IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
August 2020 Vol.:19, Issue:1

Comparative Bioavailability and Bioequivalence Study of Different Brands Cresar (Cipla) and Telma (Glenmark) of Telmisartan

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Rajeev Sharma*, Vishal Shrivastava, Parul Mehata, Janki Prasad Rai

Department of Pharmacology, School of Pharmacy, LNCT University, Bhopal, Madhya Pradesh 462026, India

Submission: 24 July 2020
Accepted: 30 July 2020
Published: 30 August 2020

Keywords: Bioavailability, bioequivalence, Telmisartan, Cmax, Tmax, AUC0-t, AUC0-∞ and Kel.

ABSTRACT

Objective of the present study was to compare the rate and extent of absorption of different brands of Telmisartan when given in equal labelled doses i.e. 40mg. Bioavailability and bioequivalence of two brands of Telmisartan namely two brands Cresar (Cipla) and Telma (Glenmark). The Balanced incomplete block design (BIBD) was appropriate for bioequivalence study as there were two brands and each volunteer was expected to receive at least two brands. The ratio analysis of pharmacokinetic parameters viz Cmax, Tmax, AUC0-t, AUC0-∞ and Kel for all brands was within limit i.e. 0.0-1.25 suggesting that the rate and extent of absorption for the three brands met bioequivalence criterion at 90% confidence level. Haematological parameters (Hemoglobin, RBC and WBC count) were measured before and after the study periods. No significant variations in haematological parameters were observed. Two-way ANOVA revealed no statistically significant difference in the rate and extent of absorption of glimepride among the four brands ($P > 0.001$), indicating that all the brands are bioequivalent and hence truly interchangeable. Finally, it can be concluded that the reference and test product of Telmisartan in this study were found to be bioequivalent.

INTRODUCTION

Hypertension is ranked as the third most important risk factor for attributable burden of disease in South Asia (2010)[1]. It exerts a substantial public health burden on cardiovascular health status and healthcare systems in India. Hypertension is the fourth contributor to premature death in developed countries and the seventh in developing countries[2,3] Angiotensin receptor blockers (ARBs), through their physiological blockade of the renin-angiotensin system, reduce morbidity and mortality associated with hypertension, heart attack, myocardial infraction, stroke, diabetic nephropathy, and chronic kidney disease. Among many attributes, excellent tolerability, and their ability to control hypertension for 24 hours with a positive effect on renal function position them as a useful choice for hypertension and related conditions. Because of the widespread action of the renin-angiotensin system on critical tissues, treatment with ATBs may be special in special population[4,5].

The angiotensin II receptor blockers (ARBs) represent a newer class of antihypertensive agents. Their mechanism of action differs from that of the angiotensin-converting enzyme (ACE) inhibitors, which also affect the renin-angiotensin system[6]. The ARBs were developed to overcome several of the deficiencies of ACE inhibitors: competitive inhibition of ACE results in a reactive increase in renin and angiotensin I levels, which may overcome the blockade effect; ACE is a relatively nonspecific enzyme that has substrates in addition to angiotensin I, including bradykinin and other tachykinins[7,8], and thus, inhibition of ACE may result accumulation of these substrates; production of angiotensin II can occur through non-ACE pathways as well as through the primary ACE pathway, and these alternative pathways are unaffected by ACE inhibition; specific adverse effects are associated with ACE Inhibitor effects on the enzyme and ARBs may offer more complete angiotensin II inhibition by interacting selectively with the receptor site.[8] All 7 drugs in this class are approved by the Food and Drug Administration for the treatment of hypertension, either alone or in combination with other drugs[9,10].

Bioavailability and Bioequivalence of drug products and drug product selection has emerged as critical issues in pharmacy and medicine during the last three decades. Concern about lowering health care costs is resulted in a tremendous increase in the use of generic drug products currently about one half of all prescriptions written are for drugs that can be substituted with a generic product[11]. This phenomenal growth of the generic

pharmaceutical industry and the abundance of multi-source products have prompted some questions among many health professionals and scientists regarding the therapeutic equivalency of these products. In this Regard Bioavailability and Bioequivalence of drug Telmisartan different brands Cresar (Cipla), and Telma(Glenmark) are used for study.

MATERIALS AND METHODS

Telmisartan tablets, each tablet containing **Telmisartan** as an active ingredient equivalent to 40mg. Three brands of Telmisartan namely **Cresar (Cipla) and Telma (Glenmark).**

Study design:

The study protocol was approved by the Institutional Ethics Committee of LNCT University. The study strictly adhered to ICH-GCP guidelines[12,13]. The studies were open label, balanced randomized, two-period, cross over bioavailability studies on Telmisartan tablets under fasting condition in healthy, adult, male and female volunteers with washout period of 10 days.

Table No. 1: Balanced Crossover Design

Volunteer's Code	Brands of Telmisartan	
	Period 1	Period 2
S1	R	T1
S2	T1	T2
S3	T2	T3
S4	T3	R
S5	R	T1
S6	T1	T2
S7	T2	T3
S8	T3	R
S9	R	T1
S10	T1	T2
S11	T2	T3
S12	T3	R

S= Subject, R= Reference (Telma), T1= Telsartan, T2= Indetel, T3= Telmikind

Selection of subject: Minimum of 12 subjects aged 18 to 50 years having within 10%-15% of ideal body weight for height & build were selected on the basis of an acceptable medical history, physical examination, and clinical laboratory test results[14].

