



An Open Label, Balanced, Randomized, Two Treatments, Two Sequences, Two Periods, Crossover, Single Dose, Bioequivalence Study of Olmesartan Medoxomil/Hydrochlorothiazide 40 mg/12.5 mg Coated Tablets of Abbott and Olmetec Plus® (Olmesartan Medoxomil/Hydrochlorothiazide) 40 mg/12.5 mg Coated Tablets of Daiichi-Sankyo in Healthy, Adult, Human Subjects Under Fasting Condition

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ABSTRACT

Olmesartan Medoxomil and Hydrochlorothiazide is a combination of an Angiotensin II receptor antagonist (Olmesartan Medoxomil) Thiazide diuretic (Hydrochlorothiazide) used in the treatment of mild to moderate essential hypertension in patients who requires combination therapy. The purpose of this study was to evaluate the bioequivalence between Olmesartan Medoxomil/Hydrochlorothiazide 40 mg/12.5 mg Coated Tablets of Abbott and Olmetec Plus® (Olmesartan Medoxomil/Hydrochlorothiazide) 40 mg/12.5 mg Coated Tablets of Daiichi-Sankyo in healthy, adult, human subjects. An open label, balanced, randomized two treatments, two sequences, two periods, crossover, single dose study with washout period of 02 days under fasting condition was carried out in 28 subjects in the age group of 21 to 44 years and 27 subjects completed the study. All the subjects included in the study were males and asians. The pharmacokinetic samples collected from subjects who completed the study were analysed to determine the plasma concentration of Olmesartan and Hydrochlorothiazide using a validated bio-analytical method. Hydrochlorothiazide is 90% confidence interval of the relative mean C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of Hydrochlorothiazide were 90.15%-101.65%, 94.67%-105.86%, 94.53%-105.73% respectively, which were within the acceptable limits of 80.00 to 125.00%. Olmesartan is the 90% confidence interval of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for Olmesartan was 96.45%-111.65%, 95.33%-108.79% and 95.35%-108.36% respectively, which were within the acceptable limits of 80.00% to 125.00%.

Keywords: Olmesartan; Hydrochlorothiazide; Bioavailability; Bioequivalence; Pharmacokinetic

ABBREVIATIONS

AUC : Area Under the Concentration versus time curve; AUC_{0-t} : Area Under the plasma Concentration versus time curve from zero to time at which last measurable concentration; $AUC_{0-\infty}$: Area Under the plasma Concentration versus time curve, from zero to infinity; BMI: Body Mass Index; C_{max} : Concentration Maximum;

CV: Coefficient of Variation; ISCV : Intra-subject Co-efficient of Variation; LCMS/MS: Liquid Chromatography Tandem Mass Spectrometry; mg: Milligram; mL: Millilitre; ng/mL: Nanogram per millilitre; PK: Pharmacokinetic; K_{el} : Elimination constant; $T_{1/2}$: Half-life; T_{max} : Time taken to reach maximum concentration; IEC :Independent Ethics Committee

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INTRODUCTION

Combination In the quest to provide the patients with affordable and effective medicines, many drug manufacturers intends manufacturing a copy of the innovator drugs which are usually very expensive. These are termed as generic drugs [1,2]. To ensure that only the safe and effective alternatives are reached to the market, the regulatory agencies like United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), ANVISA, INVIMA, ISP, Chile and few other countries had postulated few set of guidelines specific to their agency. To ensure that the alternative treatment available in the market is as efficacious as the innovator product, the requirement of bioequivalence evolved. A bioequivalence study has become a mandatory requirement for the manufacturer to obtain a marketing authorization approval from the health agency. Olmesartan Medoxomil and Hydrochlorothiazide is a combination of an Angiotensin II receptor antagonist (olmesartan medoxomil) Thiazide diuretic (Hydrochlorothiazide).

Olmesartan medoxomil

The chemical name is 2,3-dihydroxy-2-butenyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate, its molecular formula is $C_{29}H_{30}N_6O_6$, and its molecular weight is 558.6. Olmesartan Medoxomil is a white to light yellowish-white powder or crystalline powder. It is insoluble in water and sparingly soluble in methanol.

