



UST CENTER FOR DRUG RESEARCH, EVALUATION AND STUDIES
6th Floor, Clinical Division, University of Santo Tomas Hospital
A.H. Lacson St., Manila
Philippines


SUMMARY REPORT

BIOEQUIVALENCE STUDY OF CILOSTAZOL 100 mg TABLET IN HEALTHY MALE VOLUNTEERS

Study No. B08001

This document is confidential to UST CeDRES
No part of this document may be reproduced, stored in a retrieval system or transmitted,
in any form or by any means (electronic, mechanical, photocopying, recording or
otherwise) without the written permission of UST CeDRES.

April 18, 2008

SUMMARY REPORT			
	BIOEQUIVALENCE STUDY OF CILOSTAZOL 100 mg TABLET IN HEALTHY MALE VOLUNTEERS	B08001	Otsuka (Phils.) Pharmaceutical, Inc.
	Study Title	Study No.	Sponsor
			CLTZL-P08001-01
			Protocol No.

GENERAL INFORMATION

Protocol Number: *CLTZL-P08001-01*

Sponsor: **Otsuka (Phils.) Pharmaceutical, Inc.**

Study Center: **UST Center for Drug Research, Evaluation and Studies (UST CeDRES)**
6th Floor Clinical Division
University of Santo Tomas Hospital-Clinical Division
A.H. Lacson St., Manila, Philippines

Study Date: **February 29 - March 15, 2008**

Principal Investigator:

William D. Torres / President
UST Center for Drug Research, Evaluation and Studies
6/F University of Santo Tomas Hospital-Clinical Division
A.H. Lacson St., Manila, Philippines
Phone No.: 749-9744 / 731101 local 2380
Fax No.: 7499744

Co-Investigators:

Eileen Valeri V. Pastorfide / Chemist
Lennie Grace C. Estoque / Statistician
Chatlyn R. Chua / Study Pharmacist
Wilbert A. Siat / Clinical Research Assistant

UST Center for Drug Research, Evaluation and Studies
6/F University of Santo Tomas Hospital-Clinical Division
A.H. Lacson St., Manila, Philippines

***Medical Officer
Responsible for
Subject Welfare:***

Maria Rhona M. Gatpandan-Bergantin, MD
University of Santo Tomas Hospital
A.H. Lacson St., Manila, Philippines



SUMMARY REPORT			
BIOEQUIVALENCE STUDY OF CILOSTAZOL 100 mg TABLET IN HEALTHY MALE VOLUNTEERS	B08001	Otsuka (Phils.) Pharmaceutical, Inc.	CLTZL-P08001-01
Study Title	Study No.	Sponsor	Protocol No.

TABLE OF CONTENTS

	Page
PRODUCT INFORMATION:	1
STUDY DESIGN	2
STUDY METHODS	2
RESULTS AND DISCUSSION	3
CONCLUSION.....	4

APPENDICES		NO. OF PAGES
1. STUDY PROTOCOL.....		42
2. CLINICAL REPORT.....		18
3. STATISTICAL REPORT.....		52
4. ANALYTICAL REPORT.....		55
5. <i>CURRICULUM VITAE</i> OF INVESTGATORS.....		20
6. 20% CHROMATOGRAMS OF BIOLOGICAL SAMPLES.....		153

INTRODUCTION

This study was undertaken to compare and evaluate the bioavailability of a generic drug product Cilostazol 100 mg Tablet (Clazol® 100 mg Tablet) with the innovator product Pletaal® 100 mg Tablet following a single dose administration.

The study was conducted at the UST Center for Drug Research, Evaluation and Studies, Inc. (UST CeDRES) located at the 6th Floor of the Clinical Division of the University of Santo Tomas Hospital from February 29 to March 15, 2008. The protocol for the conduct of this study was approved by the Institutional Review Board of UST CeDRES on February 6, 2008 (Appendix 1).

PRODUCT INFORMATION:

Test Product (A)

Product Name:	Clazol®
Active Ingredient:	Cilostazol
Dosage Strength/Form:	100 mg/Tablet
Manufacturer/Distributor:	Macleods Pharmaceuticals Limited Plot No. 25-27, Survey No. 366, Premier Industrial Estate Kachigam, Daman 396210, (U.T.), India for OEP Philippines, Inc.
Lot Number:	C0703
Expiry Date:	06/09
Potency:	102.92%

Reference Product (B)

Product Name:	Pletaal®
Active Ingredient:	Cilostazol
Dosage Strength/Form:	100 mg /Tablet
Manufacturer/Distributor:	Korea Otsuka Pharmaceutical Co., Ltd. 903 Sangsin-ri, Hyangnam-myeon, Hwaseong-si, Gyeonggi-do, Korea for Otsuka (Phils.) Pharmaceutical, Inc.
Lot Number:	PT708037
Expiry Date:	08/10
Potency:	103.01%

After one week washout period between treatment periods, the subjects were crossed over to the alternate treatment.