Sample collection and handling:

Blood samples will be collected through an indwelling intravenous cannula placed in the forearm vein of the subject. If required, the sample may also be collected via direct venepuncture[15]. Blood samples will be collected and pre-labelled vacutainers containing K_2EDTA as an anticoagulant.

Sampling schedule:

A pre-dose sample of 5ml plus 15 was collected and post-dose blood samples of 3ml each was collected from each subject during each period[16]. The venous blood samples were withdrawn at the following times, assuming that the dosing of a subject takes place at 7:00 am.

Clinical safety measurement:

Vitals signs such as temperature, blood pressure, radial pulse was measured for all the subjects. It was checked prior dosing of the study drug and before check out in each period. Vitals signs prior to administration of the dose were taken within 1 hour of schedule dosing time. At all other times, vital signs were taken within 30minutes of the schedule time.

Statistical analysis[17]

Pharmacokinetic parameters and analysis:

Pharmacokinetic parameters were calculated at actual time of blood sample collection for Telmisartan like Area under the plasma concentration versus time curve ($AUC_{0-t)}$, Area under the plasma concentration-time curve ($AUC_{0-\infty)}$, Maximum measured plasma concentration over the time span specified (C_{max}), Time of maximum measured plasma concentration (T_{max}). Apparent first order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve $K_{el\ and}$ apparent first order terminal elimination half-life is calculated as $0.693/K_{el}$ ($T_{1/2)}$

Analysis of variance (ANOVA):

The log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were analysed using a mixed effects ANOVA model using type III sum of squares, with the mean effects of sequence, period and formulations as fixed effects and subject nested within sequence as random effect.

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 sequence mean square as the error term. All other main effects were tested as the 0.05 level of significance against the residual error (mean square error) from the ANOVA model as the error term.

Bioequivalence criteria

For Telmisartan – the 90% confidence interval for the ratio of the test and reference products averages (geometric least square means) of pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$. Should be between 80% and 125 % for the long-transformed data.

Analysis of Drug (HPLC/UV method)

Apparatus and chromatographic condition:

Plasma sample were analysed using a HPLC (Shimadzu Analytical India Pvt Ltd) instrument equipped with a degassing unit, Low pressure gradient unit, pump unit mixer[18], ultra-fast autosampler, column oven, and a UV-VIS detector with a thermostated flow cell. The detector was set at 291 nm. The mobile phase was composed of 10 mM ammonium acetate solution (pH 6.0)–methanol (65:35, v/v). The flow rate was 1 ml min^{-1}. The Injected volume was 20ul. Detection was performed with UV–Vis detector UV–Vis at k 291 nm.

Calibration standards (CS) and quality control (QC)

Samples in human plasma

Preparation of Stock solutions

Stock solutions were prepared by dissolving of Telmisartan in methanol to obtain concentration of 1 mg ml^{-1}. The solution was prepared by dissolving 100 mg of drug in

sufficient amount of methanol and the volume was completed to 100 ml volumetric flask with the same solvent[19].

Preparation of working standard solutions

Working standard solutions were prepared by transferring different volumes 0.5–5 ml of stock Telmisartn in 10 ml volumetric flask and the volume is completed with methanol. Volumes of 20 ul of working standard solution was added to 960 ul of drug-free human plasma to obtain drug concentration levels of 1–10 ug ml^{-1} for Telmisartan.

Preparation of Quality control (QC) samples

Quality control (QC) samples were prepared separately and pooled at three different concentration levels 30 ng/ml (LQC), 250 ng/ml (MQC) and 900 ng/ml (HQC) as low, medium and high, respectively[20]. A calibration curve was constructed from a blank sample, and a non-zero samples of concentrations 10, 25, 50, 75, 100, 250, 500, 750 and 1000 ng/ml.

Plasma sample preparation

The stored plasma samples were allowed to thaw at room temperature before processing. The plasma samples were centrifuged at 4000 rpm for 10 min, an aliquot (0.96 ml) was pipetted into a 10-ml polypropylene tube and acetonitrile (2.0 ml) was added. The mixture was vortex mixed briefly, and after standing for 5 min at room temperature, the mixture was centrifuged at 4000 rpm for 20 min., the supernatant was carefully transferred into vial and injected into HPLC system[21].

Method validation

The method was validated for linearity, precision (repeatability and intermediate precision), accuracy, specificity, stability and system suitability according ICH guidelines. guidelines for the validation of bioanalytical method.

Limits of detection (LOD) and limit of quantitation (LOQ)

LOD and LOQ of the developed method were estimated on the basis of standard deviation and slope of the calibration curve as 3.3 δ/m and 10 δ/m, respectively. Here, δ was the regression standard deviation of intercept and m was the slope of calibration curve[22].

Stability

The stability tests of the analytes were designed to cover expected conditions concerning the handling of clinical samples. The stabilities of the analytes in human plasma were investigated under various storage and processing conditions[23]. The results indicate that Telmisartan was stable for the entire period of the experiment.

