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(RESEARCH ARTICLE)

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Bioequivalence study of two Esomeprazole40 mg MUPS tablets in healthy adult Bangladeshi human subjects

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Abstract

Background: The primary objective of this study is to investigate the bioequivalence of two formulations (test& reference) of Esomeprazole 40 mg MUPS Tablet in healthy, adult human subjects.

Method: In this study, a single dose, two-sequence, two-way crossover randomized design was used to investigate the bioequivalence under fasting conditions. 14 healthy volunteers received the two formulations over the course of two treatment days, each followed by a seven-day washout period. Following the administration of a single dose of 40 mg of each formulation, blood samples were taken at predetermined time points and subjected to a validated LC-MS/MS method for Esomeprazole concentration analysis. The plasma concentration-time profiles of both formulations were used to determine the pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Result: Pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ did not show any statistically significant differences. The 90 % confidence intervals of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for Esomeprazole was found 89.35% (82.27-97.03%), 107.61% (99.78-116.05%), and 107.72 (99.87-116.20%) respectively which is within predetermined bioequivalence acceptance limits of 80 - 125 %.

Conclusion: In terms of absorption rate and extent, the test product of Beximcopharmaceuticals has met the regulatory requirements for bioequivalence with the reference product Nexium MUPS.

Keywords: Bioequivalence; Esomeprazole; Nexium; Pharmacokinetics

1. Introduction

One of the most widespread illnesses, gastroesophageal reflux disease (GERD), is characterized by symptoms like regurgitation, heartburn, and tissue damage brought on by the reflux of gastric contents into the esophagus [1].For the treatment of gastroesophageal reflux disease (GERD), proton-pump inhibitors (PPIs) is extensively used [2]. The most recent drug in the proton pump inhibitors family is Esomeprazole (PPIs) which was developed as the S-isomer of omeprazole to selectively inhibit the gastric H+/K+-ATPase enzyme, which is liable for secreting acid in the parietal cells of the stomach [3,4].

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Esomeprazole magnesium trihydrate is known chemically as Bis(5-methoxy-2-(S) [(4-methoxy-3,5-dimethyl-2 pyridinyl)methyl]sulfinyl-1H-benzimidazol-1-yl] magnesium and has the following structure [4]:

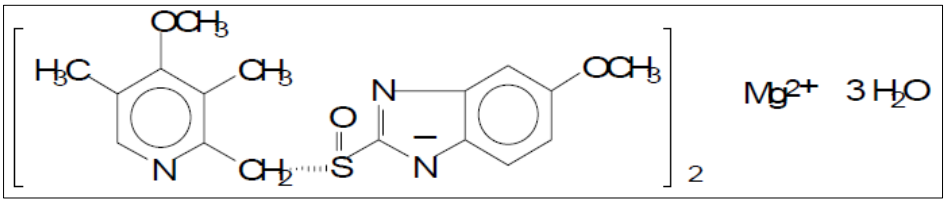

Figure 1 Structural formula of Esomeprazole

Esomeprazole's peak plasma levels happen one to two hours after the dose is given [5]. After a repeated once-daily dose, the plasma elimination half-life is approximately 1.3 hours [5].

Among all PPI, Esomeprazole has a stronger ability to inhibit gastric acid secretion [6].

The purpose of this study was to determine the pharmacokinetic profiles of the two formulations of Esomeprazole in healthy adult male Bangladeshi subjects while they were fasting.

2. Materials and methods

2.1. Identity of Investigational Medicinal Products

Table 1 Investigational Medicinal Product

Product specification	**Investigational Medicinal Products**	
	Test Product	**Reference Product**
Name with strength & dosage form	Esomeprazole Magnesium Trihydrate 40 mg MUPS Tablet	Nexium®40 mg MUPStablet
Batch number	SDJ644	X709A
Manufacturer	Beximco Pharmaceuticals Limited	Astrazeneca GmbH

2.2. Study documents approval

The study documents were approved by the following authority:

- Name of ethics committee:
  - National Research Ethics Committee (NREC) of Bangladesh Medical Research Council (BMRC)
  - Approval date: 11th October 2020
  - Registration no.: 27104022020

- Name of local regulatory authority:
  - Directorate General of Drug Administration (DGDA), Bangladesh
  - Approval date:02nd December 2020
  - Reference No.: DGDA/CTP-1/06/2016/4811

2.3. Subjects

The volunteers were chosen randomly from a database of registered volunteers and asked to take part in a pre-study screening process. On the basis of pre-study medical history, physical examination, clinical laboratory tests, ECG, X-ray, and inclusion-exclusion criteria volunteers were determined to be healthy.14 healthy male volunteers (age 19-31 years, Body Mass Index (BMI) of 19.43–27.17 kg/m^2) were enrolled in the study.Volunteers with pertinent clinical abnormalities were kept out of the trial.

