Original Research Paper Clinical Research

SAFETY, TOLERABILITY AND BIOEQUIVALENCE ASSESSMENT OF ELETRIPTAN 40 mg TABLET

Atreyee Sarkar

Dr. Shivanand Dhanure

ABSTRACT Eletriptan is a drug used to treat acute migraine. It acts as a 5-Hydroxytryptamine receptor agonist and is clinically effective for the treatment of migraine. Micro Labs is a generic drug company who had developed an Eletriptan 40 mg tablet formulation. The formulated tablets were tested in healthy adult human volunteers under fasting and fed conditions for bioequivalence as per United States (US) guideline for conduct of bioequivalence studies. The Reference product considered for bioequivalence was RELPAX® of Pfizer. The formulation developed by Micro Labs was safe and well tolerated without major Adverse Events and was found to be bioequivalent to the reference drug formulation.

KEYWORDS : Eletriptan, bioequivalence, migraine, safe

Introduction

Bioequivalence studies are very important for the development of a pharmaceutical preparation in the pharmaceutical industry. Their rationale is the monitoring of pharmacokinetic and pharmacodynamic parameters after the administration of tested drugs. The target of such study is to evaluate the therapeutic compatibility of tested drugs (pharmaceutical equivalents or pharmaceutical alternatives). The importance of bioequivalence studies is increasing also due to the large growth of the production and consumption of generic products. Generic products represent approximately 50 % of the whole consumption in many European countries and USA.

The comparison of the original and the generic product via bioequivalence study is suggested as sufficient for the registration of generic products. (Vetchý D et al 2007)

Bioequivalence is a term in pharmacokinetics used to assess the expected in vivo biological equivalence of two proprietary preparations of a drug. If two drugs are bioequivalent it means that they would be expected to be, for all intents and purposes, the same. In determining bioequivalence between two drugs such as a reference drug (Brand) and potential to be test drug (marketed generic drug), pharmacokinetic studies are conducted.

For a pharmacokinetic comparison, the plasma concentration data are used to assess key pharmacokinetic parameters such as area under the curve (AUC), peak concentration (Cmax), time to peak concentration (Tmax), and absorption lag time (tlag). Testing should be conducted at several different doses, especially when the drug displays non-linear pharmacokinetics.

If 90% Confidence interval for the ratio of the geometric least square means of natural log transformed Cmax, AUC_{0-t} and AUC_{0-inf} of Test and Reference drugs are within 80.00% to 125.00%, then bioequivalence will be established. (Srivastav Atul Kumar et al 2013)

Migraine is a commonly occurring, chronic disorder that can cause significant disability. Eletriptan is a selective serotonin 5-hydroxytryptamine 1 receptor subtype B/D (5-$HT_{1B/1D}$) agonist. It acts as a clinically effective treatment for moderate to severe migraine. (Rahul Bhambri et al 2015)

Migraine is a multifactorial, neurological and disabling disorder, also characterized by several autonomic symptoms. Triptans, selective serotonin 5-$HT_{1B/1D}$ agonists, are the first-line treatment option for moderate-to-severe headache attacks. Among triptans, Eletriptan shows a consistent and significant clinical efficacy and a good tolerability profile in the treatment of migraine, especially for patients with cardiovascular risk factors without coronary artery disease. (Matilde Capi et al 2016)

Micro Labs Ltd. had developed a generic version of Eletriptan 40 mg tablets. It had been tested in healthy human volunteers in fasting and fed condition. The bioavailability, safety and tolerability were assessed along with RELPAX® Eletriptan 40 mg Tablets of Pfizer. Approval had been taken to conduct the studies from Aditya Independent Ethics Committee, Gujarat, India and DCGI (Drug Controller General of India).

The bioequivalence studies were conducted as per US guideline for conduct of bioequivalence studies. (US guideline for conduct of Bioequivalence studies, US individual BE Recommendation for Eletriptan Tablets)

Materials and Methods

An Open Label, Randomized, Two-Period, Two-Treatment, Two-Sequence, Crossover, Balanced, Single Oral Dose Bioequivalence Study was conducted of Eletriptan Hydrobromide Tablets 40 mg of Micro Labs Limited, India and RELPAX® (Eletriptan Hydrobromide) Tablets 40 mg of Roerig Division Of Pfizer Inc, NY, NY 10017 in healthy adult human subjects under fasting and fed conditions.

The studies were conducted at Cliantha Research Limited, Sigma-1 Corporate, B/H. Rajpath Club, Opposite Mann Party Plot, Off. S.G Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India.

Volunteers selected were healthy young adults within 18-45 years age, BMI of 18.5 to 24.9 weight in kg / (height in meter) ^{2} and having no history of smoking or drug abuse. Informed consent was obtained from each volunteer before screening.