Biochemical Analysis

Age, height, weight was recorded and documented. Blood sugar level was determined by using glucometer for each volunteer pre-dose and post dose at suitable intervals of time during the study. Haemoglobin, cholesterol, triglycerides, kidney function test, liver function test including SGOT, SGPT, GGT, serum albumin, total protein and serum creatinine were determined using semiauto analyser[24].

RESULTS AND DISCUSSION

Validation of HPLC/UV Assay Method

Chromatogram of drug free plasma, plasma spiked with Telmisartan (100 ng/ml) is shown in Fig 8, the retention time was 2.5 min. all pikes were separated and there was no interference from endogenous substances in biological matrix with the drug peak.

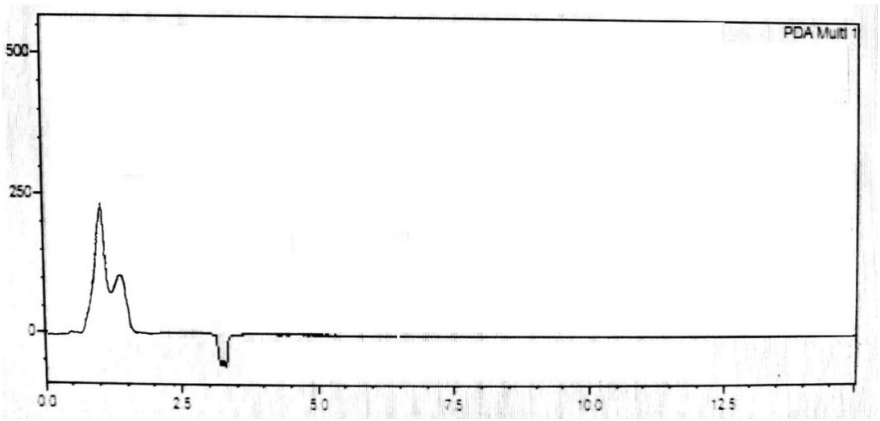

Figure No. 1: HPLC chromatogram of drug free human plasma

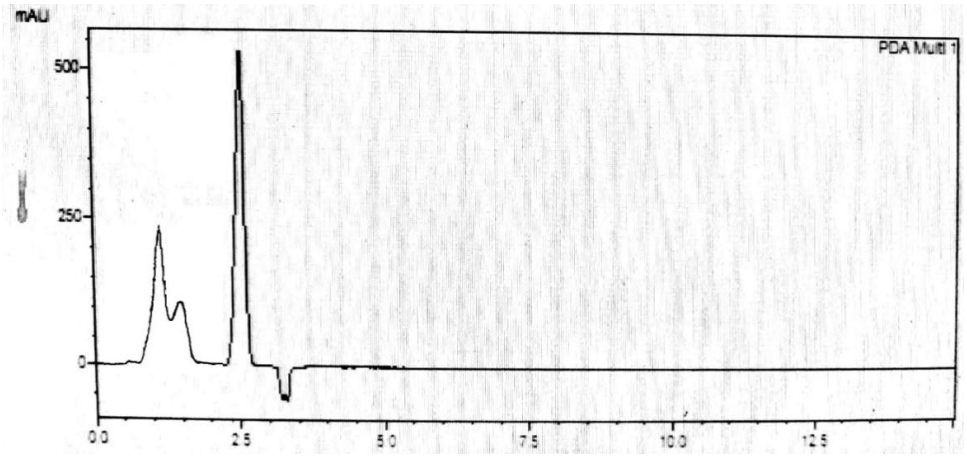

Figure No. 2: HPLC Chromatogram of Human Plasma spiked with Telmisartan (120ng/ml)

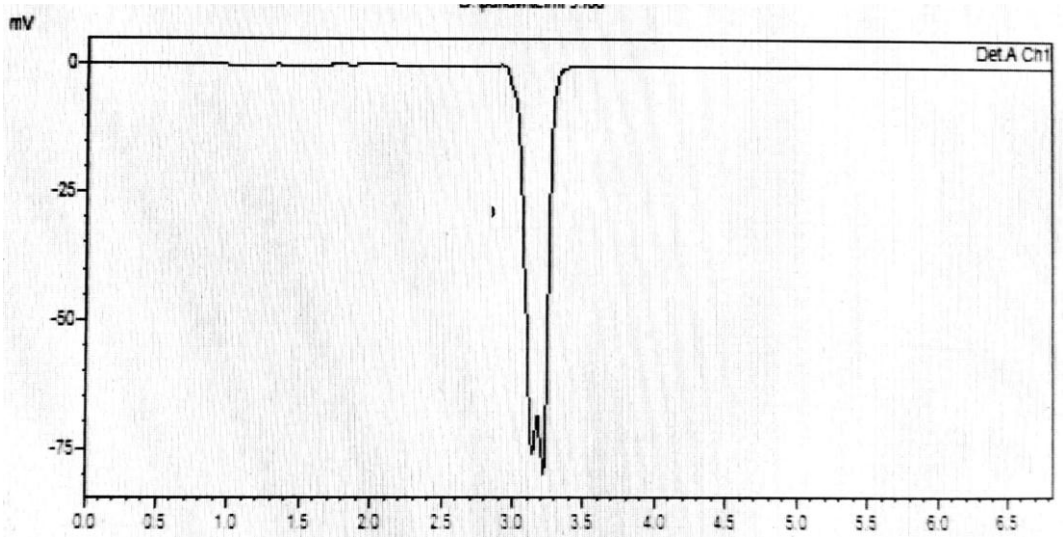

Figure No. 3: HPLC chromatogram of Blank solution (only mobile phase)

Linearity and range.

