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BIOAVAILABILITY AND BIOEQUIVALENCE OF TWO ORAL FORMULATIONS OF CEFUROXIME AXETIL 500MG FILM COATED TABLET IN 36 HEALTHY, ADULT, HUMAN MALE SUBJECTS UNDER FED CONDITIONS

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ABSTRACT

To assess the oral bioequivalence of Cefuroxime axetil 500mg Film coated tablets (Test), in comparison with Reference Zinnat® 500 mg Film coated tablets in 36 healthy, adult, human male subjects under fed conditions. Study Design: An open label, balanced, randomized, two treatment, two sequence, two period, single dose, cross over, oral bioequivalence pivotal study in 36 healthy, adult, humanmale subjects under fed conditions. A validated Liquid Chromatography and Mass Spectroscopy (LC-MS/MS) method was employed for the estimation of Cefuroxime in plasma. Sample Size: 36. Study Population: Healthy adult, male subjects. Pharmacokinetic analysis was done by Non- compartmental method of analysis using the WinNonlin® Version 5.3.ANOVA was performed using the SAS® statistical software (version: 9.2) General linear model (GLM) procedure. The 90% confidence intervals of the T/R ratio of Ln- transformed $C_{max,\ and}$ $AUC_{0-t,}$ $AUC_{0-\infty}$ were within the bioequivalence range of 80%-125%.Hence the Test and Reference products of Cefuroxime axetilwere bioequivalent. From this study, we can conclude that the therapeutic quality of the formulation, test and reference Cefuroxime axetil 500mg are identical.The test Cefuroxime is bioequivalent to reference Cefuroxime.

Keywords: Bioavailability, bioequivalence, Cefuroxime axetil.

INTRODUCTION

The concept of Bioavailability (BA) and Bioequivalence (BE) have gained considerable importance during the last three decades due to new drug discovery as well as generic drug production [1]. Now a days the use of generic drug products is increasing to minimise the healthcare cost. The rising cost of medication has been contributing to the total overall cost of health care receiving considerable attention globally [2]. A major strategy for lowering the cost of medication and thereby reducing its contribution to total health care cost, has been the introduction of generic equivalents of brand name drugs (innovator drugs) [3]. Basically bioequivalence testing is performed to see, if the products are pharmaceutically in equivalent and pharmacokinetics in terms of exposure time profile so as to ensure same therapeutic outcome [4,5].

Cefuroxime axetil belongs to a group of drugs called cephalosporin antibiotics.Cefuroxime is used to treat many kinds of bacterial infections, including severe or lifethreatening Forms.[14]This study was undertaken to evaluate the bioavailability & bioequivalence of Cefuroxime axetil (Test) with Zinnat® (Reference) in healthy adult males under fed conditions [6-10].

OBJECTIVES

To assess the oral bioequivalence of Cefuroxime axetil 500mg Film coated tablets (Test), in comparison with Reference Zinnat® 500 mg Film coated tablets in 36 healthy, adult, human male subjects under fed conditions. To monitor adverse events and ensure safety of the subjects [11-15].

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MATERIALS AND METHODS

Study Design: An open label, balanced, randomized, two treatment, two sequence, two period, single dose, cross over, oral bioequivalence pivotal studyin 36 healthy, adult, human male subjects under fed conditions.

Study Type: Prospective Bioequivalence study

Study centre: Azidus Laboratories Ltd., located at Rathnamangalam, Vandalur, Chennai-48 in collaboration with Institute of Pharmacology, Madras Medical College Chennai.

Sample Size: 36.

Study Population: Healthy adult, male subjects

Ethical consideration: The protocol was prepared and submitted to the Independent Ethical Committee, Azidus Laboratories Ltd, Chennai and approval was obtained.The volunteers were intimated by the word of mouth and were asked to come to Azidus laboratories screening room. They were explained about the study procedure and purpose. Written informed consent was obtained from those who were willing to participate in the study. Then, they underwent screening by medical history, clinical examination and laboratory investigations.

Bioanalytical methodology

A validated Liquid Chromatography and Mass Spectroscopy (LC-MS/MS) method was employed for the estimation of Cefuroxime in plasma.

Pharmacokinetic Analysis

Pharmacokinetic analysis was done by Non-compartmental method of analysis using the Win Nonlin Version 5.3.

Statistical Analysis

The descriptive statistics such as mean, standard deviation, geometric mean and coefficient of variation were reported for the relevant pharmacokinetic parameters, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and secondary parameters, T_{max}, $t_{1/2}$ and K_{el} were estimated for both Test and Reference products.

