6643

REPORT ON BIOEQUIVALENCE STUDY
(Phase I)

PROTOCOL NO.: 06-05-059

Study Title: Bioequivalence study comparing Quetiapine 150 mg tablet of Cipla Ltd., India with Seroquel™ tablet (containing Quetiapine 150 mg) of AstraZeneca UK Ltd., in healthy male human subjects under fasting conditions.

Study Design: Balanced, open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study in healthy male human subjects under fasting conditions.

	Formulations	Dose
Test	Quetiapine 150 mg tablet of Cipla Ltd., India.	One tablet
Reference	Seroquel™ tablet (containing Quetiapine 150 mg) of AstraZeneca UK Ltd.	One tablet

Date of Study Initiation (Clinical Phase) : 25th June 2007
Date of Study Completion (Clinical Phase) : 05th July 2007
Date of Completion of Analysis : 18th September, 2007
Version Status : Final
Version No. : 01
Dated : 13th November, 2007
Supersedes Version : NA
Dated : NA

Attested by me
04/9/10
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Study Centre	Sponsor
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Principal Investigator	**Sponsor's Medical Expert**
Dr. Muneesh Garg	Dr. Siddarth S. Chachad
Study Director	**Sponsor's Representative**
Mr. Krishnan Iyer	Dr. S. M. Purandare

No 14018

Note: This study was conducted in compliance with ICH-GCP including archiving of essential documents.

ATTESTED
AUTHORISED SIGNATORY
INDIAN MERCHANTS' CHAMBER
MUMBAI-INDIA.

INDIAN MERCHANTS' CHAMBER
- 4 SEP 2010
MUMBAI-INDIA

2 SYNOPSIS

Name of the Sponsor: Cipla Ltd., India	Individual Study Table Referring to part of the Dossier Volume: Page:	(For National Authority Use only)
Name of the Finished Product: Quetiapine 150 mg tablet		
Name of Active Ingredient: Quetiapine Fumarate		

Title of Study:
Bioequivalence study comparing Quetiapine 150 mg tablet of Cipla Ltd., India with Seroquel™ tablet (containing Quetiapine 150 mg) of AstraZeneca UK Ltd., in healthy male human subjects under fasting conditions.

Investigators:
Dr. Muneesh Garg, Principal Investigator;
Mr. Krishnan Iyer, Study Director;
Mr. Ratnakar Jadhav, Head Operations, Bioclinical;
Dr. K. Raghu Naidu, Head Operations, Bioanalytical.

Study Centre:
Sitec Labs Pvt. Ltd., 2nd Floor, Bldg. No. 14, CTS No. 82, 82 (1-17), Village Hariyali, LBS Marg, Vikhroli (W), Mumbai 400 083, India.

Publication (reference): Not Applicable

Study period: Date of Study Initiation (Clinical Phase) : 25th June 2007 Date of Study Completion (Clinical Phase): 05th July 2007 Date of Completion of Analysis : 18th September 2007	**Phase of development:** Phase I Study

The bioequivalence study presented here was carried out with the following objectives:

Pharmacokinetics: To compare the rate and extent of absorption of Quetiapine after administration of one Quetiapine 150 mg tablet of Cipla Ltd., India or one Seroquel™ tablet (containing Quetiapine 150 mg) from AstraZeneca UK Ltd., under fasting conditions in healthy male human subjects in a randomised crossover study.

Safety: To monitor the safety and tolerability of a single dose of Quetiapine 150 mg tablet in 44 healthy male human subjects.

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Methodology: Pre-dose sample (baseline) was taken within 1 hour prior to dosing and serial blood sampling was done up to 36.00 hours post-dose. At each time point 5 ml of blood sample was collected. Analysis of plasma samples for concentrations of Quetiapine was done using a validated LC-MS/MS method. A non-compartmental method was used to calculate pharmacokinetic parameters using drug concentrations versus time profile. Statistical comparison of the pharmacokinetic parameters of both the Investigational Products was performed to assess bioequivalence.

Number of subjects planned and analyzed

Number of Subjects:	
Planned	44 male
Recruited	44 male
Discontinued	00
Dropped out	00
Completed the Study	44
Analyzed	44
Assessed	43

Diagnosis and main criteria for inclusion:

Healthy willing volunteers between 18 to 45 years of age, having body weight within ±15% of the ideal body weight in relation to height, according to Life Insurance Corporation of India height-weight chart for Indian men and women and having no medical history of significant diseases or clinically significant abnormal findings during the pre-study screening, physical examination and laboratory evaluations. Hepatitis A, B, C and antibodies to HIV I and II to be negative or non-reactive. Test for drugs of abuse to be negative. Vital signs examination before check-in to be within clinically acceptable limits.