The mean regression equation of three standard curves for TLM was y = 6712.5x - 91480, where y presented peak area of drug and x was the plasma concentration of drug[25]. The calibration curve was linear over the studied concentration range (15–120 ng/ml) with a mean correlation coefficient more than 0.99 (Table 2 and Figure 4).

Table No. 2: Calibration standards for Telmisartan by HPLC/UV analysis

Concentration (ng/ml)	Peak Area [mean (n=3)]
15	18126.79
20	46128.65
30	73494.87
40	117585.25
50	231401.68
60	265772.03
70	338718.76
80	426864.37
90	552563.32
100	603182.7
110	693462.8
120	712736.3

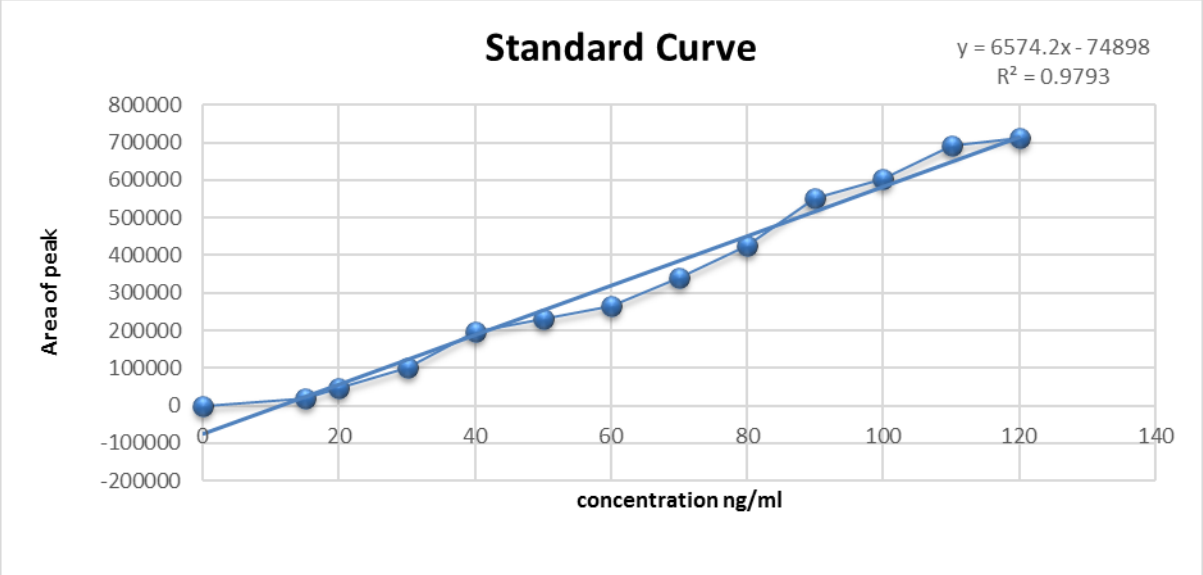

Figure No. 4: Calibration curve of Telmisartan in human plasma by HPLC/UV analysis

CLINICAL STUDY DATA

Demographic data of volunteers

Following table shows the demographic data of the 12 volunteers who participated to the study.

Table No. 3: demographic data of 12 volunteers

Sr. No.	Volunteer id	Age (yrs.)	Weight (kg)	Hight (cm)	BMI (Kg/m^2)
1	S1	24	58	167.5	21
2	S2	19	65	170	22
3	S3	19	68	180	21
4	S4	20	70	178.5	22
5	S5	19	63	185	18
6	S6	23	49	174	16
7	S7	22	61	173.5	20
8	S8	23	72	158	29
9	S9	23	67	169	23
10	S10	24	56	170	20
11	S11	22	58	172	20
12	S12	23	60	171	21
	Mean	21.75	62.25	167	22
	SD	1.959824	6.579928	48.20875	11.09737

Limits of BMI: Below 18.5 – Underweight (U); 18.5-24.9 – Normal (N); 25.0 - 29.9; Overweight; 30.0 & above – Obese

Table No. 4: Different biochemical parameter levels of 12 volunteers before the study periods