Hydrochlorothiazide

The chemical name is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its molecular formula is $C_7H_8ClN_3O_4S_2$, Hydrochlorothiazide is a white or practically white, crystalline powder. It is slightly soluble in water but freely soluble in sodium hydroxide solution. This study was designed to evaluate the relative bioavailability of the test product Olmesartan Medoxomil/Hydrochlorothiazide 40 mg/12.5 mg Coated Tablets of Abbott and reference product Olmetec Plus® (Olmesartan medoxomil/Hydrochlorothiazide) 40 mg/12.5 mg Coated Tablets of Daiichi-Sankyo in healthy, adult, human subjects under fasting condition (Figure 1) [3-5].

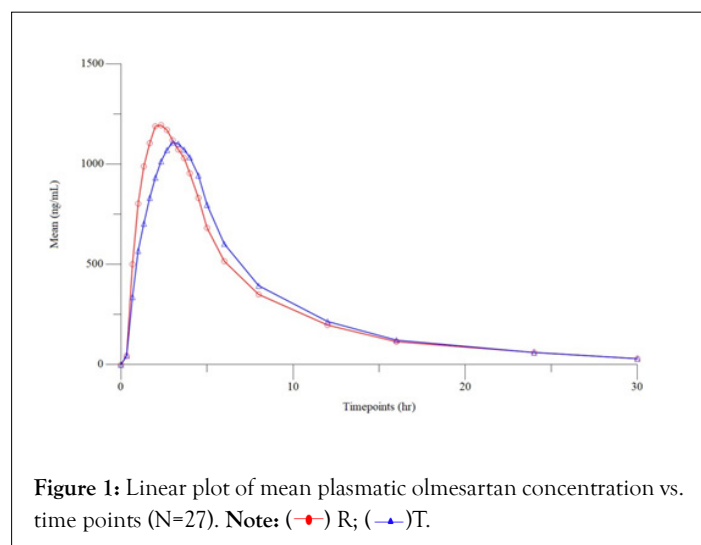


Figure 1: Linear plot of mean plasmatic olmesartan concentration vs. time points (N=27). Note: (—■—) R; (—▲—) T.

MATERIALS AND METHODS

Test product, dose and mode of administration

Olmesartan Medoxomil/Hydrochlorothiazide Coated Tablets, 01 × 40 mg/12.5 mg, Oral with 200 mL of water in sitting posture under fasting condition, 211D113.

Reference product, dose and mode of administration

Olmotec Plus® 40 mg/12.5 mg (Olmesartan Medoxomil/Hydrochlorothiazide) Film-Coated Tablets, 01 × 40 mg/12.5 mg, Oral with 200 mL of water in sitting posture under fasting condition, 331439 (Tables 1 and 2).

Methodology

The study protocol with annexes was prepared and IEC approval was obtained before initiation of the study. The subjects were screened and enrolled in the study as per the IEC approved protocol. Written informed consent was obtained from each volunteer in screening visit to initiation of screening procedure and for the study prior to enrolment. Individual counselling was then given to the willing volunteers by the Investigator in private and any questions and concerns were addressed prior to obtaining consent. The principal investigator/sub-investigator/physician reviewed all the screening results to assess eligibility of each volunteer. Subjects were enrolled in the study based on the inclusion and exclusion criteria.

This study was designed based on the known pharmacokinetic profile of the investigational product and general accepted standards for the conduct of bio-equivalence study. Twenty-eight subjects who met the eligibility criteria were enrolled and dosed with a single dose of either test or reference product in sitting posture at a fixed time in each period. Washout period of 02 days was maintained between each period, in order to minimize any possibility carryover effect from the preceding treatment. Blood samples were collected at pre-defined time intervals for the measurement of concentration and pharmacokinetic parameters of Olmesartan and Hydrochlorothiazide in both the periods. Data obtained from 27 subjects who completed the study was used for the pharmacokinetic and statistical analysis of Olmesartan and Hydrochlorothiazide. Bioequivalence was determined by statistical comparison of Ln-transformed data of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of the test and reference formulations using SAS version 9.4 (Figures 2) [6].

