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Bioequivalence Study of Two Formulations of Telmisartan 40 mg Tablets in Healthy Adult Bangladeshi Subjects under Fasting Conditions

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Abstract

Background: Telmisartan is a highly variable drug which is used to treat hypertension. This study compared to compare the bioavailability of two 40 mg Telmisartan tablets in adult and healthy Bangladeshi subjects. **Materials and Method:** This study was open label, randomized, laboratory blind, single dose, three periods, two treatments, three-sequence, partial-replicate, crossover and comparative oral bioavailability study. In this study, 18 Bangladeshi subjects were enrolled and 17 subjects were completed. Serial blood samples were collected up to 96 hours following drug administration. By using Liquid Chromatography Mass Spectrometry (LC-MS/MS) method, plasma concentrations of Telmisartan were determined. **Results:** The two formulations of Telmisartan were considered bioequivalent if 90% Confidence Interval (CI) fall within the range of 80.00% - 125.00% for AUC parameters and reference-scaled-average bioequivalence of 69.84% - 143.19% for C_{max}. The 90% Confidence Interval for C_{max}, AUC_{0-t} & $AUC_{0-\infty}$ was found 84.88% - 107.79%, 89.76% - 109.55%, and 91.20% - 114.52%, respectively. **Conclusion:** According to rate and extent of absorption with the single dose of Reference Product (R): Micardis® 40 mg Tablet, under fasting conditions, a single dose of Telmisartan 40 mg Tablet is bioequivalent.

Keywords

Bioequivalence, Telmisartan, Micardis, Pharmacokinetics

1. Introduction

Telmisartan is an Angiotensin Receptor Blocker (ARB) which is used to treat hypertension and cardiovascular risk conditions [1]. Chemical name of Telmisartan ($C_{33}H_{30}N_4O_2$) is 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'- yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid and 514.63 is its molecular weight (**Figure 1**) [2].

The AT_1 subtype of the angiotensin II receptor is specifically and effectively inhibited by the drug telmisartan [3]. Telmisartan's peak concentrations (C_{max}) are attained within 0.5 to 1 hour of oral treatment. Telmisartan has a terminal elimination half-life of roughly 24 hours and exhibits bi-exponential decay kinetics [4]. It exhibits the longest half-life in its class of ARBs since it is taken as a once-daily dose [5]. It is regarded as a Highly Variable Drug (HVD) in this research [6].

According to a review of the PubMed database for articles written till July 2020, telmisartan bioequivalence studies have frequently employed completely replicate crossover designs or combined fixed-dose regimens [7] [8] [9]. Within this study we used a three-period partial repeated design to assess the bioequivalence of two telmisartan tablet formulations in a single dosage form. The purpose of the study was to demonstrate bioequivalence between single dose of test product Telmisartan 40 mg and reference product Micardis® 40 mg in healthy adult human subjects who were fasting.

2. Methodology

2.1. Investigational Medicinal Products

Test Product: Telmisartan USP 40 mg Tablet, produced by Beximco pharmaceuticals Ltd in Bangladesh (Batch: SDF610).

Reference Product: Micardis® 40 mg tablet of Boehringer Ingelheim Pharma GmbH & Co. KG Ingelheim Am Rhein, Germany (Batch No C04677).

2.2. Ethical Consideration

On October 11th, 2020; the Bangladesh Medical Research Council's (BMRC)

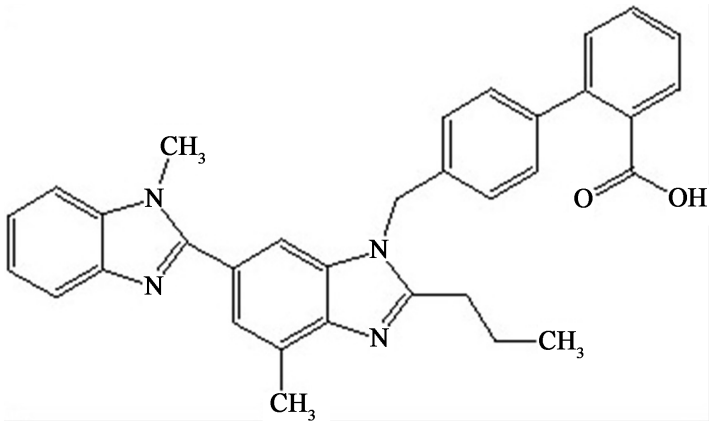

Figure 1. Structural formula of Telmisartan.