STUDY DESIGN

The study used a standard two-treatment, two-period, and two-sequence (2x2) randomized crossover design and enrolled 12 healthy, adult male, pre-screened volunteers. Each subject received either one (1) Clazol® 100 mg Tablet or one (1) Pletaal® 100 mg Tablet by oral administration according to the following scheme:

	Dosing Period	
	I	II
Sequence AB	Test	Reference
Sequence BA	Reference	Test

Subjects were randomly allocated to each treatment sequence.

After one week washout period between treatment periods, the subjects were crossed over to the alternate treatment.

STUDY METHODS

Selection of Volunteers

Twelve (12) healthy adult male volunteers (age ranges from 19 to 28 years old; average = 21.75 years, weight ranges from 48.0 – 70.0 kg.; average = 60.13 kg., and BMI ranges from 18.52 – 24.91; average = 21.81) who met the criteria for selection participated in the study. Subject details are provided in the Clinical Report section (Table 1, Appendix 2). Prior to the study, all subjects underwent a comprehensive medical examination including ECG, blood chemistries and hematological screening including tests for Hepatitis B and HIV and urinalysis including drug screen.

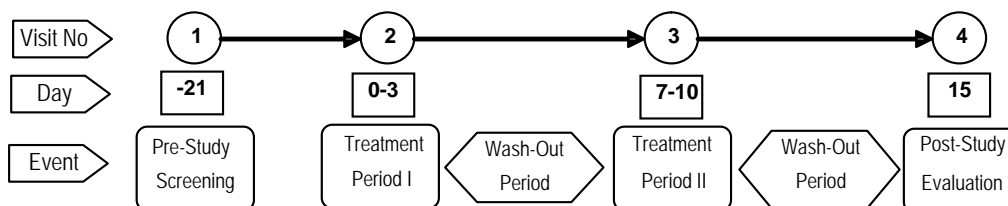
The volunteers were instructed to refrain from the use of any medication including vitamins, mineral supplements and herbal products seven days preceding the initial dose of Cilostazol and during the study period. Alcohol, grapefruit juice, xanthine or caffeine containing beverages and foods were prohibited for 48 hours prior to Cilostazol administration and throughout the sample collection. Smoking was not permitted while confined in the study center.

The study volunteers reported to the study center between 6:00 PM and 10:00 PM the evening prior to each dosing and remained in the facility until the last sample was obtained.

Drug Administration and Blood Sampling

The drug was administered at 6:00 AM with 200 mL of water and blood samples (~10 mL) withdrawn via an indwelling cannula at 0.00 (pre-dose) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 12.0, 18.0, 24.0, 36.0 and 48.0 hours post-dose. The actual time of sampling was recorded in the subjects' file. The subjects' vital signs were monitored at intervals throughout the collection period and standard snacks and meals were taken 4, 6, 9, 13, 24, 30, 33, 37 and 48 hours after dosing.

The schedule of events is given below:



Study evaluation was done on specific times for vital signs - blood pressure (sitting), respiratory rate (sitting), oral body temperature and radial pulse rate (sitting).

Analysis of Blood Samples

Plasma collected from the blood samples were analyzed for Cilostazol concentration by HPLC with UV detection using a validated method (see Analytical Report section, Appendix 4).

Determination of Pharmacokinetic Parameters and Statistical Analysis

Pharmacokinetic (PK) parameters were determined by non-compartmental methods from the drug plasma concentration-time data. For the statistical analysis of drug concentration data and all pharmacokinetic parameters, *BioeSTAT* software (developed by SQCS and validated with SAS 6.12) was utilized.

AUC_{0-t} , AUC_{0-inf} and C_{max} were considered as primary parameters for the assessment of bioequivalence. Comparisons were made between the two formulations using the mean of the raw data and log-transformed data of these parameters. Statistical significance of ratio for log-transformed data of raw data used appropriate analysis of variance (ANOVA) for the crossover design. Statistical inferences include 90% confidence interval and Schuirmann's two one-sided t-test procedures.

