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Bioequivalence Study of Two 80 Mg Valsartan Tablets Formulations in Healthy Chinese Subjects Under Fasting and Fed Condition

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Abstract

Objective: The purpose of this study was to compare the bioavalability between the two 80 mg Valsartan Tablets formulations and to evaluate the bioequivalence of Reference and Test formulations of Valsartan Tablets 80 mg in Healthy adult chinese Male and Female subjects under Fasting and Fed condition.

Methods: This study was designed as Open – Label, Randomized, Single centre, Four cycle, complete replicate cross over design for Fasting and Fed conditions. 32 healthy subjects were enrolled in each of the fasting and Fed trials, and were randomly divided into two groups to complete four cycles of administration in each study. The content of valsartan in human plasma was determined using liquid chromatography tandem mass spectrometry (LC-MS/MS), and the pharmacokinetic parameters were calculated based on a non-compartmental model using WinNonlin® 8.0, and bioequivalence was evaluated. Subjects were evaluated for relevant safety during the Study.

Results: The within-subject standard deviation (SD) of the reference product ($S_{WR)}$, for the pharmacokinetic (PK) parameters AUC and Cmax was found to be more than 0.294 under Fasting and Fed conditions. So, used the Reference-Scaled Bio Equivalence (RSABE) procedure to determine bioequivalence for the individual PK parameter(s). The 95% upper confidence bound was ≤ 0 and the Point Estimate of the Test / Reference geometric mean ratio for Pharmacokinetic parameters (AUC & Cmax) were all within the acceptable range of 0.80 – 1.25

Conclusion: The Test preparation of valsartan tablets developed by Zhuhai Rundu Pharmaceutical Co.; Ltd. is bioequivalent to the Reference Listed Drug (RLD) Diovan (Valsartan) Tablets of Novartis Pharmaceuticals Corp.

Keywords: Valsartan Tablets; LC-MS/MS; Bioequivalence

Introduction

Valsartan is a non-peptide angiotensin II receptor antagonist, which plays a key role in regulating systemic blood pressure and maintaining electrolyte balance in human body[1]. Valsartan tablets have the advantages of safety, long time effect, convenient administration, mild adverse reactions and low price, which provides good benefit for the hypertension patients. Besides, it was reported to be effective in congestive heart failure, left ventricular hypertrophy and acute myocardial infarction [1-3]. The purpose of this study was to evaluate the bioequivalence between valsartan tablets 80 mg developed by Zhuhai Rundu Pharmaceutical Co., Ltd. and Diovan Tablets 80 mg produced by Novartis Pharmaceuticals Corp. This result will provide evidence to market new valsartan Tablets formulation and to file application of the Valsartan reasonably.

Materials and Instruments

Materials

Test preparation T: Produced and provided by Zhuhai Rundu Pharmaceutical Co., Ltd (strength: 80mg, batch No.: 20200501).

Reference preparation R: Valsartan tablets (strength: 80mg, brand name: DIOVAN®, batch No.: AL9438C) Certificate holder is Novartis Pharmaceuticals Corp, and manufacturered by Patheon Manufacturing Services LLC.

Analyte: Valsartan (Source: China Institute of Food and Drug Control, Batch No.: 100651-201805, chemical purity: 98.6%), Internal standard: Valsartan--d3 (Source: Tornonto Research Chemicals Lot No.: 7-SBK-54-4, chemical purity: 98%, isotopic purity: 99.7%)

Instruments

Liquid chromatography Instrument: SHIMADZU LC-20AD (SHIMADZU, Japan); Mass spectrometer: AB SCIEX API 4000 (Applied Biosystems); High-speed refrigerated centrifuge: 5810R (Eppendorf); Ultra-low temperature freezer: U410 (Eppendorf).