Before participating in the study, each individual provided informed consent in writing and orally.

Post-study clinical examination was also carried out.

2.4. Study design

The bioequivalence study was carried out as an open-label, randomized, laboratory blind, single dose, two period, two treatments, two sequence, crossover study in which subjects received two formulations of Esomeprazole (either test or reference) with 240 ml water under fasting conditions [7]. To ensure the fasting state, individuals were housed in the facility for one night prior to the trial (10 hours before study drug administration) [7]. Study participants were confined till 24 hours post-dose. A standardized meal was given at 4 hours following dosing [7]. To reduce the impact of food on the study's results, meal consumption was closely regulated and the same food was provided to all volunteers during both periods. Two periods were separated by a washout period of 7 days. Study medications were administered in two different sequences (Test-Reference) (TR); (Reference-Test) (RT) as per the randomization scheme generated by Statistical Analysis Software (SAS).All the subjects were divided into equal sizes so that the allotment of sequences was balanced over the period and sequence.

2.5. Blood sampling

In pre-labeled vacutainer containing K_2EDTA, venous blood samples were drawn at Predose (0.00 hour) (within 1.0-hour prior dosing), 0.33, 0.50, 0.75, 1.00, 1.33, 1.50, 1.75, 2.00, 2.33, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00 and 14.00 hours post dose.

To separate plasma, blood sample vacutainers were centrifuged at 3500 Revolutions Per Minute (RPM) for 10 minutes at 5°C±3°C

2.6. Bioanalytical Method

Esomeprazole in plasma was determined by protein precipitation method using a validated Liquid Chromatography Mass Spectrometry(LC-MS/MS) method. Chromatographic separations were performed on a Hypersil Gold column (4.6 X 50 mm, 5.0µ particle size) at a flow rate of 0.600 mL/min.The method included the following: 100 µl of plasma sample, 100 µl of internal standard (rabeprazole, 0.8 µg/ml), and 1000 µl of a mixture of acetonitrile: water

2.7. Tolerability

Every subject was constantly monitored for the occurrence of any adverse events. Safety data were evaluated by monitoring vital signs at pre dose, 1.00, 3.00, 5.00, 7.00, 13.00, and 24.00 hours, check-in, and check-out in each period. Pre-study & post-study laboratory results were also evaluated for monitoring of adverse events.

2.8. Pharmacokinetics and statistical analysis

Employing the estimated plasmaconcentration-time profile, Statistical Analysis Software (SAS) was used to perform bioequivalence analysis on the primary ($C_{max,}$ $AUC_{0-t,}$ and $AUC_{0-\infty}$) and secondary (K_{el}, $T_{max,}$ and $T_{1/2}$) PK parameters [8].

In accordance with US Food and Drug Administration (FDA) requirement, the test product was considered to be bioequivalent to the reference product, if 90% confidence intervals for ratio (test/reference) of geometric least square means based on log-transformed primary PK parameters - C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ fall within 80% to 125% [9].

3. Results and discussion

3.1. Demographics

Table 2 Summary of subject demographics

Parameters	Mean ±SD	Value Range
Age (years)	22.21±3.926	19-31
Weight (kg)	66.68 ±10.631	44.3-86.1
Height (cm)	167±8.199	151-181
BMI (kg/m^2)	23.76±2.065	19.43-27.17

Following strict inclusion-exclusion criteria, fourteen healthy subjects were enrolled. Table 2represents demographic summary data for all evaluable subjects in the study.

3.2. Bioanalytical method validation

Bioanalytical method validation was carried out as per GLP & USFDA guidance on Bioanalytical Method Validation [10].