Analysis of variance (ANOVA): ANOVA was performed using the SAS® statistical software (version: 9.2) General linear model (GLM) procedure. The Ln-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were analysed using an ANOVA model with the main effects of treatment, period and sequence as fixed effects. A separate ANOVA model was used to analyse each of the parameters. The sequence effect was tested at the 0.10 level of significance using the subjects nested within the sequence mean square from the ANOVA as the error term. As other main effects were tested at the 0.05 level of significance against the residual error (mean square error) from the ANOVA.

90 % Confidence Intervals(CI): Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals for the difference between the test and reference means was calculated for the untransformed data and log transformed data. The confidence limits were expressed as percentages of the least square mean(LSM) of the reference product. Using the confidence limits of the above CI and the LSM of the reference product, an approximate 90% CI for the ratio of the test and reference product means was calculated.

BIOEQUIVALENCE CRITERIA

Based on the statistical results of 90% confidence intervals of the ratios of the means (Test/Reference) for Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, conclusion was drawn to find whether the test product is bioequivalent to the reference product or not.

Bioequivalence was concluded, if the Test to Reference (T/R) ratios and the 90% confidence interval for the ratios for the means fall within the acceptance range of 80% -125% for the pharmacokinetic parameters, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ [16-25].

RESULTS

In this two period two way cross over study, 36 subjects who met the study inclusion and exclusion criteria were enrolled but only 34 subjects completed the study entirely.There was a washout period of 5 days between each of the two periods. The overall duration of the study was 8 days including the wash out period. Blood samples were collected at the predetermined time points to elicit the pharmacokinetic profiles of Cefuroxime axetil.

Vital parameters measured at the scheduled time intervals were normal and within the acceptable range for all study subjects. There was no death or serious adverse event reported in this study. One subject reported adverse events (vomiting) and another withdrew due to personal reasons.The Plasma concentration level of Cefuroxime axetil was determined by a validated LC-MS/MS method.

Pharmacokinetic Parameters

The pharmacokinetic parameters were estimated by using WinNonlin Software version 5.

AUC_{0-t}--Area under the concentration-time curve

Mean values (±SD) of AUC_{0-t} for Cefuroxime, treatment T was 40.924 ± 7.461µg.h/ml& for Reference was 40.822 ± 7.836µg.h/ml.

The geometric mean ratio ($AUC_T/AUC_{R)}$ was found to be 100.42% and the Confidence Interval for AUC_{0-t} (Test versus Reference) of Cefuroxime was found to be 97.89% to 103.01% therefore, 90% CI lies within the 80-125% window.

$AUC_{0-\infty}$--Area under the Concentration-Time curve

Mean values (±SD) of $AUC_{0-\infty}$ for Cefuroxime, treatment T was 41.982 ± 7.497µg.h/ml& for Reference was 42.178 ± 8.023 µg.h/ml. T_{max}Time taken to reach maximum concentration

Mean values (±SD) of T_{max} for Cefuroxime, treatment Test was 3.257 ± 1.283hr & for Reference 3.223 ± 1.156 hr.

Kel(hr-1)--Terminal elimination rate constant

Mean values (±SD) of Kel for Cefuroxime, treatment Test was 0.468 ± 0.079 hr^{-1}& for Treatment Reference was 0.454 ± 0.092hr^{-1} .

$T_{1/2}$(hr)-- Terminal Half life

Mean values (±SD) of $T_{1/2}$ for Cefuroxime, treatment Test was 1.522 ± 0.256 hr& for treatment Reference was 1.648 ± 0.725 hr.

AUC_%Extrap_obs

Mean values (±SD) of AUC_%Extrap_obs for forCefuroxime, treatment Test was 2.580 ± 1.271% & for treatment Reference was 3.157 ± 3.473%.

Table 1. Mean values of various pharmacokinetic parameters for Cefuroxime

Parameters (Units)	Cefuroxime (Mean ± SD)	
	Test	Reference
Cmax (µg/ml)	10.935 ± 2.787	10.941 ± 2.672
AUC0- t (µg.h/ml)	40.924 ± 7.461	40.822 ± 7.836
AUC0-∞ (µg.h/ml)	41.982 ± 7.497	42.178 ± 8.023
Tmax (hr)	3.257 ± 1.283	3.223 ± 1.156
Kel (hr-1)	0.468 ± 0.079	0.454 ± 0.092
T1/2 (hr)	1.522 ± 0.256	1.648 ± 0.725
AUC_%Extrap_obs	2.580 ± 1.271	3.157 ± 3.473

C_{max}--Peak or maximal plasma concentration (C_{max}): Mean values (±SD) of C_{max} for Cefuroxime, treatment Test was 10.935 ± 2.787µg/ml & for Reference was 10.941 ± 2.672µg/ml.

