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REPORT ON BIOEQUIVALENCE STUDY

(Phase I)

PROTOCOL NO.: 06-10-081

Study Title: Bioequivalence study comparing Famciclovir 750 mg tablet of Cipla Ltd., India with Famvir® 750 mg tablet (containing Famciclovir 750 mg) of Novartis Pharmaceuticals, UK Ltd. in healthy male human subjects.

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	Famciclovir 750 mg tablet of Cipla Ltd., India.	One tablet
Reference	Famvir® 750 mg tablet (containing Famciclovir 750 mg) of Novartis Pharmaceuticals, UK Ltd.	One tablet

Date of Study Initiation (Clinical Phase) : 29th December, 2006
Date of Study Completion (Clinical Phase) : 15th January, 2007
Date of Completion of Analysis : 6th February, 2007

Version Status : Final
Dated : 27th April 2007
Supersedes Version : NA
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Principal Investigator	Sponsor's Medical Expert
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Study Director	**Sponsor's Representative**
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No 14019

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

ATTESTED

AUTHORISED SIGNATORY
INDIAN MERCHANTS' CHAMBER
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INDIAN MERCHANTS' CHAMBER
- 4 SEP 2010
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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: Famciclovir 750 mg tablet		
Name of Active Ingredient: Famciclovir		

Title of Study:
Bioequivalence study comparing Famciclovir 750 mg tablet of Cipla Ltd., India with Famvir® 750 mg tablet (containing Famciclovir 750 mg) of Novartis Pharmaceuticals, UK Ltd. in healthy male human subjects.

Investigators:
Dr. Muneesh Garg, Principal Investigator;
Mr. Krishnan Iyer, Study Director;
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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) : 29th December, 2006 Date of Study Completion (Clinical Phase): 15th January, 2007 Date of Completion of Analysis : 6th February, 2007	**Phase of development:** Phase I Study

Objectives: The bioequivalence study presented here was carried out with the following objectives:
Pharmacokinetics: To compare the rate and extent of absorption of Famciclovir after administration of Famciclovir 750 mg tablet of Cipla Ltd., India with Famvir® 750 mg tablet (containing Famciclovir 750 mg) from Novartis Pharmaceuticals, UK Ltd. under fasting conditions in healthy male human subjects in a randomised crossover study. As Famciclovir is rapidly metabolised in the gut wall and liver and very little is found in the systemic circulation, plasma levels of the active metabolite, Penciclovir, was used to evaluate bioavailability.

Safety: To monitor the safety and tolerability of a single dose of Famciclovir 750 mg tablet in healthy male human subjects.

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Methodology: Pre-dose blood sample (baseline) was taken within 1 hr prior to dosing and serial blood sampling was done up to 12.00 hours post-dose. At each time point 5 ml of blood sample was collected. Analysis of plasma samples for concentrations of Penciclovir 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.

No. of subjects planned and analysed:
Twenty-eight (24, plus up to 4 reserve) subjects were planned and recruited for the study. Subject number 24 was considered as dropout, as he did not arrive for period 2 due to personal reason. Plasma samples of twenty-seven subjects who completed both the periods were analysed. The pharmacokinetic and statistical assessment was done with the first 24 subjects who completed the study. Subject number 24 (Sequence B) who did not complete the study was replaced with subject number 25 (Sequence B) during the pharmacokinetic and statistical analysis.

Diagnosis and main criteria for inclusion:
Healthy willing volunteers between 18 to 45 years (inclusive) 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. Also test for drugs of abuse was negative, hepatitis A, B, C and antibodies HIV I and II were negative or non-reactive. Pre-entry vital signs check was within clinically acceptable limits.