Methods and Results

Subjects

The Ethics Review Committee at Dongguan People's Hospital reviewed and approved the study protocol. All subjects participating in this study have voluntarily signed the informed consent form. This study adopts a Open – Label, Randomized, Single centre, Four cycle, complete replicate cross over design. A number of 64 healthy subjects were enrolled for fasting and fed studies, each study included 32 subjects. Fasting study population have 24 male volunteers and 8 female volunteers between the ages of 18 to 36 years, 150.0 to 179.0 cm height, 45.1 to 76.5 kg weight and BMI between 19.9-25.8 kg/m^2. While fed study population have 26 male volunteers and 6 female volunteers between the ages of 18 to 36 years, 149.0 to 182.0 cm height, 48.9 to 79. 6kg weight and BMI between 19.2-26.0 kg/m^2. All the volunteers completed physical examination, laboratory examination and ECG examination, etc. All the examination results showed nornal. Besides, except studied drug, the subjects had not used any other medicines 14 days before the study and during the study period

Mode of Administration and Blood Sample Collection

Fasting study: 32 Subjects divided into two groups randomly, each group contains 16 subjects. After 7 days of washout period, all the subjects provided with a light diet in the night before this study and fasted for more than 10 hours. In the morning of the test

day, given the medicine with 240 mL warm water on an empty stomach. Valsartan blood samples were obtained at Time 0 (within 60 minutes pre-dose), 0.33h, 0.67h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 4.5h, 5h, 5.h, 6h, 7h, 8h, 10h, 12h, 24h, 36h, 48h of post dose.

For Fasting bioequivalence study with the following sequence assignments in a Full replicate 4-way crossover design was used

Sequence Name	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T

Fed study: 32 Subjects divided into two groups randomly, each group contains 16 subjects. After 7 days of washout period, all subjects provided with a light diet in the night before this study and fasted for more than 10 hours. On the morning of the test day, subjects were provided with a high-fat meal (within 30 minutes), and take the medicine with 240 mL warm water. Valsartan blood samples were obtained at Time 0 (within 60 minutes pre-dose), 0.33h, 0.67h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 4.5h, 5h, 5.h, 6h, 7h, 8h, 10h, 12h, 24h, 36h, 48h of post dose.

For Fed bioequivalence study with the following sequence assignments in a Full replicate 4-way crossover design was used

Sequence Name	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T

At each sampling time point,4 mL of blood samples was collected into heparin containing tubes. Then, those blood samples were centrifuged for 10 minutes at 2-8 °C and the plasma was decanted and stored at –20 °C until being checked for valsartan content.

Research methods

Chromatographic conditions and plasma sample processing

Chromatographic conditions: ZORBAX SB C_{18} Column (150 mm × 4.6 mm, 3.5 μm, Agilent); Mobile phase A: 5 mM ammonium acetate aqueous solution (containing 0.1% formic acid), Mobile phase B: Acetonitrile (containing 0.1% formic acid); Flow ratio: 3:7; Flow rate: 1 mL/min; Injection volume is 3.00 μL; Running time: 3.00min.

Mass Spectroscopy conditions: Ion source: ESI; Ionization mode: positive ion mode; Scanning mode: MRM; MRM ion pair: valsartan 436.5/235.2, valsartan d3 439.4/235.1.

Fig. 1 and Fig. 2 are Product ion scan patterns

Plasma sample processing: Take plasma sample 50 μL and add 450 μL internal standard solution, then vortex for about 1 min, followed by centrifugation at 4 ^{0}C for 10 minutes. Then, take 50 μL supernatant, in which add 150 μL acetonitrile - 5 mM ammonium acetate (containing 0.1% formic acid) and mix well for further analysis.

