CC:

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HFD-652/ J. Chaney

Endorsements: (Final with Dates)
HFD-652/ J. Chaney
HFD-652/ Y. Huang 1/9/98
HFD-617/ L. Sanchez
HFD-650/ D. Conner 1/9/98

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BIOEQUIVALENCY - DEFICIENCIES Submission date: 9/8/97

STUDY AMENDMENT (STA) Strengths: 400 mg

Outcome: AC (IC) UN NC

OUTCOME DECISIONS: (IC) - Incomplete UN - Unacceptable (fatal flaw)

WINBIO COMMENTS:

The Division's decision is unchanged and the multiple dose study conducted on Pentoxifylline Extended Release 400 mg Tablet, lot #61037, comparing it to Hoechst-Roussel's Trental 400 mg tablet, lot #0780665, remains unacceptable. The multiple dose study should be repeated with earlier sampling.

The new dissolution testing conducted on Pentoxifylline Extended Release 400 mg Tablet has been found acceptable. The dissolution testing should be conducted in 900 mL of deionized water at 37° C using USP 23 apparatus 1 (basket) at 100 rpm. The test product should meet the following tentative specifications:

1

dosage form is dissolved. Also, the Division of Bioequivalence requested the firm to submit dissolution data on the reference product biolot using the proposed method.

JUN 30 1997

Pentoxifylline
400 mg Extended Release Tablets
ANDA #74-962
Reviewer: J. Chaney
File #74962sd.996

Upsher-Smith Laboratories, Inc.
Minneapolis, MN
Submission Date:
September 17, 1996

REVIEW OF THREE IN VIVO BIOEQUIVALENCE STUDIES AND IN VITRO DISSOLUTION TESTING DATA

BACKGROUND

Pentoxifylline is a trisubstituted xanthine derivative designated chemically as 1-(5-oxohexyl)-3,7-dimethylxanthine and is a hemorrheologic agent that improves the flow properties of blood by decreasing its viscosity and improving erythrocyte flexibility. These actions increase blood flow and enhance tissue oxygenation in patients with chronic peripheral arterial disease. It is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Pentoxifylline is available as Trental® (Hoechst-Roussel) 400 mg extended-release (ER) tablet. The usual dosage is one tablet three times a day with meals.

Administration of single doses (400 mg) of pentoxifylline ER tablets results in Tmax values of 2-4 hr and mean Cmax values of 55-300 ng/mL. In one study, the apparent mean half-life of parent drug was about 3.4 hr which demonstrates the absorption-limited elimination rate of the extended release dosage form. In contrast, mean half-lives after 200-400 mg single doses of immediate-release dosage forms have been reported as follows: capsule, 0.89 hr; solution, 0.84 hr; intravenous, 1-1.6 hr. After multiple dosing of pentoxifylline ER tablets (400 mg every 8 hours for 6-7 days), mean steady-state values of pentoxifylline Cmax were 189-248 ng/mL and Tmax was 0.9-2 hours.

A metabolic reduction pathway results in 1-(5-hydroxyhexyl)-3,7-dimethylxanthine (MI) which may attain plasma levels five times higher than the parent drug. An oxidation pathway results in 1-(3-carboxypropyl)-3,7-dimethylxanthine (MV) which may attain plasma levels eight times greater than the parent drug.

More than 90% of a pentoxifylline dose is eliminated renally as metabolites. This and other urinary recovery data suggest virtually complete absorption of pentoxifylline from the extended release dosage form. After multiple dosing to steady-state (every 8 hr for 6 days), absolute bioavailability of the extended-release tablet was estimated as 19.4%. In a single dose study in healthy volunteers, the absolute bioavailability was estimated as 33%.

Based on human erythrocyte filterability studies, MI and MV were more active hemorrheologic agents than the parent compound. Reported mean values for MI (400 mg ER tablet) from single dose studies are as follows: Cmax, 143-343 ng/mL; Tmax, 3.2 hr; and t½, 3.4 hr. Mean steady-state values for MI from multiple dose studies were reported as follows: Cmax, 562-576 ng/mL; Tmax, 2-2.8 hours. For MV, the corresponding values were 943 ng/mL and 1.4 hours, respectively.

