A single-dose, open-label, two-treatment, two-period, two-sequence, two-way cross-over bioavailability & bioequivalence study to compare two formulation of Olmesartan 40 mg in healthy adults in fed state

Mohit Changani[1*], Ameet Soni[2], Ambrish Singh[3], Harsh Choksi[4], Lokesh Kumar[5]

[1,3,4,5]Medical Advisor, [2]Head- Medical Services, Cadila Pharmaceuticals Limited, India

***Corresponding Author: Mohit Changani**
Email: mohit.changani@cadilapharma.co.in

Abstract

Introduction: Olmesartan medoxomil is an ester prodrug commonly prescribed to treat high blood pressure, heart failure, and diabetic kidney disease.

Aim: To study the bioequivalence of Olvas tablets (containing olmesartan medoxomil 40mg) of Cadila Pharmaceuticals Ltd., India with Benicar® tablets (containing olmesartan medoxomil 40mg) of Daiichi Sankyo, Inc., Parsippany, New Jersey.

Materials and Methods: Forty healthy, adult, male subjects were studied in a single-dose, open-label, two-treatment, two-period, two-sequence, two-way cross-over study. Detailed demographic data along with clinical examination, vital signs, medical history, laboratory tests including hematology, biochemistry, serology and urine analysis. ECG and chest X-ray were performed. Pharmacokinetic primary parameters like C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and secondary parameters like T_{max}, $t_{1/2}$, K_{el}, and $AUC_{Extrapolation}$ were calculated for both the drug formulations.

Results: Demographic parameters were comparable for both the treatment arms. Olmesartan medoxomil 40mg of Cadila Pharmaceuticals Ltd was found to in the acceptance range for bioequivalence, 80.00-125.00% for the 90% confidence intervals for the difference of means of Ln-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Conclusion: Both Olmesartan Medoxomil tablets 40mg (containing olmesartan medoxomil 40mg) of Cadila Pharmaceuticals Ltd., India with Benicar® tablets 40mg (containing olmesartan medoxomil 40mg) of Daiichi Sankyo, Inc., Parsippany, New Jersey were found to be bioequivalent.

Keywords: Olmesartan, Bioavailability, Bioequivalence, Pharmacokinetics.

Introduction

There is an increasing burden of chronic diseases in India and hypertension is one of the most important risk factor for global morbidity and mortality. According to World Health Organization (WHO), prevalence of hypertension is increasing globally. Approximately 1 billion people currently have hypertension (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg).[1] Adults with uncontrolled blood pressure are at increased risk of all cause and cardiovascular mortality as compared to normotensive individuals.[2]

Various class of drugs are available for the treatment of hypertension like Angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), dihydropyridine calcium channel blockers, thiazide diuretics, loop diuretics, β-adrenergic blocking agents, mineralocorticoid receptor blockers, director vasodilators and centrally acting alfa-agonists.[3]

Olmesartan is a drug of ARBs group. It acts by blocking the angiotensin II type 1 receptors present in the smooth muscles of vessels.[4] Olmesartan medoxomil is a prodrug which is hydrolyzed by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. The absolute bioavailability of olmesaratan is approximately 26%. It's bioavailability is independent of the food intake. The maximum plasma concentration (C_{max}) of olmesartan is achieved after 1 to 2 hours of oral administration of the drug. Olmesartan is highly plasma protein bound molecule (99%). Elimination of olmesartan follows a biphasic pattern with the terminal elimination half-life of 13 hours approximately. Following a single dose up to 320 mg and multiple doses up to 80 mg, it follows linear pharmacokinetics.[5]

In present study we tried to establish the bioequivalence of Olmesartan Medoxomil tablets 40mg (containing olmesartan medoxomil 40mg) of Cadila Pharmaceuticals Ltd., India with Benicar® tablets 40mg (containing olmesartan medoxomil 40mg) of Daiichi Sankyo, Inc., Parsippany, New Jersey, in healthy, adult, human subjects under fed condition. The secondary objective of the study was to evaluate safety parameters, including adverse events and clinical laboratory tests.