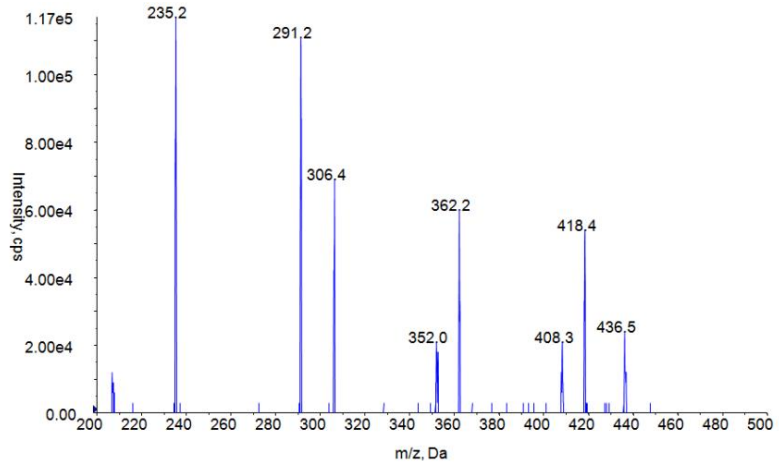


Figure 1: Valsartan (436.5/235.2) Product ion scan

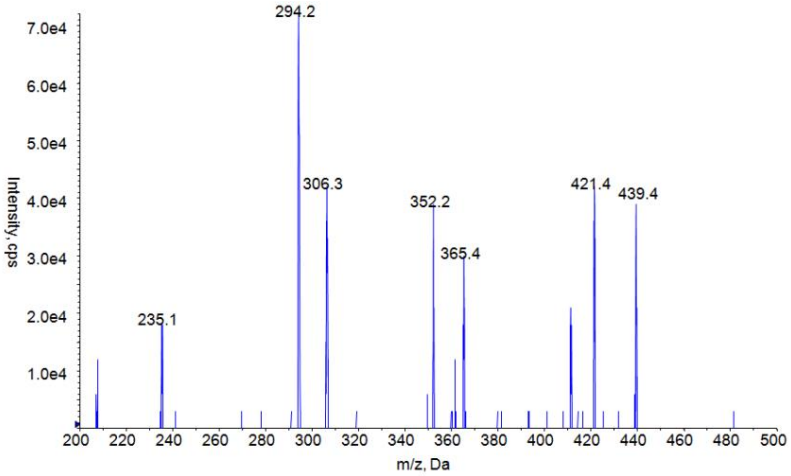
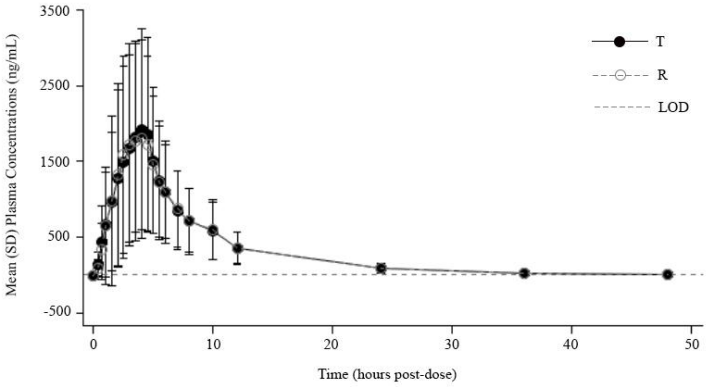


Figure 2: Valsartan – d3 (439.4/235.1) Product ion scan

Results

Plasma Concentration Curve

According to the descriptive statistical analysis results of the drug concentration of subjects at each time point and the corresponding charts, it can be concluded that the test preparation and the reference preparation have similar average drug absorption curves under the fasting and Fed conditions. The relevant plasma drug concentration-time curves are shown in Fig. 3 and Fig. 4.

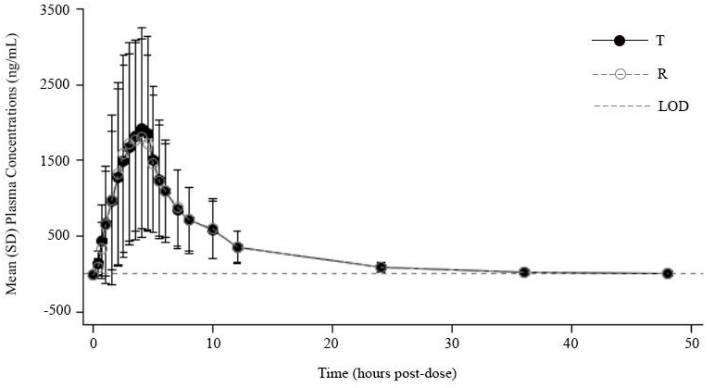


Note: T=Test formulation – Valsartan Tablets 80 mg.

R=Reference formulation Diovan® (Valsartan) Tablets 80 mg.