National Research Ethics Committee (NREC) approved the study protocol. (Ethical approval no.: 27204022020) and by the Directorate General of Drug Administration (DGDA) on 02nd December 2020 (Memo No.: DGDA/CTP-1/06/2016/4810).

2.3. Study Population

The volunteers are aged between 20 - 30 years, with a Body Mass Index (BMI) of 17.63 - 31.60 kg/m^2 selected randomly from registered database and asked for a screening procedure as per inclusion exclusion criteria within 28 days prior to dosing of period 1. Each subject has given verbal & written consent before participating in the study. After passing a clinical screening procedure within 28 days prior to dosing of period-I, volunteers were enrolled. Subject were excluded if they take more than five cigarettes per day, had history of significant disorders, had hypersensitive to telmisartan, had history of consumption of alcohol, had received any prescribed medication within 28 days prior to the start of study, participated in any clinical study within 3 months prior to the screening, and donation or loss more than 500 mL of blood within 3 months prior to the screening.

All subjects were refrained to take prescribed medicines within 28 days & Over the Counter (OTC) products within 14 days before first study drug administration until the completion of study. They were also refrained from smoking, drinking alcoholic beverages and xanthine containing foods and beverages (tea, coffee, chocolate, or cola) for 48 hours before each dose, until the last blood sample was collected. Clinical screening was repeated, upon completion of the study.

2.4. Study Design

This was an open label, randomized, laboratory blind study which had single dose, three periods, two treatments, three sequence, partial-replicated, in normal healthy adult 18 human subjects under fasting condition. There was 10 days' washout period in each period of this study. The subjects were confined within the facility one night before study to ensure the fasting condition (10 hours before study drug administration). During the study, subjects were randomized to one of the three sequences (Test-Reference-Reference) (TRR); Reference-Reference-Test (RRT); Reference-Test-Reference (RTR). The randomization list was generated using Statistical Analysis Software (SAS). On dosing day of each period, each subject received a single oral dose (1 × 40 mg Tablet) of either test product or reference product with 240 of water at ambient temperature.

Subjects were in a comfortable recumbent position up to 8 hours after dosing and remained under monitoring for up to 12 hours after dosing [10].

Subjects were fasted overnight from at least 10.00 hours (hrs) before dose administration and for at least 04.00 hrs post-dose in each study period. Water intake was allowed except for one hour before and one hour after the dose. No food was allowed until 4 hours after dose administration [11].

As per "Guidance for industry-Bioavailability & Bioequivalence studies submitted in NDAS or INDS-General consideration" of USFDA; subjects were fasted for at least 10 hours before dosing & no meal was allowed till 4 hours after dosing. Considering the sedentary lifestyle of volunteers a qualified dietician prepared the meal plan of 1000 - 1200 calories through calorie breakdown of lunch, snack, dinner & breakfast. In all the periods meal distribution was uniform.

Venous blood were collected at pre dose (0.00 hour) (within 1.0 hour prior to dosing), 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 9.00, 12.00, 16.00, 24.00, 48.00, 72.00 and 96.00 hrs post dose in a pre-labeled vaccutainers containing K_2EDTA at each period. Within 60 minutes after each time point of blood collection, Blood sample vacutainers were centrifuged at 3500 Revolution Per Minute (RPM) for 10 minutes at 5˚C ± 3˚C.

2.5. Bio Analytical Method

Using a validated liquid chromatography-mass spectrometry (LC-MS/MS) analytical technique, the amount of telmisartan in plasma was determined in a blind fashion without reference to the treatment plan. The linearity range was (10.000 - 1200.0) ng/mL according to method validation.

2.6. Safety Assessment

At pre dose, 01.00, 03.00, 05.00, 08.00, 12.00, and 24.00 hours, check-in, check-out, and throughout each ambulatory post-dose in each session, the subjects' well-being & vital parameters were assessed. Up until the very conclusion of the research, the individuals were regularly observed for adverse events and concurrent medication use during the entire confinement durations. Safety evaluation was done on the basis of outcomes of physical examination, vital signs measurement and clinical laboratory results which were performed during the study period.

2.7. Statistical and Pharmacokinetic Evaluation

The following pharmacokinetic variables were determined for Telmisartan using a non-compartmental model.