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Normal range
Bilirubin total	0.69	075	0.80	0.89	0.71	0.79	0.87	0.75	0.95	0.71	0.62	0.80	0.52-1.0
ALP	89.0	85.0	100.0	99.0	98.0	102.0	100.0	98.0	90.0	94.0	97.0	95.0	40-111
Total Protein	6.87	6.34	5.70	6.24	6.81	5.24	5.80	6.40	6.82	6.70	6.60	6.80	5.2-8.1
Albumin	4.57	4.30	3.30	3.14	3.41	3.14	3.40	3.40	4.00	3.40	3.30	3.40	3.8-4.4
Creatinine	0.75	0.90	0.87	0.79	0.80	0.89	0.78	0.85	0.90	0.84	0.80	0.90	0.6-1.8
Urea	24	29	27.6	29	30	33	31.1	25	27	22	27	25	10-40
Sodium	139	137	141	136	135	138	142.7	138	140	138	139	140	135-155
Potassium	3.85	33.99	3.70	4.10	4.34	4.00	3.84	4.02	3.80	3.90	4.00	3.90	3.5-5.5
chloride	99.0	100.0	100.9	1000	101.0	99.0	100.0	97.0	99.0	100.0	101.0	99.0	98-108
S.G.O.T	31.0	22.0	29.0	24.0	28.0	29.0	25.0	23.0	20.0	19.0	20.0	24.0	05-40
S.G.P.T.	29.0	26.0	31.0	32.0	22.0	32.0	32.0	25.0	26.0	24.0	24.0	29.0	05-40

Table No. 5: Different biochemical parameter levels of 12 volunteers after the study periods

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Normal range
Bilirubin total	0.79	0.65	0.70	0.83	0.78	0.69	0.86	0.65	0.85	0.74	0.69	0.78	0.52-1.0
ALP	89.0	89.0	98.0	91.0	96.0	100.0	101.0	99.0	93.0	93.0	94.0	91.0	40-111
Total Protein	6.67	6.84	5.78	6.34	6.52	6.23	5.43	6.64	6.93	5.84	6.72	6.84	5.2-8.1
Albumin	4.61	4.2	3.9	3.8	3.45	3.9	3.40	3.83	4.41	3.84	3.93	3.84	3.8-4.4
Creatinine	0.75	0.64	0.81	0.72	0.84	0.86	0.72	0.88	0.92	0.83	0.88	0.94	0.6-1.8
Urea	28	30	28	29	31	34	33	20	40	32	28	29	10-40
Sodium	140	141	138	139	134	144	155.4	143.4	143	148	149	145	135-155
Potassium	3.65	3.99	3.78	4.18	4.74	3.90	3.44	4.60	3.50	4.90	4.00	3.70	3.5-5.5
Chloride	99.0	102.0	100.3	100	101.2	99.8	100.3	98.6	99.6	100.0	101.6	98.0	98-108
S.G.O.T	32.0	28.0	32.0	26.0	38.0	20.0	22.0	33.0	20.0	30.0	18.0	28.0	05-40
S.G.P.T.	31.0	29.0	28.0	38.0	27.0	30.0	30.0	28.0	22.0	22.0	28.0	32.0	05-40

Haematological parameters

Hematological parameters (Hemoglobin, RBC and WBC count) were measured before and after the study periods. No significant variations in hematological parameters were observed[26].

Table No. 6: Hematological parameters of 12 volunteers before and after the study periods

Subject ID	Hematological parameters					
	Hemoglobin (mg/dl)		RBC(million/mm2)		WBC (1000/mm^2)	
	Before	After	Before	After	Before	After
1	12.8	12.6	5.1	5.1	9.8	9.8
2	14.6	14.6	4.9	5	8.4	9.1
3	13.2	13.7	4.6	4.7	10.1	10.2
4	11.9	12.1	4.3	4.4	9.6	9.2
5	13.7	13.8	5.2	5.2	7.9	7.8
6	14.6	14.6	5.2	5.4	10	10
7	14.8	14.9	5.9	5.9	9.7	9.9
8	15	15.2	4.9	4.7	6.8	7.2
9	12.5	12.6	4.4	4.3	9.1	8.8
10	13.2	13.8	5.6	5.7	9.6	9.7
11	14.6	14.5	5.8	5.8	10.5	10.2
12	15.6	15.7	4.9	4.7	10.1	9.8
Limits	**13.5-18.0**		**4.5-6.0**		**4.0-11**	

Table No. 7: Mean plasma concentration-time profile with SD of Telmisartan in 12 subjects at specified sampling times

	Reference		Test 1		Test 2		Test 3	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
0.25	44.5	3.01	38.6	3.9	42	5.2	43	7
0.5	52.6	3.9	53	1.7	55.8	4	56.6	6.8
0.75	76.8	3.4	84.5	2.2	83.5	6.5	81	8.1
1	93.1	3.1	92	2.8	88.6	5.7	83.8	6.1
1.5	84	2.4	79.8	3.1	87	4.9	76.1	5.8
2	75.1	2.2	73.5	1.8	76.1	9	67.5	6.4
2.5	62.8	1.4	63.8	4.6	67.1	7.8	59	5.1
3	49.8	3.4	46.6	5.9	54.5	4	49.8	5.4
4	36.1	5.3	37.6	4.5	39.3	3.5	36.6	4.1
6	27.1	4.1	27.6	1.8	31	4.4	27.5	3.7
8	21.6	3	21.3	2.1	22.1	2	19	3
12	13	7.7	9.6	7.5	7.1	7.8	7.3	8
24	0	0	0	0	0	0	0	0

***** Less than lower limit of quantification.

Table No. 8: Pharmacokinetic parameters of Telmisartan (Reference) in 6 volunteers