Materials and Methods

This study had been conducted as per Declaration of Helsinki and was consistent with the Code of Federal Regulations Title 21 (21 CFR) – part 50 (Protection of Human Subjects), 21 CFR – Part 54 (Financial Disclosure by Clinical Investigator) and 21 CFR – Part 312 (Investigational New Drug), ICH-GCP (E6-R2, Step 2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), Schedule Y and its amendments (Amendment version 2005, Drug and Cosmetic Rules, 2005), ICMR guidelines for Biomedical Research on Human Subjects (2006), Guidance for Industry "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA", December 2013 and CDER – Statistical Approaches to

Establishing Bioequivalence, January 2001 and all relevant SOPs of Cadila pharmaceuticals Ltd., India.

Study population

Forty healthy, adult, male human subjects were included in the study. Written informed consent was obtained from each subject before screening. Study specific informed consent was obtained from each participating subject before enrolling into the study. Out of 40, 38 subjects completed both the periods of the study.

Subjects were screened through demographic data evaluation, clinical examination along with vital signs measurements, medical history, laboratory tests (hematology, biochemistry, serology and urine analysis), ECG and chest X-ray (taken within 6 months prior to 1st dosing) within 21 days of 1st dosing. 2D-Echo was performed for volunteers/ subjects age 40 or above (only) as per Ethical Committee recommendations. Alcohol breath test and urine screen for abuse drugs were performed for all subjects on the day of check-in of each period. Subjects recruited to the study were confirmed for following inclusion and exclusion criteria.

Inclusion criteria

1. Healthy, adult, non-smoker, human subject aged from 18 to 45 years, body mass index (BMI) within normal limit of 18.50-24.90 kg/m2.
2. Willingness to sign written informed consent form (for screening & study related procedures) & to undergo pre- and post-study physical examinations and laboratory investigations.
3. No contraindications with the study medication with any previous medical or surgical history and normal general physical examination and normal ECG findings.
4. Availability of subject for the entire study period and willingness to adhere to protocol.

Exclusion criteria

1. Subjects incapable of understanding the informed consent process/ procedure.
2. Evidence of psychiatric or other systemic disorders, presence of infectious disease markers, medication with any enzyme modifying drugs in past 4 weeks, known drug hypersensitivity or idiosyncratic reaction to Olmesartan or any related drug.
3. History of or current alcohol abuse (>600 mL weekly) or history of exposure to other substance of abuse.
4. Subject who participated in any other clinical investigation using experimental drug or had bleed more than 300 mL in the past 3 months.
5. Xanthine-containing food or beverages (tea, coffee, chocolates, soft drinks like cola etc.) within 24 hours prior to the dosing of each period or alcoholic products consumption or grape fruit juice within 48 hours prior to the dosing of each period.
6. Subject without adequate venous access in their left or right arm to allow collection of all samples via venous cannula in each period.
7. Females who are falling in menstruation period during study, found positive in Urinary Pregnancy Test, using contraceptives or lactating.

Design

It was a single-dose, open-label, two-treatment, two-period, two-sequence, two-way cross-over design with 7 days washout period between two consecutive dosing periods of the study. Randomization was carried out using SAS® (SAS Institute Inc., CARY, USA) Version 9.4. It was done in blocks using PROC PLAN such that the design was balanced. The order of receiving the Test (T) and Reference (R) formulations for each subject during the two periods of the study was determined according to randomization schedule. Study Protocol, Study Protocol Amendment, Informed Consent Forms (English/ Gujarati language), Back Translated ICF (English), Translation and Back Translation Certificate and other related documents were reviewed and approved by the Independent Ethics Committee (IEC).