The effects of food on pentoxifylline kinetics were studied with an immediate-release capsule (2 X 200 mg) dosed 15 minutes after a standard breakfast. For both parent drug and MI: 1) changes in AUC_{0-10} and AUC_{0-inf} were not significant; 2) mean Cmax was decreased significantly after food (by 66% for parent and 47% for MI); 3) mean Tmax was increased significantly (by 1.7

hr for parent and 1.6 hr for MI) after food.

PRE-STUDY ANALYTICAL VALIDATION

PRE-STUDY VALIDATION OF THE __ / METHOD FOR PENTOXIFYLLINE AND ITS METABOLITES, MI AND MV, IN HUMAN PLASMA

Method

Page(s) 3

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

SINGLE DOSE BIOEQUIVALENCE STUDY OF PENTOXIFYLLINE 400 MG EXTENDED RELEASE TABLETS UNDER FASTING CONDITIONS

I. STUDY OBJECTIVE:

The objective of the study was to compare the rate and extent of absorption of the test versus the reference formulation to determine if the test and reference products were bioequivalent when administered under fasting conditions.

II. INVESTIGATORS AND FACILITIES

Clinical Research Facilities and Investigators:

Clinical Laboratory Facilities:

Analytical Facility:

Statistical Analysis:

III. STUDY DATES

Dose administration: Period I, 1/27-28/96; Period II, 2/2-3/96

Analytical completed: Between 2/7/96 and 3/4/96 using method

Between 7/19/96 and 7/25/96 using method

IV. EXPERIMENTAL

A. Exclusion Criteria:

1. recent history of drug or alcohol addiction or abuse.
2. a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease (as determined by the medical investigator).
3. positive hepatitis B surface antigen screen or a reactive HIV 1 & 2 antibody screen.
4. history of allergic response(s) to pentoxifylline or related drugs.
5. history of clinically significant allergies including drug allergies.
6. any clinically significant illness during the 4 weeks prior to Period I dosing (as determined by the medical investigator).
7. current users of tobacco products.
8. taking any drug known to induce or inhibit hepatic drug metabolism in the 30 days prior to Period I dosing.
9. donating greater than 150 mL of blood within 30 days prior to Period I dosing. All

subjects were advised not to donate blood for four weeks after completing the study.

10. donating plasma (e.g. plasmapheresis) within 14 days prior to Period I dosing.
11. receiving any investigational drug within 30 days prior to Period I dosing.
12. taking any prescription medication in the 14 days prior to Period I dosing.

B. Volunteer Instructions:

1. not to consume any nonprescription medication within 7 days of Period I dosing.
2. report any prescription or nonprescription medication consumed over the course of the study to the investigator(s).
3. abstain from consuming caffeine and/or xanthine-containing products (i.e. coffee, tea, caffeine-containing sodas, colas, and chocolate etc.) at least 48 hours prior to days on which dosing was scheduled and during the periods when blood samples were being collected.
4. abstain from consuming alcohol at least 48 hours prior to days on which dosing was scheduled and during the periods when blood samples were being collected.

C. Study Products:

Test Product - Pentoxil™ (Pentoxifylline) 400 mg Extended Release Tablets [Upsher-Smith Laboratories, Inc.; Lot No. 15868 (a sub-lot of the manufactured lot #61037 tablets) Exp. Date not shown]
Reference Product = Trental® 400 mg Extended Release Tablets [Hoechst-Roussel Pharmaceuticals, Inc; Lot No. 0780665; Exp. Date 02/97]