LOD = < 10 ng / ml

Figure 3: Mean (±SD) Valsartan Plasma concentration – Time profile under Fasting



Note: T=Test formulation – Valsartan Tablets 80 mg.

R=Reference formulation Diovan® (Valsartan) Tablets 80 mg.

LOD = < 10 ng / ml

Figure 4: Mean (±SD) Mean (±SD) Valsartan Plasma concentration – Time profile under Fed

Pharmacokinetic Parameters

By using WinNonlin®8.0 software with non-atrioventricular model method, Pharmacokinetic parameters were calculated according to actual plasma collection time and all subjects were included in the Pharmacokinetic paramters analysis set. The pharmacokinetic parameter list and its descriptive statistical analysis results are shown in Table 1 and Table 2.

Parameters(Units)	Arithmetic mean ± SD (%CV)	
	Test preparation	Reference preparation
Tmax*(*h*)	4.00 (0.996,8.00)	3.50 (1.50,6.00)
Cmax (*ng/mL*)	2220 ± 1380 (62.3%)	2160 ± 1410 (65.3%)
AUC_{0-t} (*ng·h/mL*)	14700 ± 8340 (56.7%)	14700 ± 8520 (57.8%)
$AUC_{0-\infty}$ (*ng·h/mL*)	14900 ± 8380 (56.1%)	15000 ± 8570 (57.2%)
λ_z (h^{-1})	0.101 ± 0.0284 (28.1%)	0.0968 ± 0.0267 (27.6%)
$t_{1/2}$ (*h*)	7.57 ± 3.07 (40.6%)	7.96 ± 3.44 (43.3%)

Table 1: Pharmacokinetic parameters of test and reference preparations under Fasting

Parameters(Units)	Arithmetic mean ± SD (%CV)	
	Test preparation	Reference preparation
T_{max} (*h*)	4.00 (0.996,10.0)	4.25 (0.996,10.0)
C_{max} (*ng/mL*)	982 ± 392 (39.9%)	1160 ± 575 (49.6%)
AUC_{0-t} (*ng·h/mL*)	7250 ± 3250 (44.8%)	7760 ± 3410 (44.0%)
$AUC_{0-\infty}$ (*ng·h/mL*)	7440 ± 3290 (44.3%)	9070 ± 8890 (98.0%)
λ_z (h^{-1})	0.109 ± 0.0239 (22.0%)	0.112 ± 0.0293 (26.2%)
$t_{1/2}$ (*h*)	6.75 ± 1.82 (27.0%)	7.54 ± 8.32 (110%)

*Tmax is indicated with medians (minimum, maximum).

Table 2: Pharmacokinetic parameters of test and reference preparations under Fed

Evaluation of Bioequivalence

Valsartan is a highly variable drug, Referenced-Scaled Bioequivalence (RSABE) method was used to evaluate its bioequivalence [4-5]. RSABE method calculated the S_{WR} of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of valsartan in fasting and Fed were 0.4717, 0.3471, 0.3316 and 0.4413, 0.3063, 0.2999, respectively, and all the SWR>0.294. Therefore, the Bio equivalence evaluation of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ in fasting and Fed condition adopted RSABE method.

The 95% upper confidence bound for C_{max}, AUC0-t and AUC0-∞ of the Fasting condition were -0.1219, -0.0642 and -0.0582, respectively. And the 95% upper confidence bound for all is ≤ 0 and the Point Estimate of the Test / Reference geometric mean ratio of Cmax, AUC_{0-t} and $AUC_{0-\infty}$ are 1.01, 0.98 and 0.98, respectively. These fasting group parameters were well within the predefined equivalence boundaries (detailed results were shown in Table 3). The 95% upper confidence bound for C_{max}, AUC_{0-T} and $AUC_{0-\infty}$ of Fed condition were -0.0652, -0.0321 and -0.0315, respectively. And the 95% upper confidence bound for all is ≤ 0 and the Point Estimate of the Test / Reference geometric mean ratio of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are 0.86, 0.90 and 0.90 respectively. These Fed group parameters were well within the predefined equivalence boundaries (detailed results were shown in Table 4). The above results indicated that the Test formulation met the requirement of bioequivalence with Reference formulation under fasting and fed conditions.