Name of the Sponsor: Cipla Ltd., India	Individual Study Table Referring to part of the Dossier	(For National Authority Use only)
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Name of Active Ingredient: Quetiapine Fumarate	Volume: Page:	

Test Product:	Quetiapine 150 mg tablet of Cipla Ltd., India.
Dose:	One tablet of Quetiapine 150 mg.
Mode of administration:	Administered orally with 240 ml of water.
Batch No.:	G74560
Duration of treatment:	A single dose of test or reference product of Quetiapine 150 mg tablet was administered on two separate occasions separated by a washout period of 4 days.
Reference Product:	Seroquel™ tablet (containing Quetiapine 150 mg) of AstraZeneca UK Ltd.
Dose:	One tablet of Quetiapine 150 mg.
Mode of administration:	Administered orally with 240 ml of water.
Lot :	DX 242

Criteria for evaluation:

Efficacy: The 90% parametric confidence intervals were constructed for the ratios of the means of ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Quetiapine. Bioequivalence was concluded if the confidence intervals so calculated fall within the range of 80–125% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. A wider range 75 -133% was to be considered for C_{max}, if the C_{max} data was found more variable than anticipated.

Safety: Subjects were monitored for adverse events throughout the clinical study period.

Statistical methods: ANOVA, 90% confidence intervals for the ratios of the means for ln-transformed and un-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were performed using WinNonlin® software version 5.2 (Pharsight Corporation, USA).

T_{max} was evaluated by non-parametric Mann-Whitney U or Wilcoxon Rank-Sum two-sample test procedure using NCSS 97 Software (Number Cruncher Statistical Systems).

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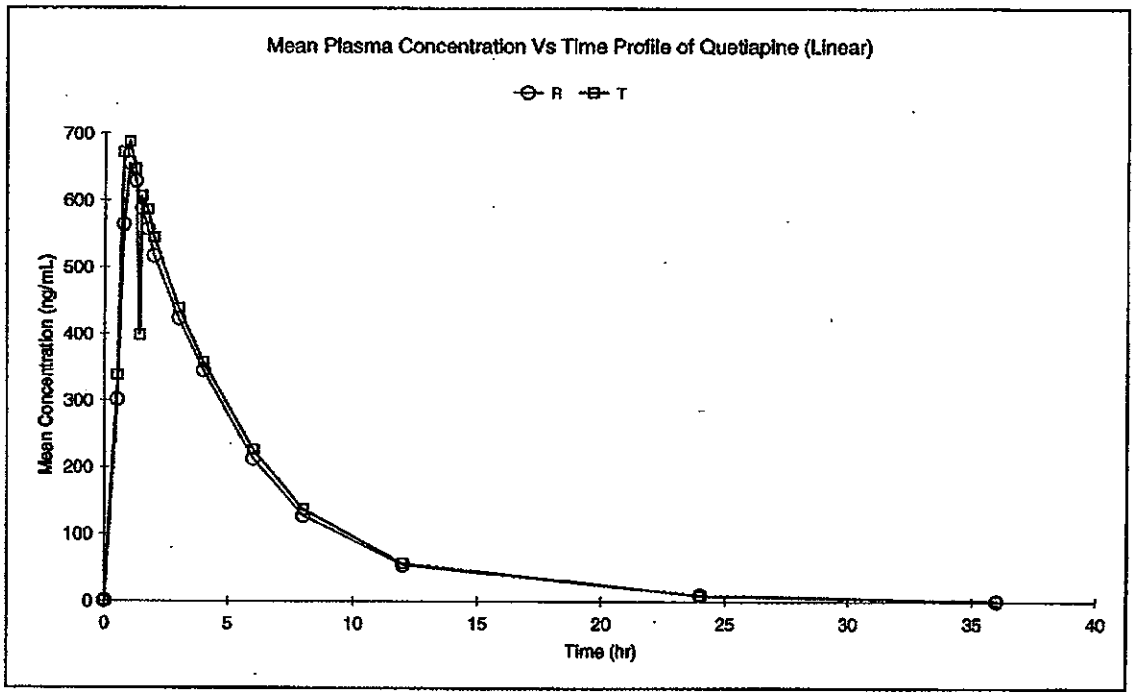
SUMMARY – CONCLUSION

EFFICACY RESULTS:



The 90% confidence intervals of ln-transformed parameters of Quetiapine are summarised below:

Quetiapine pharmacokinetic parameters	Geometric mean		(%)T/R	90% Confidence Interval for ln-transformed data
	Test (T)	Reference (R)		
N	43	43	-	-
C_{max} (ng/ml)	806.60	734.73	109.52	100.11-119.80
AUC_{0-t} (hr.ng/ml)	3303.10	3101.55	106.38	101.74-111.22
$AUC_{0-\infty}$ (hr.ng/ml)	3438.77	3222.25	106.61	101.97-111.46

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SAFETY RESULTS:

Both the products were well tolerated after a single dose in the healthy male human subjects. Giddiness, syncope, nausea, vomiting, headache, fever, dry mouth and leg cramps were the reported adverse events and all were of mild to moderate intensity. All subjects who had AE were recovered. No serious adverse events were reported during conduct of the study. No clinically significant changes were noted in laboratory data or results of physical examinations.

CONCLUSION:

The 90% confidence intervals for the Test / Reference geometric mean ratio of the ln-transformed pharmacokinetic variables C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (as primary characteristics of the rate and extent of absorption of Quetiapine) fall clearly within the conventional bioequivalence range of 80% to 125%. Therefore, the test product of Quetiapine can be considered to be bioequivalent with that of the reference product.

Date of the Report: 13th November, 2007