Study criteria for inclusion/exclusion of subjects

Healthy volunteers aged 18 to 45 years, and with BMI of 18.50-29.99 kg/m^2 and weight >50 kg were eligible to be enrolled in the study. Inclusion criteria encompassed no evidence of cardiac, pulmonary, gastrointestinal, hepatic, renal, hematologic, or neurologic disorders, or any acute or chronic disease, no history of drug or alcohol addiction, normal laboratory tests (complete blood counts, urinalysis, liver and kidney function, and blood sugar); and serological negativity for HIV and hepatitis B. Subjects were informed by an investigator about the purposes and risks of the study. They were asked to refrain from using concomitant medications, including over-the-counter products, dietary supplements and

natural products which potentially modify kinetics/dynamics of Olmesartan and Hydrochlorothiazide, 14 days prior to dosing and throughout the end of the study. Consumption of grapefruit and/or its products were not allowed within 10 days prior to the start

of the study. Caffeine and/or xanthine-containing products or alcohol were not allowed 48 hours prior the first administration of the study medications and throughout the blood sampling periods (Tables 3-5) [7].

Table 1: Statistical results of test product-T versus reference product-R for olmesartan.

Parameters	Antilog least square mean		Point estimate (%)	90% Confidence interval	ISCV (%)	Power
	Test product (T)	Reference product (R)				
Ln (C _{max})	1306.0852	1258.6402	103.77	96.45-111.65	15.82	0.9991
Ln (AUC _{0-t})	8428.1349	8276.1776	101.84	95.33-108.79	14.26	0.9998
Ln (AUC _{0-∞})	8827.4355	8684.5541	101.65	95.35-108.36	13.81	0.9999

Table 2: Statistical results of test product-T versus reference product-R for hydrochlorothiazide.

Parameters	Antilog least square mean		Point estimate (%)	90% Confidence interval	ISCV (%)	Power
	Test product (T)	Reference product (R)				
Ln (C _{max})	85.69	89.5133	95.73	90.15-101.65	12.95	1
Ln (AUC _{0-t})	596.8263	596.1814	100.11	94.67-105.86	12.04	1
Ln (AUC _{0-∞})	643.5468	643.7265	99.97	94.53-105.73	12.07	1

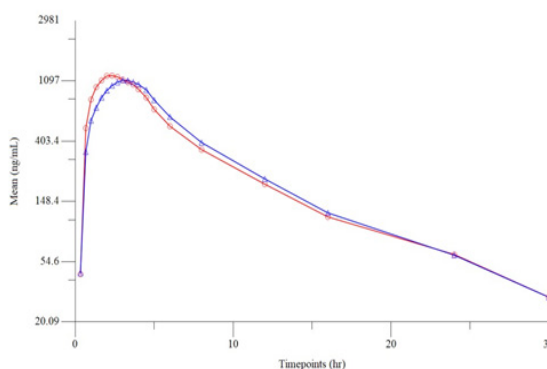


Figure 2: Semi log plot of mean plasmatic olmesartan concentration vs. time points (N=27). Note: (—■—) R; (—▲—) T.

Table 3: Summarized demographic profile of subjects who completed the study (N=27).

Parameter	Mean	SD	Minimum	Maximum
Age (years)	32	6	21	44
Height (m)	1.695	0.056	1.592	1.84
Weight (kg)	69.4	11.3	50.7	91.1
BMI (kg/m ²)	24.08	3.24	18.71	29.44

Table 4: Summary of pharmacokinetic parameters for olmesartan of reference product-R.

Parameter	N	Reference(R) (Mean ± SD)
C _{max} (ng/mL)	27	1303.168 ± 343.010
AUC _{0-t} (hr.ng/mL)	27	8537.619 ± 2200.396
AUC _{0-∞} (hr.ng/mL)	27	8947.617 ± 2268.875
AUC%Extrap_Obs	27	4.707 ± 1.290
*T _{max} (hr)	27	2.33 (1.00-4.50)
T _{1/2} (hr)	27	7.667 ± 1.149
Kel (hr-1)	27	0.093 ± 0.015
VD (mL)	27	52382.460 ± 15244.273
CL (mL/hr)	27	4751.677 ± 1253.024

Note: *Expressed in terms of median (range)

Table 5: Summary of pharmacokinetic parameters for olmesartan of test product-T

Parameter	N	Reference(R) (Mean ± SD)
C _{max} (ng/mL)	27	1333.011 ± 283.254
AUC _{0-t} (hr.ng/mL)	27	8605.222 ± 1904.806
AUC _{0-∞} (hr.ng/mL)	27	9013.233 ± 1998.263
AUC%Extrap_Obs	27	4.527 ± 1.069
*T _{max} (hr)	27	3.00 (1.00-6.00)
T _{1/2} (hr)	27	7.239 ± 1.329
Kel (hr-1)	27	0.099 ± 0.021
VD (mL)	27	47470.874 ± 9809.280
CL (mL/hr)	27	4627.213 ± 918.305