Volunteer no	**C_{max}**	**$AUC_{0\text{-}last}$**	**$AUC_{0\text{-}\infty}$**	**T_{max}**	**K_{el}**
9	93	470.625	575.565	1	0.1715
12	89	418.875	497.75	1	0.1774
5	95	339.25	428.45	1	0.213
8	90	433.375	506.572	1	0.1776
1	97	417.375	490.275	1	0.1783
4	95	396.75	469.86	1	0.1778

Table No. 9: Pharmacokinetic parameters of Telmisartan (Test 1) in 6 volunteers

volunteer no	**C_{max}**	**$AUC_{0\text{-}last}$**	**$AUC_{0\text{-}\infty}$**	**T_{max}**	**K_{el}**
1	89	441.125	527.4608	1	0.1737
2	91	336	421.9714	1	0.2093
5	92	434.875	526.8481	1	0.1739
6	90	405.875	486.5012	1.5	0.1736
9	97	361.125	465.4999	1	0.2107
10	93	415.75	488.4445	1	0.178

Table No. 10: Statistical analysis of pharmacokinetic parameters

Parameter	C_{max}			$AUC_{0\text{-}last}$			$AUC_{0\text{-}\infty}$		
	R	T1	T2	R	T1	T2	R	T1	T2
Mean	93.17	92	92.66	412.7	399.1	410	494.7	486	501
SD	2.853	2.582	1.7	39.77	38.28	50.4	44.18	36.3	42.9
%CV	3.062	2.807	1.834	9.637	9.591	12.3	8.931	7.47	8.57
Geo Mean	93.12	91.96	92.65	410.7	397.2	407	492.8	485	499
Min	89	89	90	339.3	336	341	428.5	422	439
Max	97	97	95	470.6	441.1	471	575.6	527	550

Table No. 11: Statistical analysis of pharmacokinetic parameters

Parameter	T_{max}			Kel		
	R	T1	T2	R	T1	T2
mean	1	1.083	1.125	0.183	0.187	0.19
SD	0	0.186	0.28	0.014	0.017	0.02
%CV	0	17.2	24.85	7.552	8.935	8.67
geo mean	1	1.07	1.091	0.182	0.186	0.19
min	1	1	0.75	0.172	0.174	0.18
max	1	1.5	1.5	0.213	0.211	0.21

Table No. 12: Shows ratio analysis of the pharmacokinetics parameters viz. Cmax, Tmax, AUC0-t, AUC0- , Kel(h-1) of three Test brands

Brand	Cmax(ng/ml)	Tmax(hr)	AUC0-t	AUC0 (nghr/ml)	Kel(h-1)	limits
T1	0.98	0.96	0.98	1.08	1.02	0.80-1.25
T2	0.99	0.99	1.01	1.12	1.06	0.80-1.25

Table No. 13: Two-way analysis without replication (ANOVA) results at P level 0.001 for the pharmacokinetic meter C_{max} (ng/ml)

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*P value*	*F crit*
Rows	0.000963	5	0.000193	1.823738	0.168599	P>0.001	2.901295
Columns	0.001679	3	0.00056	5.29949	0.010842	P>0.001	3.287382
Error	0.001584	15	0.000106				
Total	0.004225	23					

Table No. 14: Two-way analysis without replication (ANOVA) results at P level 0.001 for the pharmacokinetic meter $AUC_{0\text{-last}}$

Source of Variation	SS	df	MS	F	P-value	P value	F crit
Rows	0.001882	5	0.000376	0.097129	0.991221	P>0.001	2.901295
Columns	0.006507	3	0.002169	0.559708	0.64973	P>0.001	3.287382
Error	0.05813	15	0.003875				
Total	0.066519	23					

The study protocol was first reviewed and approved by the LNCT University Madhya Pradesh India. Twelve healthy, adult volunteers who ranged from 20 to 25 years of age (mean, SD); 21.75, 1.959824, weighed 62.25, 6.579928 kgs and average 167, 48.20875 cm in height. Participated in the studies[27], coded as V1:V2 up to V12. Written informed consent was obtained from all volunteers after educating them about the nature and details of the studies. The following laboratory test for haemoglobin, cholesterol, triglyceride and Liver functions creatinine, GGT were performed.

The Balanced incomplete block design (BIBD) was appropriate for bioequivalence study as there were two brands namely Cresar (Cipla) and Telma (Glenmark) and each volunteer was expected to receive at least two brands. It was claimed to be statistically powerful. It was relatively less complicated than the unbalanced design and allowed comparisons of within subject vacancies for the rest and reference products[28]. Vitals signs of oral temperature, sitting blood pressure and pulse rate were measured and recorded during studies to ensure we-being of subjects. Temperature, Blood Pressure and Pulse rate was normal, no significant difference was observed.

The liquid-liquid extraction procedure for sample extraction was quite simple with acceptable and reproducible percentage of greater than 90%. The method was suitable for routine quantitation of Telmisartan in human plasma over a concentration range of 10 to 120 ng/ml and it was successfully used to analysis plasma sample of Telmisartan for this bioequivalence study.