In each period of the study, enrolled subjects fasted (overnight) for at least 10 hours prior to schedule start-time of breakfast. Each subject received high–fat, high-calorie breakfast exactly 30 minutes prior to the schedule start-time of dosing and completed the same within 30 minutes or less of the schedule start-time of breakfast. Each subject then received a single oral-dose of either Test (T) or Reference (R) product in sitting posture along with 240 mL of drinking water at ambient room temperature as per the randomization schedule. Subjects were instructed not to chew or crush the drug but to consume it as a whole. All the in-house subjects received a standard meal at about 04.00, 08.00 and 12.00 hours after dosing in each period. During housing, all meal plans were identical for the both periods of the study. For monitoring the safety of subjects, clinical examination and vital signs measurements were performed at regular interval as mentioned in the protocol.

Blood sampling

In the present study, blood samples were collected up to 72.00 hrs post-dose, because the elimination half-life of the Olmesartan Medoxomil is approximately 13 hours. Blood samples were withdrawn by placing an indwelling cannula placed in a forearm vein or fresh clean vein puncture using a disposable sterilized syringe or a needle in case of clotting of cannula.

For this a total of 23 blood samples (5.0 ml each) were collected. The pre-dose blood sample was collected within a period of 01.00 hour and within ±02 minutes of the scheduled-time till 24.00 hours. Ambulatory blood sample at 36.00 and 48.00 hours post-dose were collected within ±60 minutes of the scheduled sampling time. At 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.00, 02.25, 02.50, 02.75, 03.00, 03.50, 04.00, 05.00, 06.00, 08.00, 12.00, 16.00, 24.00, 48.00 and 72.00 hours post-dose samples were collected.

The blood samples were collected in pre-labelled vacutainer containing K2EDTA as an anticoagulant. After collection of blood samples, study-personnel centrifuged the samples at 3000 rpm for 10 minutes at 4 ºC as soon as possible but not more than 60 minutes of the actual-time of sample collection. After centrifugation the obtained plasma samples were divided into two aliquots and stored in two different pre-labeled RIA vials. The labelled RIA vials were than stored at –20±5°C or colder till withdrawn for analysis.

Statistical and analytical methods

Pharmacokinetic primary parameters like C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and secondary parameters like T_{max}, $t_{1/2}$, K_{el}, and $AUC_{Extrapolation}$ were calculated using plasma concentration vs. time profile (actual time of sample collection) data of Olmesartan Medoxomil of all the subjects who had completed both the periods of the study from the data obtained through bio-analytical department using non-compartmental model using WinNonlin Professional Software (Version 5.3), Pharsight Corporation, USA.

The area under the plasma concentration versus time curve [AUC_{0-t}] was calculated using the linear trapezoidal rule from the zero time-point to the last quantifiable concentration. The maximum observed plasma concentration [C_{max}] time to reach maximum plasma concentration [T_{max}] was obtained from the plasma concentration time profile. The terminal elimination rate constant [K_e] was obtained from the slope of the line, fitted by linear least squares regression, through the terminal points of the log (base e) of the concentration versus time plot for these points. Throughout this report K_e may be designated as K_{el}. The half-life [$T_{½}$] was calculated by the equation $T_{½} = 0.693/K_{el}$. Throughout this report half-life designated as $t_{½}$. The intra-subject coefficient of variance percentage [CV] for the log-transformed pharmacokinetic parameters was calculated by the equation $100 \times \sqrt{[e^{mse} - 1]}$, where MSE is the Mean Square Error from the Analysis of Variance.

Statistical analysis was performed on pharmacokinetic parameters using SAS, Statistical Software, Version 9.4, SAS Institute Inc., CARY, USA. The T_{max} from Tests (T) and Reference products (R) was compared using a non-parametric method (90% confidence interval of the difference of median T_{max} of tests and reference formulation by Wilcoxon signed rank test and was accepted within a clinically determined limits).

ANOVA was performed for both un-transformed and in-transformed pharmacokinetic parameters of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ as well as un-transformed pharmacokinetic parameters of T_{max} were calculated for Olmesartan Medoxomil using PROC GLM procedure of SAS® Version 9.4 or higher. The confidence intervals expressed as a percentage relative to the LSM of the reference treatments. The difference between T_{max} was analyzed non-parametrically using Wilcoxon sign rank test.