2.7.1. Primary PK Parameters

C_{max} (Maximum observed plasma Concentration of drug), AUC_{0-t} (Area under the plasma concentration-time curve from 0 hr to last quantifiable concentration at time t) and $AUC_{0-\infty}$ (Area under the plasma concentration-time curve from 0 hr to infinity).

2.7.2. Secondary PK Parameters

$AUC_{0-t}/AUC_{0-\infty}$, Rate Constant K_{el} (Apparent first–order terminal elimination rate constant), T_{max} (Time to observe maximum drug concentration), $T_{1/2}$ (Time required for the plasma drug concentration to decrease to one-half ($T_{1/2}$ = 0.693/Kel).

If the 90% confidence interval of the ratio of the AUC_{0-t} and $AUC_{0-\infty}$ parameters falls within the range of 80.00% - 125.00%, the test drug formulation was deemed to be bioequivalent to the reference preparation. For the C_{max} parameter, a scaled average bioequivalence technique was applied. The 90% geometric confidence intervals of the ratio T/R of least squares means of the ln-transformed C_{max} should be within the permissible range of 80.00% - 125.00% to conclude bioequivalence if the intra-subject Coefficient of Variation (CV) was less than or equal to 30% (≤30%). On the other hand, the bioequivalence acceptability criteria for this pharmacokinetic parameter had to be adjusted based on the within-subject variability of the reference product to a maximum of 69.84% - 143.19% if the intra-subject CV for the reference product was greater than 30% (>30%) for C_{max} [11].

3. Result & Discussion

3.1. Study Population

Among 18 Subjects, 17 subjects completed all the three periods of the study and that was evaluated. Demographic data of all evaluable subjects are presented in Table 1.

3.2. Bioanalytical Method Validation

Good linearity was obtained for all standard curves (correlation coefficient r > 0.999). The standard calibration curve for telmisartan was linear from 10 - 1200 ng/mL. Table 2 shows the precision and accuracy of the quality control samples

Table 1. Demographic summary data for all evaluable subjects in the study.

Parameters	Mean (± SD)	Value range
Age (years)	24.117 ± 3.103	20 - 30
Weight (kg)	64.26 ± 8.921	50 - 85
Height (cm)	167.117 ± 5.389	158 - 177
BMI (kg/m^2)	23.09 ± 3.579	17.63 - 31.60

Table 2. Precision and accuracy of the analytical method.

Nominal Concentration (ng/mL)	Intra-batch			Inter-batch		
	Mean ± SD (ng/mL)	% CV	% Accuracy	Mean ± SD (ng/mL)	% CV	% Accuracy
10	10.403 ± 0.1413	1.36	104.0	10.452 ± 0.3773	3.61	104.5
30	26.994 ± 0.3583	1.33	90.0	28.757 ± 1.7840	6.20	95.9
150	138.669 ± 2.6596	1.92	92.4	149.368 ± 9.2869	6.22	99.6
600	579.726 ± 26.3210	4.54	96.6	615.749 ± 33.8241	5.49	102.6
900	950.011 ± 29.4310	3.10	105.6	941.153 ± 30.6556	3.26	104.6

SD: Standard Deviation, CV: Coefficient of Variance.

during pre-study validation.

The bioanalytical method has been validated according to the Guideline on Bioanalytical Validation, EMA 2011 [12].

3.3. Safety Evaluation

Administration of a single oral dose of either the test or reference formulation was found to be safe in healthy subjects. No severe, serious, or life-threatening side effects were reported throughout the study.

3.4. Pharmacokinetics and Statistical Evaluation

Data from total 17 subjects completed the study was used in calculation of pharmacokinetic parameters and statistical analysis for calculation of intra-subject variability of Reference Product and to assess the bioequivalence.

The mean telmisartan concentration versus time profiles Untransformed and log-transformed data for both formulations are presented in **Figure 2** & **Figure 3**.

Descriptive statistics of the pharmacokinetic parameters for telmisartan test and reference are summarized in **Table 3**.

AUC_% Extrapolation

The mean AUC_% Extrapolation was 22.410% (range: 8.929% to 40.258%) for reference product (R) and 25.652% (range: 9.718% to 54.168%) for test product (T), respectively.

Analysis of Variance (ANOVA)

There were no sequence and formulation effects observed for pharmacokinetic parameters C_{max}, AUC0-t and AUC0-inf.

