218 - Bmc - Notary

MINAKY 2

331

PROJECT NO.: BE_090_04

STUDY REPORT

TITLE: Open label, balanced, randomized, two-treatment, two-sequence, four-period (replicate design), single-dose, crossover bioequivalence study of fexofenadine hydrochloride 180 mg tablets, Cipla Limited, India and Telfast® 180 mg tablets, Aventis Pharma Ltd, UK in healthy, adult, male, human subjects under fasting condition.

Test Product: Fexofenadine hydrochloride 180 mg tablets, Cipla Limited, India.
Reference Product: Telfast® 180 mg tablets, Aventis Pharma Ltd, UK.

Sponsor: Cipla Limited, Mumbai, India.	
Authorised Signatory for Sponsor:	Sponsor's Medical Officer
Dr S M Purandare Head, Regulatory Affairs Cipla Limited Belasis Road; Opposite Hotel Sahil Mumbai Central Mumbai 400008. Phone No.: +91-22- 23082891; 23095521 Fax No.: +91-22-23002213; 23020297	Dr. Jaideep Gogtay Cipla Limited Belasis Road; Opposite Hotel Sahil Mumbai Central Mumbai 400008. Phone No.: +91-22- 23082891; 23095521 Fax No.: +91-22-23002213; 23020297

Study initiation date (check-in for period 01): 06 Jan 2005

Study completion date (last sample for period 04): 03 Feb 2005

Phase of development: Bioequivalence study

INVESTIGATORS' DECLARATION

We, the undersigned, have read and understood this report and hereby assure that the study was conducted in accordance with the approved protocol and in compliance with all the requirements regarding the obligations of investigators and all other pertinent requirements of the ICH (Step 5) 'Guidance on Good Clinical Practice'. We further undertake that all the essential documents pertaining to this study will be archived for a period of 15 years.

	Principal Investigator	Project Director	Management's Representative
Name	Dr. Padmavathi Vutukuru	Dr. Ayaaz Hussain Khan	Dr. Vinay P Shedbalkar
Sign			
Date	25 Jul 2005	25 Jul 2005	25 Jul 2005

Version No.: 05
Date: 25 Jul 2005
Supersedes Version No.: 04
Date: 02 Jun 2005

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No 751971

INDIAN MERCHANTS' CHAMBER
31 JAN 2007

ATTESTED
AUTHORISED SIGNATORY
INDIAN MERCHANTS' CHAMBER
MUMBAI-INDIA

2.0 SYNOPSIS

Title of the study	Open label, balanced, randomized, two-treatment, two-sequence, four-period (replicate design), single-dose, crossover bioequivalence study of fexofenadine hydrochloride 180 mg tablets, Cipla Limited, India and Telfast® 180 mg tablets, Aventis Pharma Ltd, UK in healthy, adult, male, human subjects under fasting condition.
Investigators	Principal Investigator: Dr. Padmavathi Vutukuru, MBBS, MD (Pharmacology) Clinical Pharmacologist
Study Center(s)	Clinical, Analytical, Pharmacokinetic & Statistical Facility GVK BIOSCIENCES PVT. LTD. CLINICAL R&D DIVISION 7th Floor, Swarna Jayanthi Commercial Complex, Ameerpet Hyderabad – 500 038 India. Phone No.: +91-40-5562 8888; 5563 5555 Fax No.: +91-40-5562-2655
	Clinical Chemistry Services Elbit Medical Diagnostics Limited AG Heights, 8-2-703, Road No. 12 Banjara Hills, Hyderabad-500034 Phone No.: +91-40-2337 2731/ 32/ 33/ 34 Fax No.: +91-40-2337 2740
	Radiological Services Mythri Multispeciality Hospital Plot No. 4, Mythri Vihar Behind Mythrivanam Building Ameerpet, Hyderabad-500038 Phone No.: +91-40- 5563 3929/ 30/ 31/ 32
Study Period	Study initiation date (check-in for period 01): 06 Jan 2005
	Study completion date (last sample for period 04): 03 Feb 2005
	Phase of development: Bioequivalence study
Objectives	The objective of the study was to compare the single-dose oral bioavailability of fexofenadine hydrochloride 180 mg tablets, Cipla Limited, India and Telfast® 180 mg tablets, Aventis Pharma Ltd, UK in healthy, adult, male, human subjects under fasting condition.
Methodology	Open label, balanced, randomized, two-treatment, two-sequence, four-period (replicate design), single-dose crossover comparative bioavailability study in healthy, adult, male, human subjects under fasting condition.
Number of Subjects	A total of 40 subjects (including 04 Standbys) were to be enrolled in the study as per the IEC approved protocol. Only 37 entered the study in the first period out of which 35 completed all the periods and were included in the final analysis.
Main inclusion criteria	• Male subjects aged between 18 and 45 years (including both). • Subjects' weight within ± 15% of the ideal height-weight chart of Life Insurance Corporation of India for non-medical cases. • Subjects with normal health as determined by personal medical history, clinical examination, and laboratory examinations and serology tests.
Main exclusion criteria	• Subjects having contraindications or hypersensitivity to fexofenadine or related group of drugs. • History or presence of any medical condition or disease according to the opinion of the physician • Major illness during 3 months before screening • Difficulty in swallowing solids like tablets or capsules
Investigational Products	
Reference	
Product	Telfast® 180 mg tablet
Manufactured By	Aventis Pharma Ltd, UK
Batch No.	024673