Note: *Expressed in terms of median (range)

Sample size and power

For an expected mean difference of 5% between the formulations, with an expected intra subject CV: Olmesartan (16.5% for C_{max} and 16.3% for AUC) Hydrochlorothiazide (18.1% for C_{max} and 12.8% for AUC). Therefore, 21 subjects were required to prove bioequivalence at 0.90 power. Based on crossover design and considering possible dropouts due to expected adverse drug reaction (ADR), a sample size of 28 subjects were sufficient to establish bioequivalence between formulations. ISCV of C_{max} of hydrochlorothiazide was considered for sample size calculation (Figure 3).

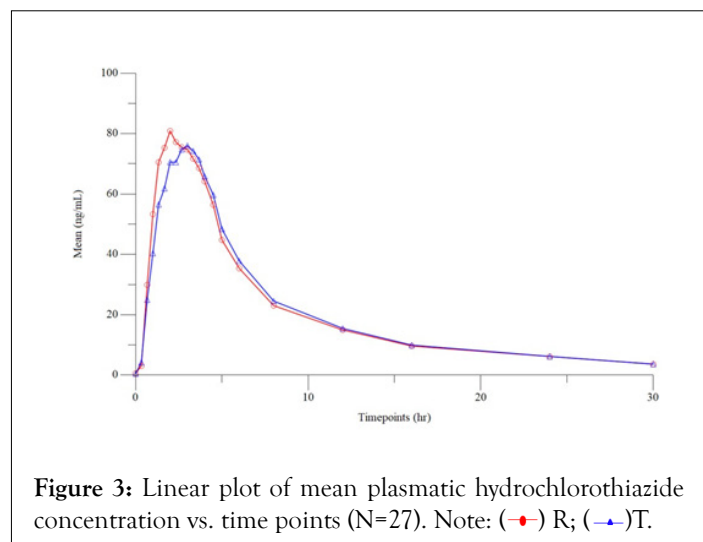


Figure 3: Linear plot of mean plasmatic hydrochlorothiazide concentration vs. time points (N=27). Note: (—♦—) R; (—■—) T.

Subjects drug administration and blood sampling

After an overnight fasting of 10 hours, subjects were administered with a single oral dose of either test product or reference product with 200 mL of water according to the sequence assigned to each subject in sitting posture in each period. Compliance to drug administration was assessed by examination of the oral cavity and hands of the subject immediately after dosing. All the subjects remained in sitting posture for 02 hours after dosing. During this restriction period, the subjects were permitted to walk for reasons such as but not limited to the following: natural exigencies. Subjects were restricted from consumption of water for 01 hour before and 01 hour after dosing in each period and allowed to drink water ad libitum thereafter. The pharmacokinetic profile of both test and reference products (in terms of rate and extent of absorption) were evaluated based on measured concentration of drug in the human plasma samples collected during the clinical phase. Blood samples for pharmacokinetic analysis were designed appropriately for characterizing the pharmacokinetic profile for the given treatments at the dose administered. A total of 21 Blood samples, of 04 mL each one, were collected at 00.00 (Pre-dose), 00.33, 00.67, 01.00, 01.33, 01.67, 02.00, 02.33, 02.67, 03.00, 03.33, 03.67, 04.00, 04.50, 05.00, 06.00, 08.00, 12.00, 16.00, 24.00 and 30.00 hours post dose for measurement of pharmacokinetic parameters. The samples collected were subjected to centrifugation and separated to 02 aliquots which were stored at -70°C. During bio analysis, the samples were thawed, and a validated method was used to analyse the samples. Olmesartan was selectively extracted from human plasma by Solid Phase Extraction as per in-house procedure and Hydrochlorothiazide was selectively extracted from human plasma by Liquid-Liquid extraction as per the in-house procedure. The plasma samples were quantified using a validated bio-analytical method in LCMS/MS (Table 6).

Table 6: Summary of pharmacokinetic parameters for hydrochlorothiazide of reference product-R.