RESULTS AND DISCUSSION

The results of monitoring of the vital signs of volunteers are presented in detail under the Clinical Report section (Table 7, Appendix 2). Four (4) adverse events were recorded for study periods one (1) and two (2). During the first period, subject no. 3, under treatment B experienced mild dizziness which lasted for 1 hour. For the second period, subject no. 6, under treatment B experienced continuous severe headache for 1 hour and 5 minutes. Subjects no. 11 and 12 both under treatment A, experienced single moderate headache for 2 hours and continuous moderate viral conjunctivitis which lasted for 168 hours respectively. No serious adverse event was observed throughout the study and all twelve (12) subjects who entered the study completed all two periods.

A comprehensive report generated by *BioeSTAT* is presented in the Statistical Report section (Appendix 3) which include summary statistics of drug concentration data, individual and mean plots of plasma concentration-time curves on linear and logarithmic scales, tabular and graphical comparisons of PK parameters for each

subject by drug products, ANOVA of all PK parameters and of log transformed C_{max} and AUC, Least Square Means and their standard errors for all PK parameters, 90% confidence intervals for relative mean difference between test and reference products of the PK parameters, Schiurmann's two one-sided t-tests, and the 90% confidence interval for the geometric mean ratio of the $\text{Ln}[C_{max}]$, $\text{Ln}[AUC_{0-t}]$ and $\text{Ln}[AUC_{0-inf}]$, nonparametric 90% confidence interval for T_{max} and estimates of the inter and intra-subject variability.

The mean plasma Cilostazol concentration-time profiles for the two products are presented in Figure 1. Table 1 compares the Mean Pharmacokinetic Parameters for the two formulations. Table 2 presents a summary of bioequivalence assessments based on (a) the 90% confidence interval of the mean difference between the test and reference products, (b) Schiurmann's two one-sided t-test, and (c) the approximate confidence interval of the % ratio of the geometric means of the test and reference drug products.

Based on the 90% confidence intervals of the ratios of the geometric means for the parameters C_{max} , AUC_{0-t} , and AUC_{0-inf} for the test product and the reference product (C_{max} : 92.9% - 132.5%, AUC_{0-t} : 96.3% - 121.2%, AUC_{0-inf} : 74.1% - 101.9%), the data indicated that the bioavailability of the test product is not comparable to that of the reference product. The test drug is suprabioavailable compared to the reference.

CONCLUSION

On the basis of the above findings therefore, the generic drug product, Clazol® 100 mg Tablet is **not bioequivalent** to the reference/innovator drug product, Pletaal® 100 mg Tablet.


William D. Torres, Ph.D.
Principal Investigator

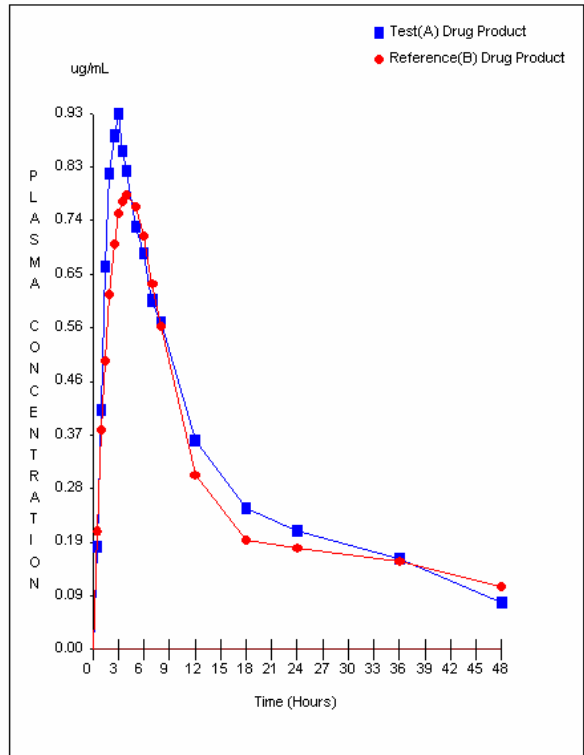


Figure 1a. Plots of mean plasma concentration-time curves of test (A) and reference (B) drug products