Based on the statistical results of the 90% confidence intervals for the difference of least square means of Ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Olmesartan, conclusions were drawn whether the test formulation was bioequivalent to the reference formulation under fed condition. The acceptance range for bioequivalence was 80.00-125.00% for the 90% confidence intervals for the difference of means of Ln-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Results

Forty healthy, adult, male, human subjects were enrolled in the study and out of which 38 subjects completed both the periods of the study. The plasma samples from 38 subjects were assayed and analyzed for Olmesartan.

Demographic variables included age, age groups, height, weight and BMI. All the included subjects were Indian and male.

The demographic details are provided below in table-1.

Table 1: Demographic and other baseline characteristics

Demographic Data (N=40)				
Age Groups				
< 18	00			
18 – 40	38 (95%)			
> 40	02 (05%)			
	Age (Years)	Weight (Kg)	Height (cm)	BMI (kg/m^2)
Mean ± SD	30.83 ± 5.93	62.18 ± 6.56	166.73 ± 5.24	22.34 ± 1.86
Median	31.00	62.00	166.20	22.26
Range	21.00 – 44.00	46.90 – 75.00	154.00 – 179.50	18.53 – 24.87

Various pharmacokinetic parameters like least squares means, ratio of means, and their associated 90% confidence intervals based on ANOVA (untransformed); geometric means, ratio of means, and their associated 90% confidence intervals based on ANOVA (Ln-transformed); and statistical comparisons are summarized in tables 2 – 4.

Table 2: Summary of Pharmacokinetic parameters of olmesartan, untransformed data (N=38)

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)	
	Test (T)	Reference (R)
AUC_{0-t} (ng.hr/mL)	9919.899 ± 3785.26 (38.2)	9412.542 ± 3662.33 (38.9)
$AUC_{0-\infty}$ (ng.hr/mL)	10332.322 ± 3917.02 (37.9)	9824.785 ± 3635.35 (37.0)
C_{max} (ng/mL)	1716.195 ± 481.19 (28.0)	1625.088 ± 487.28 (30.0)
T_{max} (hr)	2.94 ± 0.7 (25.1)	3.14 ± 1.1 (35.1)
K_{el} (1/hr)	0.106 ± 0.02 (19.0)	0.107 ± 0.02 (17.2)
$T_{1/2}$ (hr)	6.80 ± 1.3 (19.1)	6.66 ± 1.1 (17.0)
AUC_{Extrap}	4.161 ± 2.47 (59.5)	4.618 ± 2.37 (51.4)

Table 3: Statistical Comparisons Olmesartan (N=38)

Parameter	Test (T)	Reference (R)
Median T_{max} (hr)	3.00	3.00
P-value	0.2163	

Table 4: Statistical summary of Ln-transformed Pharmacokinetic parameters of Olmesartan (N=38)

Parameter	Geo LSM R	Geo LSM T	Ratio T/R (%)	90% CI	Intra CV (%)	Power
Ln C_{max} (ng/mL)	1552.154	1657.866	106.81	100.06%-114.01%	16.96	99.99
Ln $AUC_{0\rightarrow t}$ (hr.ng/ml)	8816.037	9288.145	105.36	99.51%-111.55%	14.82	100.00
Ln $AUC_{0\rightarrow\infty}$ (hr.ng/ml)	9245.684	9694.541	104.85	99.43%-110.58%	13.78	100.00

*Bioequivalent if confidence intervals are within 0.8000–1.2500 (80.00 to 125.00%).

Assessment of bioequivalence

Based on the statistical results of the 90% confidence intervals for the difference of least square means of Ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Olmesartan, the test drug was found to be in the acceptance range for bioequivalence, 80.00-125.00% for the 90% confidence intervals for the difference of means of Ln-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. There was no statistical significant effect observed for Sequence, Treatment and Period effects for Ln-transformed and un-transformed C_{max}, AUC_{0-t} & $AUC_{0-\infty}$ pharmacokinetic parameters at 5% level of significance. Mean Concentration versus time plots (linear and Ln-linear) are presented in figure 1 & 2 for Olmesartan Medoxomil (N=38).