The Test / Reference (T/R) ratio of least square mean of log transformed C_{max} was found to be 99.59% with 90% confidence interval LCL= 94.12% and UCL= 105.38% therefore 90% CI lies within the 80-125% window.

Fig 1. Linear Plot Of Mean Plasma Cefuroxime concentration Vs Timepoints

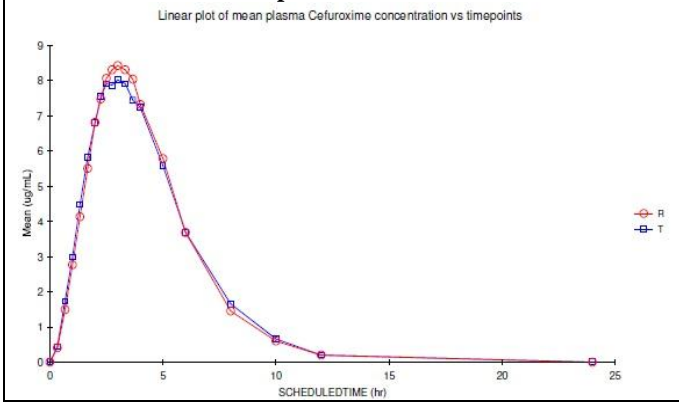
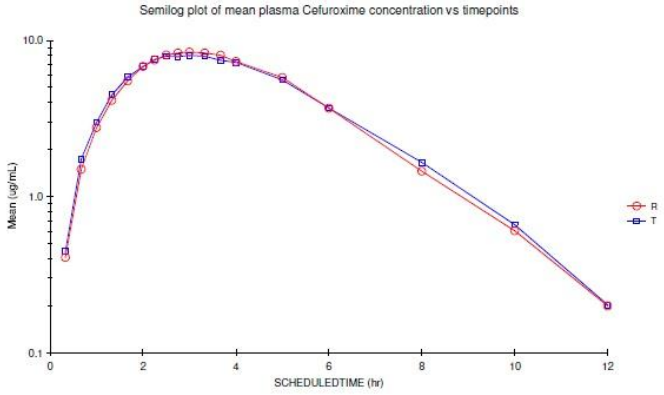


Fig 2. Semilog Plot Of Mean Plasmacefuroxime Concentration Vs Time Points



DISCUSSION

In this study, Test and Reference product containing Cefuroxime axetil 500mg Film tablets were evaluated for the safety upon single dose administration to normal healthy adult male subjects under fed conditions. This study was conducted with Cefuroxime axetil 500mg Film tablets (test) and Cefuroxime axetil 500mg Film tablets (reference) to establish the drugs concentration versus time profile and the results of the pharmacokinetic analysis of Cefuroxime of the test(T) product were compared with the reference (R) product. Analysis of variance for Ln-transformed pharmacokinetic parameters revealed that there was no significant variation between test and reference formulation for these three primary pharmacokinetic parameters C_{max} and $AUC_{0-t,}$ &$AUC_{0-\infty}$.

C_{max}:

The statistical analysis did not show any significant difference between the groups. The geometric mean ratio was within the limits of reference confidence interval which was found to be 94.12% - 105.38% (80 to 125%). This confirms the bioequivalence of the products.

$AUC_{0-t:}$

The statistical analysis did not show any significant difference between the groups. The geometric mean ratio was within the limits of reference confidence interval that was found to be 97.89%-103.01% (80 to 125%). Therefore, bioequivalence can be concluded.

90% Confidence Interval:

The 90% confidence intervals of the T/R ratio of Ln- transformed $C_{max,\ and}$ $AUC_{0-t,}AUC_{0-\infty}$ were within the bioequivalence range of 80%-125%.Post study assessment of the haematological and biochemical parameters showed no significant changes on comparing with the respective baseline parameters. The above parameters are similar which suggested that Cefuroxime (Test) and Cefuroxime (Reference) were bioequivalent.

CONCLUSION

From this study, we can conclude that the therapeutic quality of the formulation, test and reference Cefuroxime axetil 500mg are identical. The test Cefuroxime is bioequivalent to reference Cefuroxime. Both the test and reference products have comparable safety profile.

CONFLICT OF INTEREST STATEMENT

No conflict of interest.

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None

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