D. Procedures:

1. Study Design:
   a. General: A randomized, single dose, two-way crossover study was initiated in thirty-six healthy male subjects and four alternates to compare the relative bioavailability of the test and reference pentoxifylline 400 mg Extended Release Tablets under fasting conditions.
   b. Blood sampling: Blood collection (19x10 mL per subject each period) for drug content analysis occurred within one hour prior to dosing (0 hour) and after dose administration at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 30 hours.
   c. Confinement: At least 10 hours prior to until at least 24 hours after dosing
   d. Number of Subjects: Thirty-six healthy adult men and four alternates initiated the study. There were two dropouts over the course of the study who were not replaced.
   e. Washout between doses: 7 days
   f. Physical Activity: The subjects were not permitted to lie down or sleep for the first four hours after dose administration. However, if dizziness or light-headedness occurred, subjects were permitted to lie down. During confinement, only non-strenuous activity was permitted.
   g. Subject Safety and Monitoring: The subjects were continuously monitored by PRACS Institute, Ltd. staff throughout the confinement portion of the study. Blood pressure and heart rate were measured prior to dosing, at 12

and 24 hours after each dose, and upon completion of the study.

2. Dosing: Drug administration was assisted with L of room temperature water consumed under direct observation.
3. Fluid and Food Intake:
   a. Fluid Intake: No fluid except that given with the drug administration was allowed from 1 hour prior to dose administration until 2 hours after dosing. At 2 hours post-dose, all subjects consumed of water. Four hours after the dose, water was allowed ad lib if requested but was generally controlled during confinement and limited to approximately nL from the time of dosing until release from the study.
   b. Fasting: All subjects fasted from 10 hours prior to dose administration until at least 4 hours after dosing. However, clear fluids, such as water, were allowed during fasting.
   c. Type of Meals: Subjects were served standardized meals and beverages. Meals were the same in content and quantity during each confinement period.
   d. Diet Restriction: No caffeine or xanthine-containing food or drink was allowed during the confinement portion of the study.
4. Sample Processing, Storage & Transport:
   a. Processing: The samples remained at the blood collection station until all samples had been collected for that collection period. The vacutainer samples were then transferred to the processing laboratory and processed under yellow lighting. The blood was centrifuged at minutes at 4°C and the plasma pipetted immediately with polyethylene pipettes into polypropylene screw-top transport tubes.
   b. Storage: The plasma samples were immediately placed in a freezer, and stored at a temperature of -20°C or colder.
   c. Transport: The Sample Inventory Record was shipped with the frozen plasma samples as per Standard Operating Procedures.

V. ANALYTICAL

Determination of Pentoxifylline and its Major Metabolites, MI and MV, in Human Plasma Samples by HPLC/UV

Method

VI. PHARMACOKINETICS AND STATISTICAL ANALYSIS:

The pharmacokinetic parameters and pentoxifylline, MI and MV plasma concentrations were evaluated statistically by ANOVA for differences due to treatments, study days, dosing sequence, and subjects within sequence. The F value for sequence was calculated by using the

Type III MS for sequence and the Type III MS for subject (sequence) as the error term. The 90% confidence interval (two one-sided test) using LS means and standard error of estimate for pharmacokinetic parameters was calculated. The power of the ANOVA test to detect 20% difference ($\alpha = 0.05$) between treatments was determined for all of the pharmacokinetic parameters. Log transformed data was used where indicated.

VII. CLINICAL NOTES

On study days 1 and 8, a single oral dose (1 x 400 mg tablet) of test pentoxifylline tablets or reference pentoxifylline tablets (Trental®) was administered to volunteers. Meals and fluid intake were controlled during each 24 hour post-dose confinement period. Thirty-eight of forty volunteers successfully completed the study. Subjects 28 (DAL) and 33 (GRS) dropped prior to Period II dosing.

There were three deviations from the protocol instructions of no nonprescription medications within 7 days of Period I dosing. The self-medications (Vitamin C, Multivitamin, Extra Strength Tylenol) and problems were considered unremarkable by the subjects and investigators. The reported vitamins were considered dietary supplements and should not influence study integrity. Based on pharmacokinetic parameters, the acetaminophen should have been completely eliminated from the body prior to Period I dosing. Therefore in the opinion of the clinical investigators, the reported self-medications should not compromise the outcome or validity of the study, and subject enrollment was allowed.