Pharmacokinetic parameters evaluated were C_{max}, $AUC_{o\text{-}t}$, $AUC_{0\text{-}\infty}$, $T_{1/2}$, and K_{el}.

To establish Bioequivalence, the calculated 90% confidence interval for AUC and C_{max} should fall within the bioequivalence range, usually 80- 125%. This is equivalent to the rejection of two one sided t-test with the null hypothesis of non-bioequivalent at 5% level of

significance[29]. The non-parametric 90% confidence interval for T_{max} should lie within a clinically acceptable range.

To test bioequivalence three parameters were evaluated using ANOVA and Confidence Interval viz C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Bioavailability parameters for all brands. The statistical analysis of C_{max} of these products showed no significant difference. Therefore, all the three brands are bioequivalence at C_{max} level as the ratio analysis values are within acceptable limit of 0.8-1.25 at 90% confidence interval[30]. The statistical analysis of AUC_{0-t} of these products showed no significant difference. Therefore, all the two brands are bioequivalence at AUC_{0-t} level as the ratio analysis values are within acceptable limit of 0.8-1.25 at 90% confidence interval.

The ratio analysis of peak time T_{max} for Test 1, Test2 and Test 3 with respect to Reference was calculated as 0.96, 0.99, and 0.91. Therefore, it was found that at 90% confidence level, the rate of drug absorption for all three brands met the criterion for bioequivalence. K_{el} was found that at 90% confidence level, the rate of drug elimination for all three brands met the criterion for bioequivalence.

Multivariate analysis of variance is an informative method to assess not only the formulation effect but also the subject's variability it removes some of the random variability. The statistical power approach for assessing bioequivalence using two-way ANOVA was also done on C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el} under the hypothesis of no differences between AUC, C_{max} and T_{max} of reference and other three branded formulations[31,32]. ANOVA was applied to determine the effect of factors like period, sequence, subject within sequence and treatment on study results. No significant effect was noted for period, sequence and treatment.

The 90% confidence interval for log transformed data was calculated for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. For C_{max} the lower limit and the upper limit with respect to Reference was 0.99, 1.0002 and 0.9956, AUC_{0-t} was 1.0047, 0.9999 and 0.9589, and $AUC_{0-\infty}$ was 0.9964, 1.0012 and 0.9754 for Test1, Test2 and Test3 respectively. Therefore, it was found that at 90% confidence level, all three brands met the criterion for bioequivalence and all are equivalent.

CONCLUSIONS

The bioavailability and bioequivalence of two brands of Telmisartan namely two brands Cresar (Cipla) and Telma (Glenmark). The ratio analysis of pharmacokinetic parameters viz Cmax, Tmax, AUC0-t, AUC0-∞ and Kel for all brands was within limit i.e. 0.0-1.25 suggesting that the rate and extent of absorption for the three brands met bioequivalence criterion at 90% confidence level. Two-way ANOVA revealed no statistically significant difference in the rate and extent of absorption of glimepride among the four brands ($P > 0.001$), indicating that all the brands are bioequivalent and hence truly interchangeable. Finally, it can be concluded that the reference and test product of Telmisartan in this study were found to be bioequivalent. Branded drugs play an important role in medications, but generics are their cost-effective alternatives. Indian pharmaceutical market of generic drugs is increasing day by day. A generic drug is identical or bioequivalent to a brand name drug in dosage form, safety, strength, rout of administration, quality, performance characteristics and intended use, they are typically sold at substantial discounts from the branded price.

REFERENCES

1 Burnier M, Brunner HR. Angiotensin II receptor antagonists. Lancet 2000; 355:637–645.

2 Kakuta H, Sudoh K, Sasamata M, *et al.* Telmisartan has the strongest binding affinity to angiotensin II type 1 receptor: comparison with other angiotensin II type 1 receptor blockers. Int J Clin Pharmacol Res. 2005; 25:41–46.

3 Takeuchi K1, Yamamoto K, Ohishi M, *et al.* Telmisartan modulates mitochondrial functions in vascular smooth muscle cells. Hypertens Res. 2013:36(5):433-9.

4 Cassis P, Conti S, Remuzzi G, Benigni A. Angiotensin receptors as determinants of life span. Pflugers Arch. 2010: 459(2):325-32.

5 Scalera F, Martens-Lobenhoffer J, Bukowska A, Lendeckel U, Tager M, Bode-Boger SM. Effect of Telmisartan on nitric oxide--asymmetrical dimethylarginine system: role of angiotensin II type 1 receptor gamma and peroxisome proliferator activated receptor gamma signaling during endothelial aging. Hypertension. Mar 2008;51(3):696-703.

6 Shiuchi T, Iwai M, Li HS, *et al.* Angiotensin II type-1 receptor blocker valsartan enhances insulin sensitivity in skeletal muscles of diabetic mice. Hypertension. 2004 May;43(5):1003-10.

7 Tamboli AM, Todkar P, Zope P, Sayyad FJ An Overview on Bioequivalence: Regulatory; Consideration for Generic Drug Products. J Bioequiv Availab 2010; 086-092.

8 Setiawati E, Deniati SH, Yunaidi DA, Handayani LR, Harinanto G, *et al.* Bioequivalence Study with Two Naproxen Sodium Tablet Formulations in Healthy Subjects. J Bioequiv Availab1: 2009; 028-033.