The 90% geometric ratios confidence intervals and intra-subject CVs of reference product for primary parameters are shown in **Table 4**.

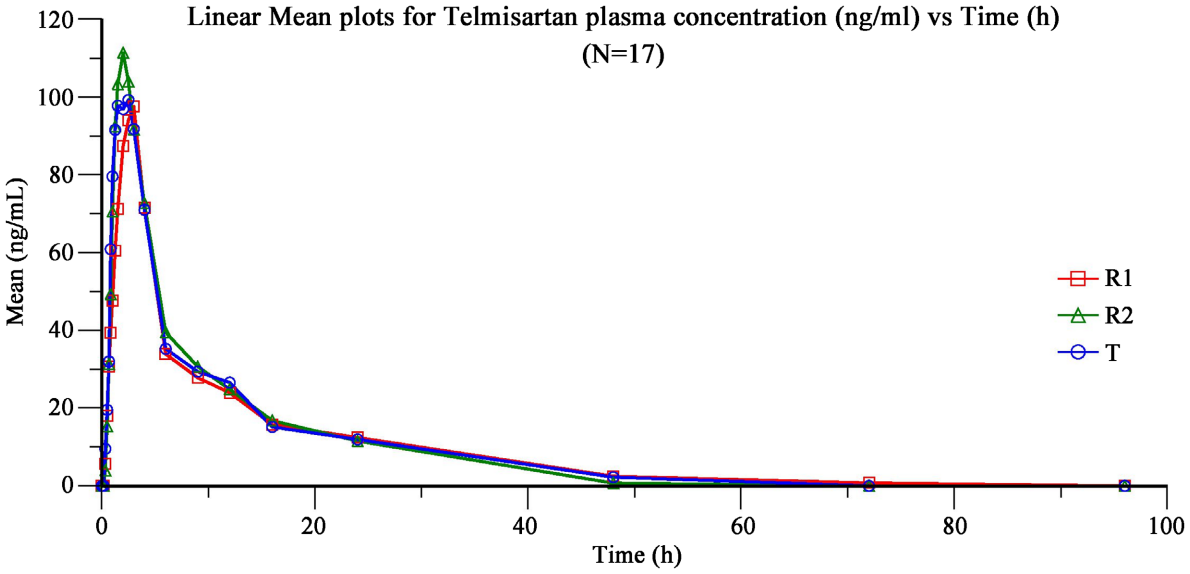

Figure 2. Linear plot of mean plasma concentration versus time for test and reference product.

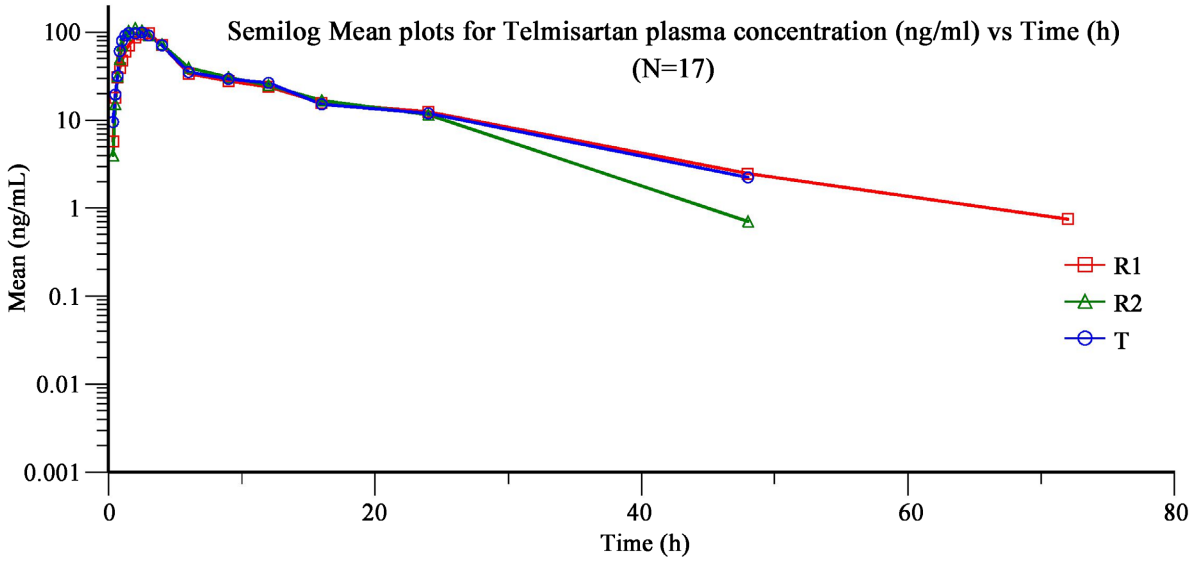

Figure 3. Semi log plot of mean plasma concentration versus time for test and reference product.