The method was sensitive & selective.The obtained chromatograms showed no interferences.Lower limits of quantification were 0.02µg/ml & the method's range was 0.02 to 4.00 µg/ml.With a coefficient of determination of 0.9969, the method was determined to be linear over this concentration range.

Esomeprazole's intra-assay %CV (Coefficient of Variance) ranged from 2.26% to 9.56%, and its accuracy ranged from 90.9% to 109.8%. In contrast, its inter-assay %CV ranged from 4.84% to 10.44%, and its accuracy ranged from 98.4% to 102.8%.

3.3. Tolerability

No incidence of serious adverse effects was reported in this study. Thus, in this study, the test product and reference product were safe and well tolerated by the subjects under fasting conditions.

3.4. Pharmacokinetics and statistical evaluation

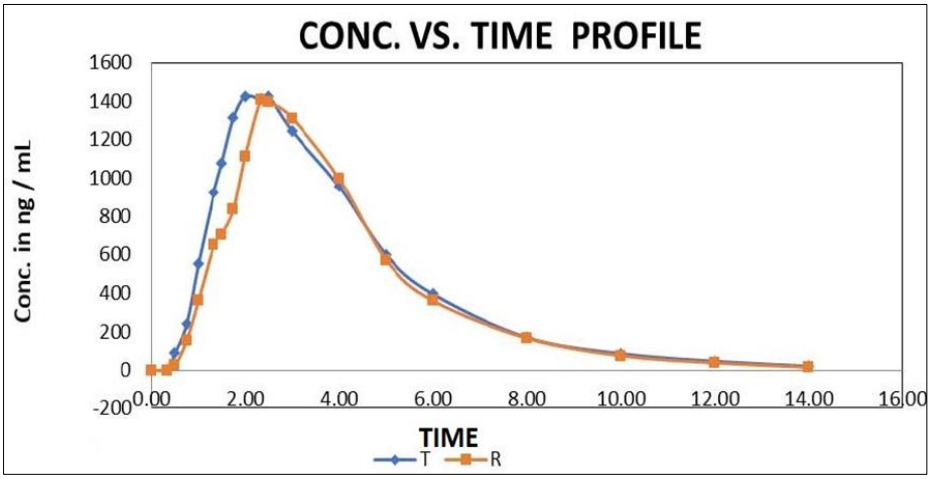

Figure 2 Linear Plot of Mean Plasma Concentrations versus Time profile of Esomeprazole

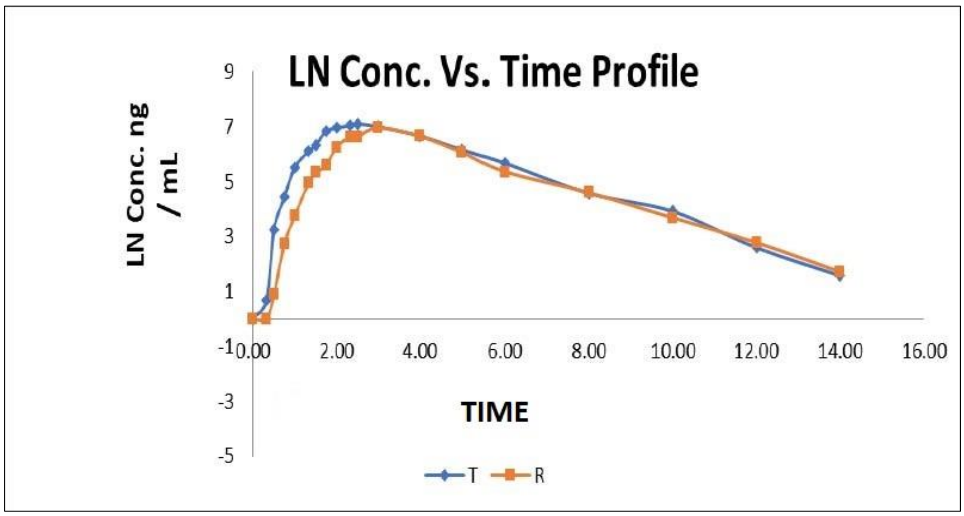

Figure 3 Semilog plot of mean plasma concentration versus time profile of Esomeprazole

Pharmacokinetic parameters and statistical analyses were calculated using data from all 14 participants who completed the research.

Figures 2 and 3 depict the mean plasma concentration versus time curves for the two formulations, which are identicaland superimposable.