There were sixteen problems reported in the fourteen days prior to Period I dosing including: headache, sore neck, stuffy nose, runny nose, head congestion, sleeplessnes, cough, and upset stomach. In the opinion of the clinical investigators, the problems should have no impact on the integrity of the study, and subject enrollment was allowed.

In assessing the subjects and reported values for heart rate and blood pressure, none of the reported changes, though numerically significant at times, were clinically significant. It is the opinion of the investigators, that none of the changes could be directly attributed to the drug product tested.

A few subjects reported usage of either ibuprofen, pseudoephedrine, vitamin C, multivitamin, and a multi-mineral over the course of the study. The reported medication dosing occurred after completion of Period I and prior to Period II dose administration. Based on pharmacokinetic parameters, the ibuprofen and pseudoephedrine consumed should have been eliminated from the body prior to Period II dosing. In the opinion of the clinical investigators, the problems and medication usage reported were not related to study medication or study participation and should not affect the integrity of the study.

Eleven adverse events were reported in nine of forty subjects dosed and included the following events: coughing (l), dizziness (light-headed) (1), fatigue(l), headache (4), sore neck (1), hematoma (1), stuffy head (1), and chills (1). Three subjects experienced headaches that were considered to be probably or possibly related to the study test drug. There were no adverse events or any events which required terminating any subject from the study.

Overall, the clinical laboratory measurements were generally unremarkable over the course of the study. All screening clinical laboratory samples and requested repeat samples were collected and the results interpreted prior to Period I dosing.

Some hematology laboratory results were outside the reference range at screening. The results were deemed not clinically significant by the medical investigator, and subject enrollment allowed.

IX. PHARMACOKINETIC STUDY RESULTS

Table 1

Mean Plasma Concentrations of Pentoxifylline in 38 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions (ng/mL)

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0.00	0.00	0.00	0.00	.
0.5	55.35	29.81	59.44	33.04	0.93
0.75	60.99	28.38	60.96	30.14	1.00
1	57.71	27.47	57.34	24.53	1.01
1.5	55.39	28.17	56.36	32.64	0.98
2	52.98	26.04	52.05	34.43	1.02
2.5	45.99	25.33	41.83	22.89	1.10
3	37.32	19.67	36.68	21.47	1.02
3.5	35.41	21.20	34.86	20.42	1.02
4	31.47	18.55	30.11	19.58	1.05
4.5	39.44	23.63	39.68	23.02	0.99
5	35.76	16.74	40.50	21.90	0.88
6	29.57	16.42	35.46	20.91	0.83
8	21.53	11.10	27.47	13.58	0.78
10	20.06	10.81	24.98	14.45	0.80
12	23.01	13.61	26.17	13.07	0.88
16	18.94	10.29	18.20	14.63	1.04
24	6.79	5.89	4.61	2.93	1.48
30	0.62	2.14	0.21	0.76	3.01

UNIT: PLASMA LEVEL=ng/mL TIME=Hrs
MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table 2

Arithmetic and Geometric Mean Pentoxifylline Pharmacokinetic Parameters in 38 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	656.75	262.25	666.84	289.34	0.98
AUCT	540.52	246.67	565.42	282.66	0.96
CMAX	73.31	32.99	75.00	37.10	0.98
KE	0.11	0.04	0.12	0.06	0.90
*LAUCI	609.04	----	610.25	----	1.00
*LAUCT	486.94	----	504.55	----	0.97
*LCMAX	66.01	----	67.26	----	0.98
THALF	7.58	3.37	7.43	4.27	1.02
TMAX	1.43	1.28	1.04	0.72	1.38

UNITS: AUC=ng*hr/mL CMAX=ng/mL T=hr
MEAN1=Test mean, MEAN2=Ref mean, RMEAN12=T/R ratios
* These values represent the geometric means (antilog of the means of the logs).