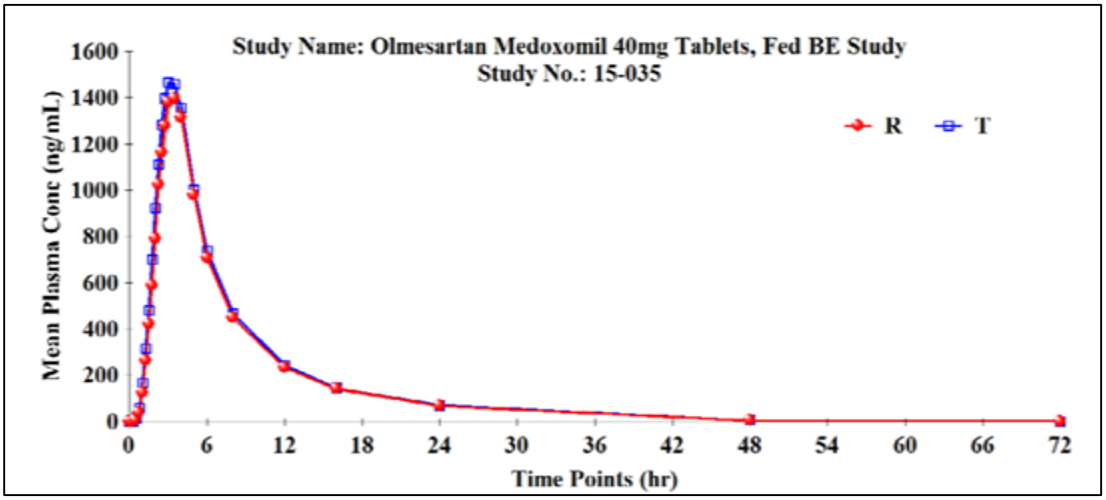

Fig. 1: Least-squares mean plasma concentrations versus time graph for olmesartan medoxomil (linear) (n=38)

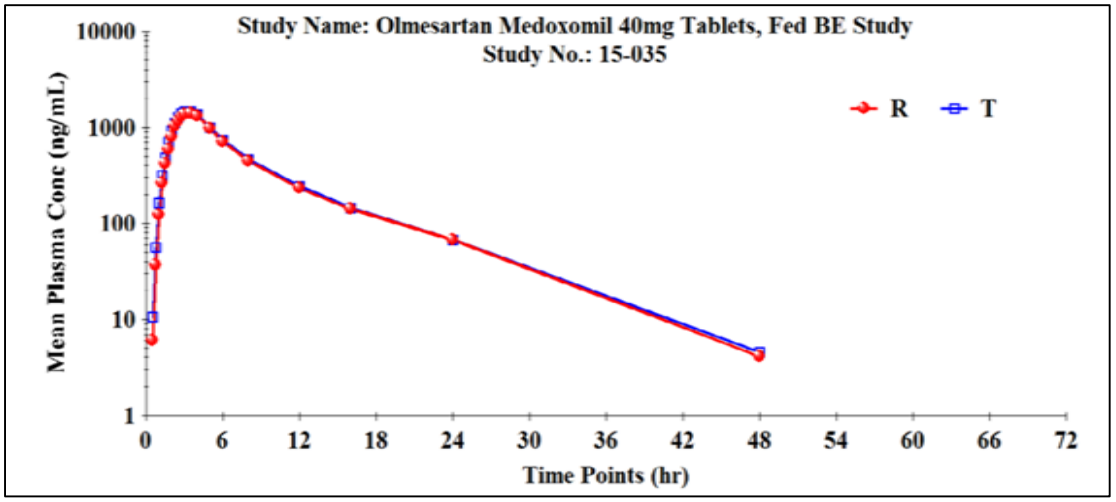

Fig. 2: Least-squares mean plasma concentrations versus time graph for olmesartan medoxomil (ln-linear) (n=38)

Safety

A total of two adverse events were reported in the present study, namely cough and itching. Both the adverse events were resolved and had an unlikely relationship with the study medication. No vital sign abnormalities occurred during the study. No clinically significant adverse events were observed during the clinical examination of the subjects in both the periods of the study.