Pharmacokinetic results of Esomeprazole test and reference are reported in Table 3

Table 3 Summary of Pharmacokinetic Parameters (N=14)

Nexium MUPS (Esomeprazole Magnesium Trihydrate) 40 mg Tablet (Reference Product)				
Variable	**Arithmetic Mean**	**SD**	**CV%**	**Geometric Mean**
C_{max} (ng/mL)	1995.089214	735.988772	36.89	1855.7306
AUC_{0-t} (ng/mL). hr	5464.260336	2544.082927	46.56	4744.0777
$AUC_{0-\infty}$ (ng/mL). hr	5539.536393	2568.824156	46.37	4814.883
T_{max} (hrs)	2.147857	0.833530	38.81	1.9796
K_{el} (hr^{-1})	0.440364	0.136047	30.89	0.4248
$T_{1/2}$ (hr)	1.680843	0.392392	23.34	1.6315
Esomeprazole Magnesium Trihydrate 40 mg MUPS Tablet (Test Product)				
Variable	**Arithmetic Mean**	**SD**	**CV%**	**Geometric Mean**
C_{max} (ng/mL)	1831.181929	765.712751	41.82	1658.0077
AUC_{0-t} (ng/mL). hr	5949.724350	2885.007664	48.49	5104.9989
$AUC_{0-\infty}$ (ng/mL). hr	6054.338393	2976.995932	49.17	5186.8149
T_{max} (hrs)	2.207857	0.831145	37.64	2.0900
K_{el} (hr^{-1})	0.422464	0.146058	34.57	0.4034
$T_{1/2}$ (hr)	1.788529	0.497243	27.80	1.7183

C_{max}: maximum plasma concentration of drug, AUC_{0-t}: area under the plasma concentration–time curve from time zero to the time of the last measurable concentration, $AUC_{0-\infty}$: area under the plasma concentration–time curve from time zero to infinity, T_{max}: time to reach maximum plasma Concentration, K_{el} : elimination rate constant, $T_{1/2}$: half-life of drug,

Summary of statistical analysis is presented in Table 4

Table 4 Summary of Statistical Analysis (N=14)

(Bioequivalence Assessment of Esomeprazole)								
Parameters	**Geometric Least Square Mean(GLSM)**		**T/R Ratio (%)**	**Intra-subject CV (%)**	**Power**	**90% Confidence Interval**		**The outcome of Bioequivalence result**
	Test Product GLSM	**Reference Product GLSM**				**Lower Limit**	**Upper Limit**	
C_{max}(ng/mL)	1658.0077	1855.7306	89.35	12.16	98.93	82.27	97.03	Bioequivalent
AUC_{0-t} (ng/mL). hr	5104.9989	4744.0777	107.61	11.13	99.53	99.78	116.05	
$AUC_{0-\infty}$ (ng/mL). hr	5186.8149	4814.883	107.72	11.16	99.52	99.87	116.2	

The 90% Confidence Intervals (CI) of the ratios (Test/Reference) between the two formulations regarding C_{max}, $AUC_{0-t,}$ and $AUC_{0-\infty}$ were found 89.35% (82.27-97.03%), 107.61% (99.78-116.05%), and 107.72 (99.87-116.20%) respectively which included into the range of bioequivalence acceptance limit of 80.00-125.00% (Table 4).

Limitations

The use of only healthy young males and the use of individuals who were fasting are some of the limitations of this study.

4. Conclusion

The test product (T) Esomeprazole Magnesium Trihydrate 40 mg MUPS Tablet of Beximco Pharmaceuticals Ltd., Bangladesh when compared to the reference product (R) Nexium MUPS(Esomeprazole Magnesium Trihydrate) 40 mg Tablets of Astrazeneca GmbHmet the bioequivalence acceptance criteria in healthy adult human subjects under fasting conditions.

Compliance with ethical standards

Acknowledgments

The authors express their gratitude to all the volunteers who participated in the study & study sponsor, Beximco Pharmaceuticals Limited.

Disclosure of conflict of interest

The author hereby declares that there are no conflicts of interest concerning this paper. Beximco Pharmaceuticals Limited sponsored the study and supplied the trial medication.

Statement of informed consent

All participants in the study gave their informed consent after receiving complete and pertinent information about the research.

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