Test Product	: Famciclovir 750 mg tablet of Cipla Ltd., India.
Dose	: Single dose of Famciclovir 750 mg tablet.
Mode of administration	: Administered orally with 240 ml of water.
Batch No.	: G67436
Duration of treatment	: Single dose of test and reference product of Famciclovir 750 mg tablet was administered on two separate occasions separated by washout period of 6 days.
Reference Product	: Famvir® 750 mg tablet (containing Famciclovir 750 mg) of Novartis Pharmaceuticals, UK Ltd.
Dose	: Single dose of Famvir® 750 mg tablet.
Mode of administration	: Administered orally with 240 ml of water.
Lot	: B5007

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: Famciclovir 750 mg tablet		
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Criteria for evaluation:

Efficacy: The 90% parametric confidence intervals were calculated for the ratios of the least square means of ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Penciclovir (active metabolite of Famciclovir). Bioequivalence was concluded if the confidence intervals so calculated fall within the range of 80–125% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. 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 geometric means for ln-transformed and un-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were performed using WinNonlin® software version 5.0.1 (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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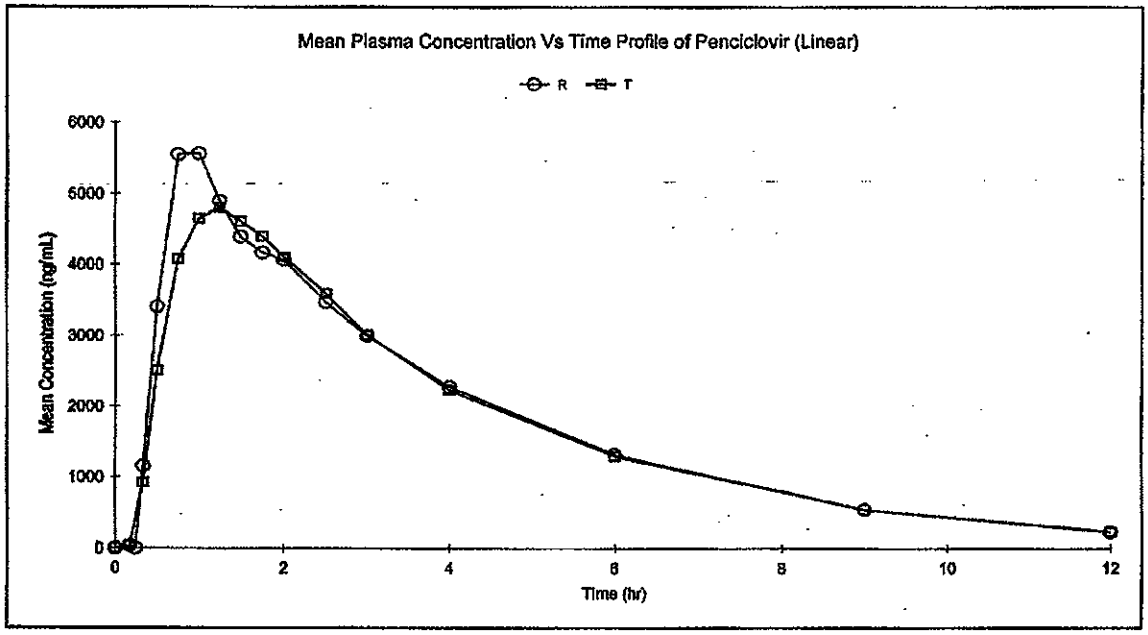
SUMMARY – CONCLUSION

EFFICACY RESULTS:



The 90% confidence intervals of ln-transformed parameters of Penciclovir are summarized below:

Penciclovir Parameters	Geometric mean		(%)T/R	90% Confidence Interval for ln-transformed data
	Test (T)	Reference (R)		
N	24	24	-	-
C_{max} (ng/ml)	5679.54	6285.64	90.36	80.50 -101.42
AUC_{0-t} (h.ng/ml)	20212.70	21003.11	96.24	93.77-98.77
$AUC_{0-\infty}$ (h.ng/ml)	21013.67	21775.53	96.50	94.02-99.05

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SAFETY RESULTS:

No serious adverse events were reported during conduct of the bioequivalence study. Both the products were well tolerated.

CONCLUSION:

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

Date of the Report: 27th April 2007