Table 3

LSMeans and 90% Confidence Intervals For Pentoxifylline in 38 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCI	657.36	669.53	87.72	108.64
AUCT	541.42	567.63	86.75	104.02
CMAX	73.60	75.27	95.57	109.99
*LAUCI	610.41	612.99	89.19	111.19
*LAUCT	487.84	506.78	87.40	106.02
*LCMAX	66.25	67.46	87.33	110.45

UNIT: AUC=ng hr/mL CMAX=ng/mL TMAX=hr

LSM1=LSmean,test; LSM2=LSmean,ref. LowCI12=Lower C.I. for T/R, UPPCI12=Upper C.I. for T/R.

* These values represent the LS geometric means(antilog of the means of the logs). The geometric LSM ratios for AUCI, AUCT and CMAX are 1.00, 0.96 and 0.98, respectively.

For the data of pentoxifylline, the C_{max} values for 14 subjects (#'s 4, 6, 9, 12, 15, 17, 23, 25, 26, 30, 32, 36, 38, and 40) during test and/or reference treatment were the first nonzero concentrations. Therefore, data from these 14 subjects for both treatments were deleted and the statistics were recalculated by the reviewer. The results are presented below in Table 4.

Table 4

Statistical Reanalysis on Pentoxifylline in 24 Subjects (Excluding 14 Subjects Whose C_{max} Was the First Nonzero Concentration) Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions

Parameter	T/R	90% Confidence Interval
AUC_{0-t}	0.99[a]	87.8-100.1
$LAUC_{0-t}$	0.97[b]	89.6-103.9
AUC_{0-inf}	0.99[a]	87.8-108.1
$LAUC_{0-inf}$	1.00[b]	91.0-110.7
C_{max}	0.97[a]	84.4-110.5
LC_{max}	1.02[b]	91.5-113.6

a = Ratio of LSMeans

b = Ratio of Geometric LSMeans

Table 5

Mean Plasma Concentrations of MI in 38 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0.00	0.00	0.00	0.00	.
0.5	94.17	54.18	92.03	45.66	1.02
0.75	157.80	66.90	152.98	65.26	1.03
1	191.63	80.41	183.21	70.39	1.05
1.5	234.58	88.77	229.13	85.45	1.02
2	249.84	89.84	238.68	104.99	1.05
2.5	255.25	93.08	231.93	105.00	1.10
3	230.87	91.49	219.23	107.29	1.05
3.5	213.16	86.48	208.45	111.27	1.02
4	200.17	88.27	185.86	105.73	1.08
4.5	171.42	82.56	166.46	85.44	1.03
5	156.64	67.26	156.88	76.62	1.00
6	125.80	61.06	132.22	64.52	0.95
8	91.29	47.10	116.21	55.69	0.79
10	85.77	37.10	109.01	48.13	0.79
12	89.22	43.50	106.30	44.26	0.84
16	85.69	40.26	82.83	54.29	1.03
24	23.59	36.16	16.28	16.21	1.45
30	2.57	6.20	1.55	3.36	1.66

UNIT: PLASMA LEVEL=ng/mL TIME=Hrs

MEAN1=Test, MEAN2=Reference, RMEAN12=T/R ratio

Table 6

Arithmetic and Geometric Mean MI Pharmacokinetic Parameters in 38 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	2755.24	1462.62	2653.49	1042.57	1.04
AUCT	2502.50	893.25	2512.68	1046.22	1.00
CMAX	267.76	93.80	265.76	116.52	1.01
KE	0.14	0.06	0.14	0.05	0.97
*LAUCI	2507.49	----	2461.76	----	1.02
*LAUCT	2357.40	----	2310.17	----	1.02
*LCMAX	251.77	----	244.29	----	1.03
THALF	5.97	3.95	5.40	1.85	1.10
TMAX	2.33	0.64	2.18	0.77	1.07

UNIT: AUC=ng hr/mL CMAX=ng/mL Time=hr

MEAN1=Test mean, MEAN2=Ref mean, RMEAN12=T/R ratios.

* These values represent the geometric means (antilog of the means of the logs).