Fasting study dosing: In each period, a single oral dose of one capsule of either Test formulation (Test T) or Reference formulation (Reference R), both containing 40 mg of Eletriptan, was administered with about 240 mL drinking water at ambient temperature in fasting condition (at least 10.00 hours before dosing) and fed condition (30 minutes after start of a high calorie and high fat breakfast) as per randomisation schedule in the morning.

PK Blood Draw Time Points (both Fasting and Fed studies): pre-dose (within 1.00 hour prior to dosing) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0 and 24.0 hours post-dose.

Vital signs like Blood Pressure (B.P.), pulse rate, temperature and respiratory rate were measured at regular intervals. Subjects were asked about their well-being status from time to time.

There were thirty six (36) healthy, adult, eligible human subjects enrolled in the fasting and fed studies. Out of 36 enrolled subjects, thirty three (33) subjects completed the fasting study and thirty four (34) subjects completed the fed study.

Results

The bioequivalence assessment between the formulation manufactured by Micro Labs and RELPAX® (Eletriptan Hydrobromide) Tablets 40 mg is presented below in fasting and fed conditions:

Table 1: Fasting study summary of Pharmacokinetic Data for Eletriptan (n=33) Dose: 40 mg (Reference Product: RELPAX® (eletriptan HBr) Tablets 40 mg)

Pharmacokinetic parameter	Arithmetic mean	Standard deviation	Coeff of Variation (%)
AUC_t (ng.h/mL)	810.028	272.648	33.659
AUC_i (ng.h/mL)	863.382	291.466	33.759
Cmax (ng/mL)	115.790	40.031	34.572

(Test Product: Eletriptan Hydrobromide Tablets 40 mg)

Pharmacokinetic parameter	Arithmetic mean	Standard deviation	Coeff of Variation (%)
AUC_t (ng.h/mL)	807.456	326.360	40.418
AUC_i (ng.h/mL)	864.895	353.268	40.845
Cmax (ng/mL)	108.809	49.088	45.114

Table 2: Test & Reference Geometric mean, Ratio, 90% Confidence Intervals, Intra-Subject CV (%) and Power based on Log-transformed data for Eletriptan (n=33)

Pharmacokinetic parameter	Geometric mean (Test)	Geometric mean (Reference)	Ratio (%)
AUC_t (ng.h/mL)	744.624	765.661	97.25
AUC_i (ng.h/mL)	795.615	815.590	97.55
C_{max} (ng/mL)	99.529	109.112	91.22
Pharmacokinetic parameter	**90% Confidence Intervals**	**Intra-Subject CV (%)**	**Power**
AUC_t (ng.h/mL)	(92.01%;102.80%)	13.340	1.0000
AUC_i (ng.h/mL)	(92.26%;103.14%)	13.409	1.0000
C_{max} (ng/mL)	(85.18%; 97.68%)	16.498	0.9997

Table 3: Fed study summary of Pharmacokinetic Data for Eletriptan (n=34) Dose: 40 mg (Reference Product: RELPAX® (Eletriptan Hydrobromide) Tablets 40 mg)

Pharmacokinetic parameter	Arithmetic mean	Standard deviation	Coeff of Variation (%)
AUCt (ng.h/mL)	1009.031	321.868	31.899
AUCi (ng.h/mL)	1100.018	364.912	33.173
Cmax (ng/mL)	132.976	48.461	36.443

(Test Product: Eletriptan Hydrobromide Tablets 40 mg)

Pharmacokinetic parameter	Arithmetic mean	Standard deviation	Coeff of Variation (%)
AUCt (ng.h/mL)	1081.445	392.954	36.336
AUCi (ng.h/mL)	1183.254	450.491	38.072
Cmax (ng/mL)	133.182	46.287	34.755

Table 4: Test & Reference Geometric mean, Ratio, 90% Confidence Intervals, Intra-Subject CV (%) and Power based on Log-transformed data for Eletriptan (n=34)

Pharmacokinetic parameter	Geometric mean (Test)	Geometric mean (Reference)	Ratio (%)
AUCt (ng.h/mL)	1020.121	952.172	107.14
AUCi (ng.h/mL)	1112.412	1034.043	107.58
Cmax (ng/mL)	126.595	124.921	101.34
Pharmacokinetic parameter	**90% Confidence Intervals**	**Intra-Subject CV (%)**	**Power**
AUCt (ng.h/mL)	(102.46%; 112.02%)	10.873	1.0000
AUCi (ng.h/mL)	(102.47%; 112.94%)	11.854	1.0000
Cmax (ng/mL)	(94.47%;108.71%)	17.180	0.9996

Figure 1: Mean plot of Test and Reference formulation under fasting condition:

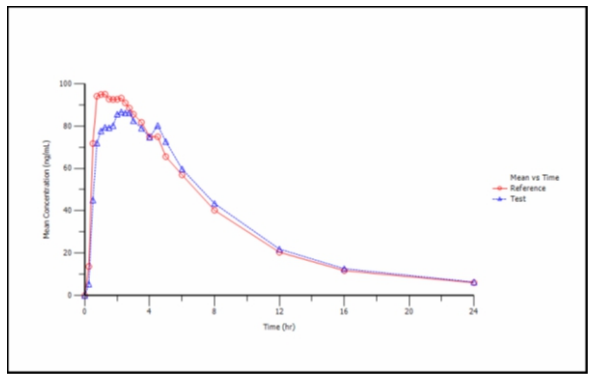


Figure 2: Logarithmic plot of Test and Reference formulation under fasting condition:

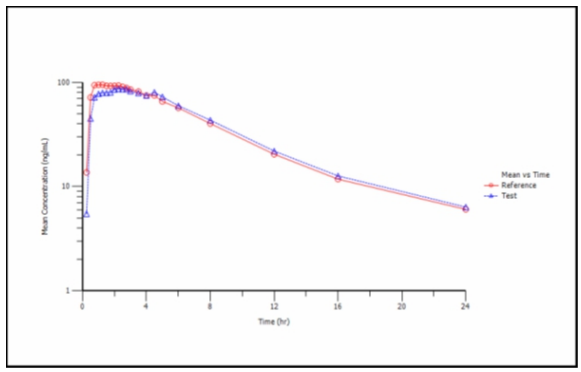


Figure 3: Mean plot of Test and Reference formulation under fed condition:

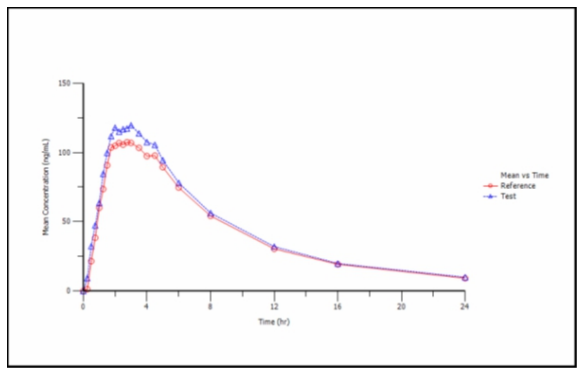
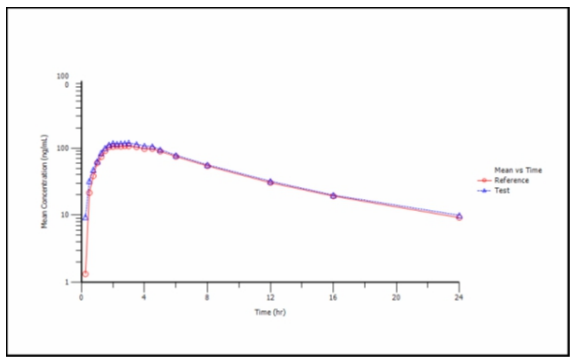


Figure 4: Mean plot of Test and Reference formulation under fasting condition:



The safety assessment in the fasting and fed conditions is presented below:

Fasting study:
There were no adverse events reported during the study.

Fed study
There was one adverse event of mild Headache due to administration of Reference formulation. It was possibly related to the drug.

Discussion

Bioequivalence:
Fasting
For the log transformed Eletriptan data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80% to 125% limits for AUC_t (92.01%;102.80%), AUC_i (92.26%;103.14%) and C_{max} (85.18%; 97.68%).

Fed
For the log transformed Eletriptan data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80% to 125% limits for AUC_t (102.46%;112.02%), AUC_i (102.47%;112.94%) and C_{max} (94.47%; 108.71%).

Based on the above presented results, ELETRIPTAN HYDROBROMIDE TABLETS 40 mg by MICRO LABS LIMITED, India and RELPAX® (Eletriptan Hydrobromide) Tablets 40 mg, Manufactured by Pfizer Ireland Pharmaceuticals Ringaskiddy, Ireland, Distributed by Roerig Division of Pfizer Inc, NY, NY 10017, were bioequivalent under fasting and fed conditions.

Safety and tolerance:
From the assessment of safety presented above, it may be concluded that Eletriptan was safe and well tolerated when administered in healthy adult human volunteers under fasting and fed conditions. No major Adverse Events were observed due to the drug administration.

References

1. Vetchý D et al. Bioequivalence studies of Pharmaceutical Preparations. Pubmed NCBI 2007; 146: 431-3.
2. Srivastav Atul Kumar et al. A Review Article on Bioavailability and Bioequivalence Studies. International Journal of Pharm Tech Research 2013; 5; 1711-1721.
3. Rahul Bhambri et al. A review of the pharmacoeconomics of eletriptan for the acute treatment of migraine. International Journal of General Medicine 2015; 8: 27–36.
4. Matilde Capi et al. Eletriptan in the management of acute migraine: an update on the evidence for efficacy, safety, and consistent response. Therapeutic Advances in Neurological Disorders 2016; 9: 414–423.
5. Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations, U.S. Department of Health and Human Services; 2003.
6. US Individual BE Recommendation, Guidance on Eletriptan Hydrobromide.