<table>
<tr><td>Expiry Date</td><td>Feb 2007</td></tr>
<tr><td>Method of Administration</td><td>As per randomization schedule one tablet of Telfast® 180 mg was administered with 240 mL of water at ambient temperature in each period. Subjects were instructed not to chew or crush the tablet but to consume as a whole.</td></tr>
<tr><td>Test</td><td></td></tr>
<tr><td>Product</td><td>Fexofenadine hydrochloride 180 mg tablet</td></tr>
<tr><td>Manufactured By</td><td>Cipla Limited, India</td></tr>
<tr><td>Batch No.</td><td>K40989</td></tr>
<tr><td>Expiry Date</td><td>Oct 2006</td></tr>
<tr><td>Method of Administration</td><td>As per randomization schedule one tablet of fexofenadine hydrochloride 180 mg was administered with 240 mL of water at ambient temperature in each period. Subjects were instructed not to chew or crush the tablet but to consume as a whole.</td></tr>
<tr><td>Criteria for Evaluation:

Pharmacokinetic Parameters

Safety</td><td>

Peak plasma concentration (C_{max}), time to achieve peak plasma concentration (T_{max}), area under the plasma concentration vs. time curve till last measured time point (AUC_{0-t}), area under the plasma concentration vs. time curve extrapolated to infinity (AUC_{0-Inf}), plasma elimination half-life ($t_{½}$) and elimination rate constant (K_{el}) were calculated for fexofenadine.
The acceptance range for bioequivalence is 80-125% for the 90% confidence intervals for the difference of means of log-transformed C_{max} ,AUC_{0-t} and AUC_{0-inf}

Subjects were monitored for their well-being by recording vital signs and clinical examination at regular intervals. Adverse events if any were recorded and handled appropriately.

Post study safety evaluation was carried out for hematology and biochemistry after completion of study.</td></tr>
<tr><td>Statistical Methods</td><td>ANOVA, two one-sided tests for bioequivalence (90% Confidence Intervals) for log-transformed C_{max}, AUC_{0-t} and AUC_{0-Inf} for test and reference formulations. Ratio analysis of log-transformed C_{max}, AUC_{0-t} and AUC_{0-Inf} were done.</td></tr>
<tr><td>Summary Conclusions:

PK Results</td><td>

The results of Log- transformed PK Parameters are tabulated below.

<table>
<tr><td rowspan="2">PK Parameters</td><td colspan="2">Log-transformed</td></tr>
<tr><td>Ratio% T/R</td><td>90% Confidence Interval</td></tr>
<tr><td>C_{max}</td><td>96.6</td><td>86.90-107.46</td></tr>
<tr><td>AUC_{0-t}</td><td>97.9</td><td>87.34-109.81</td></tr>
<tr><td>AUC_{0-Inf}</td><td>98.9</td><td>88.75-110.15</td></tr>
</table>

The confidence intervals of C_{max}, AUC_{0-t} and AUC_{0-Inf} are within the bioequivalence acceptance limits of 80-125%.</td></tr>
<tr><td>Safety Results</td><td>In this study fexofenadine seemed to be well tolerated upon single-dose administration to healthy, adult, male human subjects.

3 subjects complained of 5 mild adverse events and all were resolved satisfactorily. There was no clinically significant change in the post study evaluation (hematology & biochemistry).</td></tr>
<tr><td>Conclusion</td><td>Based on the above results the Test formulation i.e., fexofenadine hydrochloride 180 mg tablets produced by Cipla Limited, India is bioequivalent to Reference formulation i.e., Telfast® 180 mg tablets produced by Aventis Pharma Ltd, UK in healthy, adult, male, human subjects under fasting condition.</td></tr>
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