Discussion & Conclusion

This study was conducted to establish the bioequivalence of Olvas tablets 40mg (containing olmesartan medoxomil 40mg) of Cadila Pharmaceuticals Ltd., India with Benicar® tablets 40mg (containing olmesartan medoxomil 40mg) of Daiichi Sankyo, Inc., Parsippany, New Jersey 07054 in healthy, adult, human subjects under fed condition.

Olmesartan is ACE inhibitor, used for the treatment of hypertension. After oral administration, the absolute bioavailability of the drug is approximately 26% with the peak plasma concentration C_{max} is reached after 1 to 2 hours. The bioavailability of Olmesartan is not affected by the food.

Hypertension is one of the leading cause affecting the functioning of kidney. Pharmacokinetic profiles of olmesartan is said to be affected by both age as well as altered kindly functions.[6,7] In comparison with healthy subjects, the AUC of olmesartan is reported to be altered in patients of mild and moderate renal insufficiency. In these patients, AUC is increased by 39% and 82% respectively.[8]

Based on the statistical analysis of Olmesartan under fed conditions, Olvas tablets (containing 40mg Olmesartan Medoxomil) of Cadila Pharmaceuticals Limited, India meet the 90% CI criteria for log transformed C_{max}, AUC_{0-t} & $AUC_{0-\infty}$, therefore have been shown bioequivalent to an equal dosage of the reference formulation, Benicar® tablets 40mg (containing olmesartan medoxomil 40mg) of Daiichi Sankyo, Inc., Parsippany, New Jersey 07054. In terms of safety, both the formulation of the drug is well tolerated during both the period of the study with no outstanding safety issues.

Source of funding

None.

Source of funding

None.

References

1. Gupta R, Gaur K, S Ram CV. Emerging trends in hypertension epidemiology in India. *J Hum Hypertens* 2018 https://doi.org/10.1038/s41371-018-0117-3
2. Zhou D, Xi B, Zhao M, Wang L, Veeranki SP. Uncontrolled hypertension increases risk of all-cause and cardiovascular disease mortality in US adults: the NHANES III Linked Mortality Study. *Sci Rep* 2018;8(1):9418.
3. Sinha AD, Agarwal R. Clinical Pharmacology of Antihypertensive Therapy for the Treatment of Hypertension in CKD. *CJASN* 2019;14(5):757-64.
4. Lee J, Kim A, Yu KS, Chung JY, Yim SV, Kim BH et al. Pharmacokinetics and bioequivalence of two different 20 mg olmesartan tablets: A randomized, single-dose, two-period crossover study in healthy Korean male volunteers. *Transl Clin Pharmacol* 2015;23(2):49-53.
5. FDA label - Benicar. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021286s020lbl.pdf. Accessed on 20 Nov 2019
6. Johns EJ. The neural regulation of the kidney in hypertension and renal failure. *Exp Physiol* 2014;99:289-94.
7. Monhart V. Hypertension and chronic renal insufficiency-chronic kidney failure. *Vnitr Lek* 2003;49:388-94.
8. Von Bergmann K, Laeis P, Puchler K, Sudhop T, Schwocho LR, Gonzalez L et al. Olmesartan medoxomil: influence of age, renal and hepatic function on the pharmacokinetics of olmesartan medoxomil. *J Hypertens Suppl* 2001;19:S33-S40.

How to cite this article: Changani M, Soni A, Singh A, Choksi H, Kumar L. A single-dose, open-label, two-treatment, two-period, two-sequence, two-way cross-over bioavailability & bioequivalence study to compare two formulation of Olmesartan 40 mg in healthy adults in fed state. *Indian J Pharm Pharmacol* 2019;6(4):121-5.