Table 7

LSMeans and 90% Confidence Intervals for MI in 38 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet Under Fasting Conditions

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCI	2751.70	2660.96	89.72	117.10
AUCT	2505.67	2522.24	91.10	107.59
CMAX	268.24	266.64	90.73	110.47
*LAUCI	2506.96	2465.40	91.34	113.20
*LAUCT	2358.96	2315.33	92.23	112.54
*LCMAX	252.00	244.71	92.56	114.57

UNIT: AUC=ng hr/mL CMAX=ng/mL TMAX=hr

LSM1=LSmean,test; LSM2=LSmean,ref. LowCI12=Lower C.I. for T/R, UPPCI12=Upper C.I. for T/R.

*** These values represent the LS geometric means(antilog of the means of the logs). The geometric LSM ratios for AUCI, AUCT and CMAX are 1.02, 1.02 and 1.03, respectively.**

Table 8

Mean Plasma Concentrations of MV in 38 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	346.97	108.80	318.45	104.27	1.09
0.75	533.32	139.51	513.34	138.01	1.04
1	620.92	159.37	590.61	130.97	1.05
1.5	685.66	153.64	666.71	134.90	1.03
2	672.42	159.92	627.95	130.27	1.07
2.5	629.37	152.66	560.13	123.71	1.12
3	552.47	158.98	510.29	131.84	1.08
3.5	491.92	146.28	471.89	137.44	1.04
4	455.00	160.90	421.95	137.78	1.08
4.5	422.58	166.85	402.34	120.75	1.05
5	365.24	108.11	360.68	87.99	1.01
6	301.47	71.86	326.58	78.51	0.92
8	221.02	74.72	281.79	72.91	0.78
10	207.47	57.05	256.76	74.98	0.81
12	202.54	69.99	236.59	80.96	0.86
16	204.26	103.05	173.65	81.89	1.18
24	58.94	68.19	38.97	39.27	1.51
30	6.75	15.68	4.42	10.29	1.53

UNIT: PLASMA LEVEL=ng/mL TIME=Hrs

MEAN1=Test, MEAN2=Reference, RMEAN12=T/R ratio

Table 9

Arithmetic and Geometric Mean MV Pharmacokinetic Parameters in 38 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	6753.57	2344.08	6328.24	1224.66	1.07
AUCT	6208.29	1312.65	6029.79	934.10	1.03
CMAX	728.21	152.00	706.55	120.96	1.03
KE	0.14	0.06	0.18	0.06	0.79
*LAUCI	6486.51	----	6223.23	----	1.04
*LAUCT	6074.27	----	5958.32	----	1.02
*LCMAX	712.73	----	696.27	----	1.02
THALF	5.91	4.08	4.50	2.05	1.31
TMAX	1.76	0.59	1.71	0.64	1.03

UNIT: AUC=nghr/mL CMAX=ng/mL TIME=hr

MEAN1=Test mean, MEAN2=Ref mean, RMEAN12=T/R ratios

* These values represent the geometric means (antilog of the means of the logs).

Table 10

LSMeans AND 90% Confidence Intervals For MV in 38 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet Under Fasting Conditions

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCI	6724.43	6311.80	96.43	116.65
AUCT	6191.60	6021.09	99.25	106.41
CMAX	726.62	705.89	98.51	107.37
*LAUCI	6465.10	6208.40	97.43	111.30
*LAUCT	6059.28	5949.95	98.45	105.34
*LCMAX	711.27	695.70	98.14	106.51

UNIT: AUC=ng hr/mL CMAX=ng/mL TMAX=hr

LSM1=LSmean,test; LSM2=LSmean,ref. LowCI12=Lower C.I. for T/R, UPPCI12=Upper C.I. for T/R.

* These values represent the LS geometric means(antilog of the means of the logs). **The geometric LSM ratios for AUCI, AUCT and CMAX are 1.04, 1.02 and 1.02, respectively.**

The plasma concentration - time profiles for the parent drug, MI and MV under fasting conditions are shown in Figures 1, 2 and 3, respectively.