Table 3. Brief summary of the pharmacokinetic parameters of-reference product (combined).

Micardis® 40 mg (Telmisartan 40 mg) Tablet (Reference Product-R) – combined (first & second administration)						
variable	**Arithmetic Mean**	**SD**	**CV%**	**Minimum**	**Median**	**Maximum**
C_{max} (ng/mL)	122.270	69.790	57.100	46.417	96.247	289.163
AUC_{0-t} (ng·hr/mL)	825.619	600.223	72.700	127.526	598.879	2194.198
$AUC_{0-\infty}$ (ng·hr/mL)	1072.310	735.102	68.600	153.249	826.691	2575.168
T_{max} (hrs)*	2.402	1.179	49.100	0.585	2.500	6.000
Half Life ($T_{1/2}$) (hrs)	11.141	7.788	69.900	1.067	10.094	28.292
K_{el} (hrs^{-1})	0.172	0.203	118.000	0.025	0.079	0.651

C_{max}: The mean C_{max} obtained was 122.270 ng/mL in Reference Product (R) and Test Product (T) was 122.606 ng/mL respectively. AUC_{0-t}: The mean area under the curve from zero to last measurable concentration was 825.619 (ng.hr/mL) in Reference Product (R) and test product (T) was 852.698 (ng.hr/mL) respectively. $AUC_{0-\infty}$: The mean area under the curve from zero to infinity was 1072.310 (ng.hr/mL) in Reference Product (R) and test product (T) was 1159.513 (ng.hr/mL) respectively. T_{max}: The median of Tmax was 2.500 hour (range = 0.585 to 6.000 hours) for reference product (R and 2.500 hour (range = 0.670 to 4.000 hours) for test product (T), respectively. Terminal Half Life ($T_{1/2}$): The mean terminal half-life was 11.141 (range: 1.067 to 28.292) for reference product (R) and 13.700 hour (range: 1.237 to 36.811 hours) for test product (T), respectively. Elimination Rate Constant K_{el}: The mean elimination rate constant was 0.172 hrs^{-1} (range: 0.025 to 0.651 hrs^{-1}) for reference product (R) and 0.105 hrs^{-1} (range: 0.019 to 0.560 hrs^{-1}) for test product (T), respectively.

Table 4. Ratio analysis and 90% confidence intervals.

Parameter	**Geometric Least Square Mean (GLSM)**		**T/R Ratio (%)**	**90% Confidence Interval**		**Power (%)**	**Intra-subject CV for Reference product (%)**	**Global Intra-subject CV (%)**
	Test Product	**Reference Product**		**Lower Limit %**	**Upper Limit %**			
C_{max} (ng/mL)	102.51	107.17	95.65	84.88	107.79	86.59	22.86	24.02
AUC_{0-t} (ng/mL).hr	607.73	612.88	99.16	89.76	109.55	95.57	-	19.94
$AUC_{0-\infty}$ (ng/mL).hr	813.57	796.07	102.20	91.20	114.52	89.56	-	22.13

The intra-subject CV of telmisartan for C_{max} was 22.86% (<30%), hence wider acceptance criteria were not applicable for this study. The 90% Confidence Intervals (CI) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were found 84.88% - 107.79%, 89.76% - 109.55%, and 91.20% - 114.52% respectively which included into the range of bioequivalence acceptance limit of 80.00% - 125.00%.

4. Limitations

We could not assess pharmacokinetic parameters of female volunteers and pharmaco dynamic parameters couldn't be evaluated.

5. Conclusion

Based on the statistical analysis, it has been concluded that the Test Product (T) of Beximco pharmaceuticals limited: a single dose of Telmisartan 40 mg Tablet is bioequivalent in terms of rate and extent of absorption with the single dose of Reference Product (R): Micardis® 40 mg Tablet, under fasting conditions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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