9 Shak S.K, Jhade D.N Evaluation of antifertility potential of *Piper betle* (Petiole) on female wistar rats "rising approaches of herbal contraception'' Biochemistry and Biophysics Reports 15 (2018) 97–10298.

10 Kamal K. Midha, Gordon McKay, Bioequivalence; Its History, Practice, and Future, The AAPS Journal, 2009:11, 4, 12-28.

11 Tandon V. Bioavailability and bioequivalence. In: Schoenwald R, editors. Pharmacokinetics in Drug Discovery and Development. New York: CRC Press; 2002. p. 97-100.

12 Tsume Y, Amidon GL, Takeuchi S Dissolution Effect of Gastric and Intestinal pH fora BCS class II drug, Pioglitazone: New *in vitro* Dissolution System to Predict *In vivo* Dissolution. J Bioequiv Availab 2013:5: 224-227.
13 Khandave SS, Onkar SV, Sawant SV and Joshi SS Evaluation of Performance of the Truncated Area under Curve (AUC) as a Primary Pharmacokinetic Parameter in Bioequivalence Studies. 2010:2: 077- 080.
14 Akarasereenont P, Chatsiricharoenkul S, Pongnarin P Bioequivalence Study of 1,500 mg Glucosamine Sulfate in Thai Healthy Volunteers. 2012: 4: 091-095.
15 Zhao Q, Purohit V, Cai J, LaBadie RR, Chandra R Relative Bioavailability of a Fixed- Combination Tablet Formulation of Azithromycin and Chloroquine in Healthy Adult Subjects. J Bioequiv Availab 2013:5: 001-005.
16 Shah S.K., Garg G., Jhade D.N., *Ficus racemosa* Linn: Its Potentials Food Security and Rural Medicinal Management, /J. Pharm. Sci. & Res. Vol. 8(5), 2016, 317-322.
17 Sanmukhani J, Tripathi CB. Ethics in clinical research: The Indian perspective. Indian J Pharm Sci 2011;73(2):125-30.
18 Ethical Guidelines for Biomedical Research on Human Subjects. New Delhi: Indian Council of Medical Research; 2006.
19 Shaik M, Thirunagari BL, Sathe A. The basic regulatory considerations and prospects for conducting bioavailability/bioequivalence (BA/BE) studies – An overview. Comp Eff Res 2011; 2011:1-25.
20 Galgatte UC, Jamdade VR, Aute PP, Chaudhari PD. Study on requirements of bioequivalence for registration of pharmaceutical products in USA, Europe and Canada. Saudi Pharm J 2014; 22:391-402.
21 Tatane Sagar, *et al*.: Development of UV Spectrophotometric Method of Telmisartan in Tablet Formulation. JAPHR, 2011;1: 23- 26.
22 Reddy Rami, *et al.:* Spectrophotometric Determination of Telmisartan Sulphate in Pharmaceutical Dosage Forms. Asian journal of pharmaceutical and health science 2011; 1(3):142-144.
23 Rani Tulja, Sankar Gowri, Madhavi, Satyanarayana B: Extractive visible spectrophotometric method for determination of Telmisartan and Irbesartan in bulk and pharmaceutical formulations. Asian journal of pharmaceutical and clinical research 2012; 5(1):41-44.
24 Khushboo Rawat, Validated method development and validation for estimation of Telmisartan as api and in pharmaceutical dosage form by uv-spectroscopy, research journal of pharmaceutical, biological and chemical sciences, 2014;5(4),679-685.
25 Jaydeep M. Patel *et al*., Development and validation of bioanalytical HPLC method for estimation of Telmisartan in rat plasma: application to pharmacokinetic studies, Dhaka Univ. J. Pharm. Sci. 11(2): 121-127, 2012.
26 J. Shen *et al*., HPLC determination of Telmisartan in human plasma and its application to a pharmacokinetic study, Pharmazie, 2005, 60: 418–420.
27 Daniel Ponce-Navarrete *et al*, Bioavailability of two different tablet formulations of Telmisartan of two different strengths (40 mg and 80 mg) in healthy male Mexican volunteers, bioequivalence & bioavailability, 2015, 7(4): 164-169.
28 Bodh I Jugdutt, Clinical effectiveness of Telmisartan alone or in combination therapy for controlling blood pressure and vascular risk in the elder, Clinical Interventions in Aging, 2010:5 403–416.
29 Domenico Galzerano *et al.*, New standards in hypertension and cardiovascular risk management: focus on Telmisartan, Vascular Health and Risk Management 2010:6 113–133.
30 Terry KW Ma *et al*, Renin–angiotensin–aldosterone system blockade for cardiovascular diseases: current status, British Journal of Pharmacology 2010: 160, 1273–1292.
31 Agrawal V, Manohar G, Kasliwal RR, Angiotensin II Receptor Blockers: Current Perspective, JAPI, 2003:51 2003, 706-713.
32 Patel D. and Sawant K.K., Oral bioavailability enhancement of acyclovir by self-micro emulsifying drug delivery systems (SMEDDS). Drug Dev. Ind. Pharm. 2007:33, 1318-1326.