Parameters (Units)	ABE			RSABE			Result
	Ratio (%)	90% confidence limits	Reference preparations Intra-CV%	Swr (≥0.294)	Point Estimate [0.80 - 1.25]	Critical Bound ≤ 0	
$AUC_{0-\infty}$ (*ng·h/mL*)	97.6	89.42 - 106.52	34.09	0.3316	0.98	-0.0582	Bioequivalent
AUC_{0-t} (*ng·h/mL*)	97.85	89.20 - 107.33	35.78	0.3471	0.98	-0.0642	Bioequivalent
Cmax (ng/mL)	101.05	90.41 - 112.95	49.92	0.4717	1.01	-0.1219	Bioequivalent

Table 3: Bioequivalence results of valsartan tablets taken under Fasting condition

Parameters (Units)	ABE			RSABE			Result
	Ratio (%)	90% confidence limits	Reference preparations Intra-CV%	Swr (≥0.294)	Point Estimate [0.80 - 1.25]	Critical Bound≤ 0	
$AUC_{0-\infty}$ (*ng·h/mL*)	90.26	84.19 - 96.77	30.68	0.2999	0.90	-0.0315	Bioequivalent
AUC_{0-t} (*ng·h/mL*)	89.90	83.66 - 96.60	31.36	0.3063	0.90	-0.0321	Bioequivalent
C_{max} (*ng/mL*)	86.19	76.88 - 96.63	46.37	0.4413	0.86	-0.0652	Bioequivalent

Table 4: Bioequivalence results of valsartan tablets taken under Fed condition

Discussion

In this study, liquid chromatography-mass spectrometry (LC-MS/MS) was used to determine valsartan concentration in plasma. This method has the advantage of rapid, specific and accurate [6-7].

According to the analysis of the study data, there were significant differences in the absorption of valsartan within individual subjects, and the individual coefficients of variation of Cmax, AUC0-t and AUC0-∞ in fasting and Fed studies were all > 30%, meeting the standards of high variation drugs. In particular, the intra-individual coefficient of variation of Cmax was large. The intra-individual coefficient of variation of fasting study Cmax was 49.92%, and Fed study Cmax was 46.39%, which was basically consistent with literature reports [8-11]. To reduce the bioequivalent risk of highly variable drugs, 64 healthy Chinese subjects were enrolled in this study using Open – Label, Randomized, Single centre, four cycle, complete replicate cross over design for Fasting and Fed conditions. After the subjects adminstrated with valsartan tablets on fasting and Fed conditions, the variation trend of the plasma concentration of the test product and the reference product over time was similar, and the main pharmacokinetic parameters Cmax and AUC of the two preparations met the standards through equivalence analysis, indicating that the two preparations were bioequivalent. In addition, the time to reach peak plasma concentrations was longer in the Fed condition in comparison with Fasting for both the test preparation and the reference preparation. The Cmax and AUC of plasma concentration in the Fed study were significantly lower than fasting study, indicating that food may have a greater impact on the

rate and extent of absorption of valsartan in the human body.

Conclusion

Since, The within-subject standard deviation (SD) of the reference product ($S_{WR)}$, for the pharmacokinetic (PK) parameters AUC and Cmax was found to be more than 0.294 under Fasting and Fed conditions. So, used the Reference-Scaled Bio Equivalence (RSABE) procedure to determine bioequivalence for the individual PK parameter(s).The 95% upper confidence bound was ≤ 0 and the Point Estimate of the Test / Reference geometric mean ratio for Pharmacokinetic parameters (AUC & Cmax) were all within the acceptable range of 0.80 – 1.25 under fasting and fed conditions, which is in line with the limits proposed by Drug regulatory bodies for Highly Variable drugs. The Test preparation of valsartan tablets developed by Zhuhai Rundu Pharmaceutical Co.; Ltd. is bioequivalent to the Reference Listed Drug (RLD) Diovan (Valsartan) Tablets of Novartis Pharmaceuticals Corp.

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