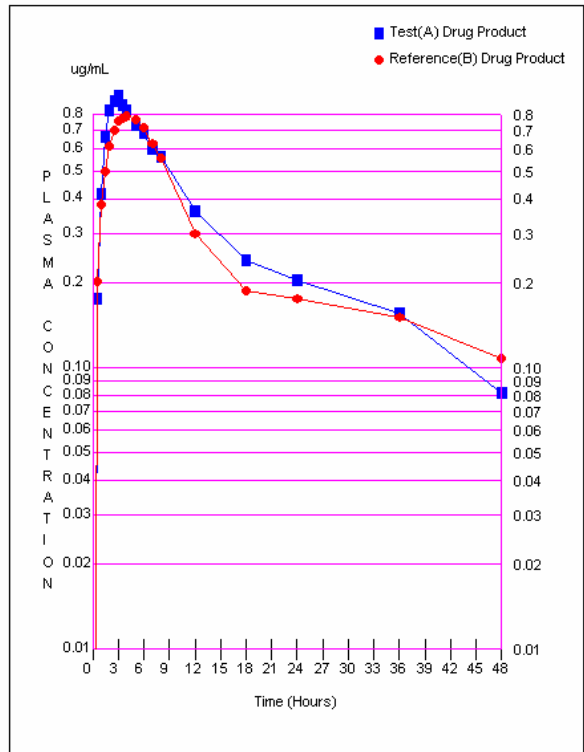


Figure 1b. Logarithmic plots of mean plasma concentration-time curves of test (A) and reference (B) drug products

Table 1
Comparison of Means and Tests of Hypotheses

PK Parameter	Drug Product	LSMean	Std Error of Mean	Pr> T Ho: $\mu=0$	Difference (A-B)	Std Error of Difference	Pr> T Ho: $\mu_A=\mu_B$
Tmax	A	3.3858	0.3408	0.0001	0.1775	0.4820	0.7204
	B	3.2083	0.3408	0.0001			
Cmax	A	0.9564	0.0625	0.0001	0.0821	0.0883	0.3748
	B	0.8743	0.0625	0.0001			
AUC(0-t)	A	13.8154	0.6728	0.0001	1.1433	0.9515	0.2572
	B	12.6721	0.6728	0.0001			
AUC(0-inf)	A	16.1405	1.4849	0.0001	-3.3842	2.1000	0.1381
	B	19.5247	1.4849	0.0001			
Kel	A	0.0618	0.0080	0.0000	0.0287	0.0113	0.0293
	B	0.0330	0.0080	0.0020			
t _{1/2}	A	15.2585	3.8302	0.0026	-16.4748	5.4167	0.0124
	B	31.7333	3.8302	0.0001			
Ln[Cmax]	A	-0.0992	0.0692	0.1824	0.1037	0.0979	0.3143
	B	-0.2029	0.0692	0.0150			
Ln[AUC(0-t)]	A	2.5588	0.0448	0.0001	0.0775	0.0634	0.2495
	B	2.4813	0.0448	0.0001			
Ln[AUC(0-inf)]	A	2.7045	0.0621	0.0001	-0.1409	0.0879	0.1399
	B	2.8454	0.0621	0.0001			

Table 2a
Assessment of Bioequivalence Based on the Classical (Shortest) Confidence Interval

PK Parameter	LS Means		Mean Difference	90% Confidence Interval		Acceptance Limits
	A	B		Lower	Upper	
Tmax	3.3858	3.2083	0.1775	78.3%	132.8%	80-120
Cmax	0.9564	0.8743	0.0821	91.1%	127.7%	
AUC(0-t)	13.8154	12.6721	1.1433	95.4%	122.6%	
AUC(0-inf)	16.1405	19.5247	-3.3842	63.2%	102.2%	
Kel	0.0618	0.0330	0.0287	124.9%	248.8%	
t½	15.2585	31.7333	-16.4748	17.1%	79.0%	

Table 2b
Assessment of Bioequivalence Based on Schuirmann's Two One-Sided t-Tests

PK Parameter	LS Means		Mean Difference	± THETA	t-Statistics	
	A	B			TL	TU
Tmax	3.3858	3.2083	0.1775	0.6417	1.6996	-0.9630
Cmax	0.9564	0.8743	0.0821	0.1749	2.9085*	-1.0507
AUC(0-t)	13.8154	12.6721	1.1433	2.5344	3.8651*	-1.4620
AUC(0-inf)	16.1405	19.5247	-3.3842	3.9049	0.2480	-3.4711*
Kel	0.0618	0.0330	0.0287	0.0066	3.1267*	1.9566*
t½	15.2585	31.7333	-16.4748	6.3467	-1.8698*	-4.2132*

*Significant (alpha=0.05)

Table 2c
Assessment of Bioequivalence Based on Approximate Confidence Interval of %Ratio of the Geometric Means of Test to Reference Drug Product

PK Parameter	Geometric Means		% Ratio	90% Confidence Interval		Acceptance Limits
	A	B		Lower	Upper	
Ln[Cmax]	0.9056	0.8163	110.9307	92.9%	132.5%	80-125
Ln[AUC(0-t)]	12.9199	11.9569	108.0539	96.3%	121.2%	
Ln[AUC(0-inf)]	14.9468	17.2084	86.8577	74.1%	101.9%	