Parameter	N	Reference (R) (Mean ± SD)
C _{max} (ng/mL)	27	91.584 ± 20.048
AUC _{0-t} (hr.ng/mL)	27	610.396 ± 128.850
AUC _{0-∞} (hr.ng/mL)	27	659.877 ± 143.138
AUC%Extrap_Obs	27	7.390 ± 1.870
*T _{max} (hr)	27	2.00 (1.00-4.00)
T _{1/2} (hr)	27	9.223 ± 1.110
Kel (hr-1)	27	0.076 ± 0.010
VD (mL)	27	263565.888 ± 67948.825
CL (mL/hr)	27	19872.234 ± 4592.973

RESULTS AND DISCUSSION

Tolerability

Subjects were monitored for adverse events during both periods of the study. Subjects were instructed to inform clinical personnel of any untoward medical symptoms and/or events that arose during the study. Each adverse event reported by the subjects during the study was assessed for its severity, relationship with the study drug and outcome of the adverse event. The Principal Investigator/sub-investigator/physician also evaluated the subjects for subsequent dosing. Subjects' Safety was assessed via continuous monitoring and scheduled recording of safety measurements throughout the study through clinical examinations, vital signs assessment, 12-lead

Electrocardiogram (ECG), Rapid COVID-19 antigen test, clinical laboratory parameters (e.g., Hematology, Biochemistry, Urine analysis and Serology test) and monitoring subjects' well-being, symptoms and signs for adverse events. All the subjects were assessed for their well-being throughout the conduct of the study. Two non-serious adverse events were reported by 02 subjects; one adverse event took place following administration of test product and the other occurred during the post study safety evaluation. There were no adverse events reported following administration of reference product and no serious adverse events were reported in this study. All adverse events resolved completely without any sequelae. The incidence of AEs in the study test product was (3.57%). The study medications were relatively well tolerated by the selected study population at the administered dose levels (Table 7).

Table 7: Summary of pharmacokinetic parameters for hydrochlorothiazide of test product-T.

Parameter	N	Test (T) (Mean ± SD)
C_{max} (ng/mL)	27	87.284 ± 18.021
AUC_{0-t} (hr.ng/mL)	27	609.334 ± 129.874
$AUC_{0-\infty}$ (hr.ng/mL)	27	658.852 ± 149.407
$AUC\%Extrap_Obs$	27	7.235 ± 2.235
* T_{max} (hr)	27	2.33 (1.00-3.67)
$T_{1/2}$ (hr)	27	9.023 ± 1.423
Kel (hr-1)	27	0.079 ± 0.012
VD (mL)	27	256622.061 ± 60251.354
CL (mL/hr)	27	19942.562 ± 4540.013

Pharmacokinetic and statistical analysis

The pharmacokinetic and statistical analysis of Olmesartan and Hydrochlorothiazide were performed using the concentration data obtained from 27 subjects who completed both the periods of the study. In order to test the two one-sided tests for bioequivalence, ratio analysis, 90% confidence intervals for the difference between treatments' least-square mean was calculated for Ln-transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of Olmesartan and Hydrochlorothiazide. Pharmacokinetic parameters were calculated using non-compartmental model of Phoenix® WinNonlin® version 8.3 and statistical analysis was carried out using the SAS® statistical software, version 9.4 of SAS Institute Inc, USA. The mean, standard deviation, standard error, geometric mean, coefficient of variation, minimum, median, maximum and range were calculated for C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , $t_{1/2}$, Kel, VD, CL and $AUC\%Extrap_Obs$ [8].

Twenty-eight subjects in the age group of 21 to 44 years, who met the study eligibility criteria, participated in the study and twenty-seven subjects completed the study. All the 28 subjects enrolled in the study were males and Asians. The recruitment of subjects to

the study was open for both male and female subjects. However, as only male subjects are interested to participate in this study, only male subjects were included. This does not impact the study as the test product is comparable with that of the reference product and is interchangeable. One subject withdrew his consent due to personal reason in period II, hence was withdrawn. The clinical study was conducted over a period of 05 days. Blood sampling was done at pre-defined intervals up to 30.00 hours in both the periods, separated by a washout period of 02 days. The pharmacokinetic plasma samples collected from 27 subjects were analysed to determine concentration of Olmesartan and Hydrochlorothiazide using a validated bio-analytical method in LCMS/MS.

