-calorie breakfast.
  Test product (Treatment C):
  A single oral dose of test product was opened and contents were sprinkled on one-tablespoon full applesauce. Approximately 15 mL of applesauce was used. This was swallowed by the subject along with 240 mL (milliliter) of drinking water, at an ambient temperature after an overnight fasting of at least 10 hours
- **Meal composition:**

	Food Stuff	Quantity (gm/ml)	Energy (cal)	Carbohydrate (g)	Proteins (g)	Fat (g)
01	Egg and Cheese McMuffin	1 serving	306	30	13	15
02	Chicken McNuggets	6 pieces	291	16.7	15.8	17.9
03	Hash Brown Potatoes	1 serving	147	16	2	8
04	Milk (full cream)	240 ml	152	12	8	8
05	Butter	14 g	100	-	-	14
		Total:	**996**	**74.7**	**38.8**	**62.9**
			Kcal.	**298.9**	**155.2**	**540.1**
			%	**30.1**	**15.6**	**54.3**

Source: Clinical Study Report Study No. MPL_200C_0180_16 (Version No. 01)

- **Sampling times (h):** pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9,10,11,12,1,3,14,1,5,16,18, 20, 22, 24, 26, 30, 48 and 72 h post-dose.
- **Pharmacokinetic parameters calculated:** AUC_{0-t}, $AUC_{0-\infty}$, AUC% Extrap, C_{max}, T_{max}, Kel and $T_{1/2}$

Analytical Method:

- A validated LC-MS method for the estimation of metoprolol in human K_3EDTA plasma using [redacted] (b) (4) as internal standard was used (Details reported in the analytical method SOP No. OP011996, Version 1.0. [High performance liquid chromatography tandem mass spectrometric method for the estimation of metoprolol in human K_3EDTA plasma using [redacted] (b) (4) as an internal standard]).
- The analytical range for metoprolol in plasma was 0.503 ng/mL - 301.691 ng/mL

Reviewer comment: The performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.

Statistical Methods:

- The log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were analyzed using Type III sum of squares with the main effects of formulation, period, sequence, and subjects nested within sequence.
- A separate ANNOVA was used to analyze each of the parameters. The sequence effect was tested at the 10% level of significance using the subjects nested within sequence mean square as the error term and formulation and period effects were tested at the 5% level of significance against the residual error (mean square error) from the ANOVA model as the error term.

Result:

29 subjects completed the study. A total of 2631 blood samples were collected for the estimation of drug in plasma.

Table 1. Demographics

Age range	20 -41 years
Males	29 (100 %)
Weight	49.4 – 80.2 kg

Source: Clinical Study Report Study No. MPL_200C_0180_16 (Version No. 01)

Table 2. Statistical summary of comparison of treatments A and B:

Parameter	Geometric Least Squares Mean (%CV)		B/A Ratio (%)	90% C. I
	Treatment A	Treatment B		
C_{max} (ng/mL)	94.61	98.30	104.34	97.97 – 111.13
AUC_{0-t} (ng.hr/mL)	1742.98	1779.57	104.41	95.47 – 114.18
$AUC_{0-\infty}$ (ng.hr/mL)	1758.00	1792.94	104.30	95.42 – 114.03

σWT (within-test standard deviation)/σWR (within-reference standard deviation).

Source: Clinical Study Report Study No. MPL_200C_0180_16 (Version No. 01)

Table 3. Statistical summary of comparison of treatments A and C:

Parameter	Geometric Least Squares Mean (%CV)		C/A Ratio (%)	90% C. I
	Treatment A	Treatment C		
C_{max} (ng/mL)	94.61	93.59	98.52	92.60 – 104.81
AUC_{0-t} (ng.hr/mL)	1742.98	1769.17	101.74	93.17 – 111.09
$AUC_{0-\infty}$ (ng.hr/mL)	1758.00	1784.82	101.70	93.18 – 111.01

Source: Clinical Study Report Study No. MPL_200C_0180_16 (Version No. 01)

Table 4. Summary of Pharmacokinetic Parameters

Parameter	A Arithmetic Mean (%CV)	B Arithmetic Mean (%CV)	C Arithmetic Mean (%CV)
C_{max} (ng/mL)	111.65 (58.68)	115.98 (59.36)	110.33 (58.24)
AUC_{0-t} (ng.hr/mL)	2382.10 (87.23)	2349.11 (81.55)	2372.09 (86.92)
$AUC_{0-\infty}$ (ng.hr/mL)	2405.38 (87.82)	2367.31 (81.86)	2392.77 (87.30)
T_{max} (hr)*	11.86 (30.80)	11.79 (24.77)	11.66 (26.95)
$t_{1/2}$ (hr)	6.56 (32.36)	6.20 (34.45)	6.13 (27.26)

* Median (minimum-maximum), SD standard deviation

Source: Clinical Study Report Study No. MPL_200C_0180_16 (Version No. 01)

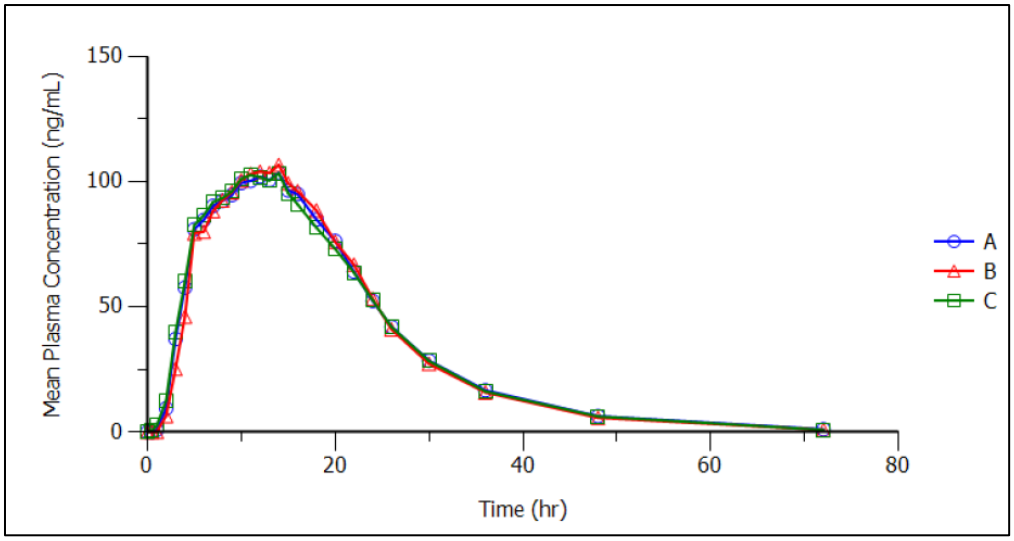

Figure 1. Linear scale plot of mean plasma concentration vs time profiles of metoprolol – by treatment

Source: Clinical Study Report Study No. Study No. MPL_200C_0180_16 Version No. 01

Conclusion:

Fed state administration of the metoprolol succinate extended release capsules and administration by sprinkling the capsule contents on applesauce does not have a significant effect on the oral absorption of metoprolol. The ER capsules may be administered without regards to meals.

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