The pharmacokinetic and statistical analyses of Olmesartan and Hydrochlorothiazide were performed using the concentration data obtained from 27 subjects who completed both the periods of the study. Olmesartan: The 90% confidence interval of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for Olmesartan were 96.45%-111.65%, 95.33%-108.79% and 95.35%-108.36% respectively, which were within the acceptable limits of 80.00 to 125.00% Hydrochlorothiazide: The 90% confidence interval of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for Hydrochlorothiazide were 90.15%-101.65%, 94.67%-105.86% and 94.53%-105.73% respectively, which were within the acceptable limits of 80.00 to 125.00%. The study was carried out in healthy male subjects. The tolerability of Olmesartan and Hydrochlorothiazide was already well established. As indicated in the package insert of the product, the study was conducted under fasting conditions. Olmesartan and Hydrochlorothiazide is expected to be less variable and the ISCV reported in the literature indicates the same. Hence, a conventional two-way crossover design was opted to evaluate the bioequivalence with optimal number of subjects. Washout period opted did not result in any carryover of the drug to subsequent period (Figure 4) (Tables 8 and 9) [9].

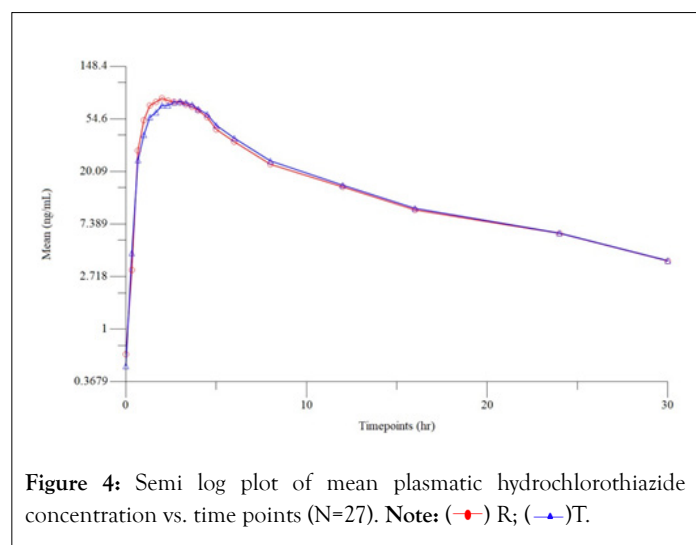


Figure 4: Semi log plot of mean plasmatic hydrochlorothiazide concentration vs. time points (N=27). Note: (—●—) R; (—▲—) T.

Table 8: p-Value for C_{max} and AUC of olmesartan.

Parameters	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	Significance
Sequence effect	0.475	0.6821	0.7346	Insignificant for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$
Period effect	0.3872	0.698	0.6663	Insignificant for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$
Treatment (Formulation) effect	0.3958	0.6419	0.6666	Insignificant for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$
Subjects nested within sequence effect	0.0004	0.0001	<0.0001	Significant for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$

Note: $p < 0.10$ for Sequence effect and $p < 0.05$ for all other effects considered to be significant

Table 9: p-Value for C_{max} and AUC of hydrochlorothiazide.

Parameters	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	Significance
Sequence effect	0.7497	0.9126	0.9814	Insignificant for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$
Period effect	0.3132	0.048	0.0329	Insignificant for C_{max} and Significant for AUC_{0-t} and $AUC_{0-\infty}$
Treatment (Formulation) effect	0.2256	0.9739	0.9933	Insignificant for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$
Subjects nested within sequence effect	0.0002	<.0001	<0.0001	Significant for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$

Note: $p < 0.10$ for Sequence effect and $p < 0.05$ for all other effects considered to be significant

CONCLUSION

Hence, the washout selected is considered adequate and accurate. Pharmacokinetic parameters estimated in the study are comparable with that of the published data. Abbott (sponsor) had included this study in the dossier submission for the generic drug approval in Chile. Bioequivalence was demonstrated between Olmesartan Medoxomil/Hydrochlorothiazide 40 mg/12.5 mg coated Tablets of Abbott and Olmetec Plus® (Olmesartan medoxomil/Hydrochlorothiazide) 40 mg/12.5 mg coated Tablets of Daiichi-Sankyo, in healthy, adult, human subjects under fasting condition.

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