

Bioequivalence Study of Two Valsartan 160 mg Formulations: An Open-Label, Randomised-Sequence, Single-Dose, Two-Way Crossover Study in Healthy Volunteers under Fasting Conditions

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Abstract

The aim of the study was to evaluate the rate and extent of absorption of a local generic valsartan formulation against that of the innovator product (reference formulation) in order to establish bioequivalence between both products. The study was an open-label, randomised-sequence, single-dose, two-way crossover study in 24 healthy volunteers under fasting conditions. The washout period was set at 7 days between the two treatment periods. Blood samples were collected up till 24-hour post dose. Plasma level of valsartan was determined by high performance liquid chromatography with fluorescence detector. Non-compartmental model was used to analyse the pharmacokinetic parameters, which included T_{max} , C_{max} , AUC_{0-1} , $AUC_{0-\infty}$, $t_{1/2}$ and k_e . Analysis of variance (ANOVA) was used to analyse values of C_{max} , AUC_{0-1} , $AUC_{0-\infty}$, and k_e , while Wilcoxon Signed Rank Test for paired samples was used to analyse T_{max} . Tolerability of the test formulation was assessed throughout the study. All parameter assessed were found to be within the acceptable limit of 80.00% to 125.00%. No adverse event was reported. In conclusion, the test formulation was bioequivalent to the reference formulation, based on the rate and extent of absorption of both products.

Keywords: Bioequivalence; Generic; Valsartan; Angiotensin receptor blocker; Hypertension

Introduction

Valsartan is an antagonist to the angiotensin type I receptor (AT1), of which plays an integral role in hypertension [1]. The renin angiotensin aldosterone system (RAAS) produces an effector compound called angiotensin II, where it mediates its effect through the stimulation of AT1 and AT2 receptors. Angiotensin receptor blockers (ARBs) are recommended as alternative treatments to patients who are intolerant to ACE inhibitors and who has suffered acute myocardial infarction with a left ventricular ejection fraction less than 40%, or clinical (or radiological) evidence of heart failure [2].

Valsartan is a non-heterocyclic, potent, and orally active antagonist to the AT1 receptors (IC_{50} of 2.7 nmol/L on rat aorta) [3]. It is rapidly absorbed after ingestion but has low absolute bioavailability. Administration of valsartan together with food reduces the extent of drug absorption by approximately 50%. Valsartan is highly bound to plasma protein, particularly albumin. It is largely eliminated in faeces, with an average elimination half-life of 6 hours [4].

Malaysia practices a universal healthcare system whereby all citizens' healthcare expenses are largely covered by the Ministry of Health. While the system is beneficial to the public, the consequential financial burden is significant. The Ministry had launched the National Strategic Plan for Non Communicable Diseases in 2010 to combat the increasing disease burden, particularly hypertension [5,6].

ARBs such as valsartan are recommended by clinical practice guidelines to treat hypertension [5]. However the innovator product is relatively expensive to allow optimum use among patients especially those who are economically under privileged. A generic product is a suitable alternative to both physicians and patients in the management of the disease.

This study aimed to evaluate the rate and extent of drug absorption of a generic formulation of valsartan 160 mg tablet (test formulation, manufactured by Hovid Limited, Perak, Malaysia) against that

of a reference formulation (Diovan[®], manufactured by Novartis Pharmaceutica S.A., Spain) in order to assess bioequivalence.

Methods

Study protocol

The study was approved by the Malaysian Medical Research Ethics Committee (MREC), and was conducted in accordance to the Malaysian Good Clinical Practice (GCP) Guideline. Informed consent was obtained from all study participants before commencement of any trial related procedures. Study centres included a clinical facility situated at the Clinical Research Centre, Seberang Jaya Hospital (Penang, Malaysia) and the bioanalytical laboratory at the University Sains Malaysia (Penang, Malaysia).

Participants

All study participants were recruited at the clinical research centre by GCP-certified investigators, and were deemed eligible to participate in this study. The inclusion criteria were male between the age of 21 to 55, within 20% of ideal body weight for height and build according to the Metropolitan Life Insurance Company Standard, or body mass index between 18.5 to 29.9, in good health and physical condition as determined by medical history and laboratory test. Laboratory tests conducted included the following: renal function test (serum, creatinine

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, blood, urea and nitrogen), liver function test (total protein, total albumin, total globulin, total bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT), full blood count (haemoglobin, red cell count, haematocrit, total white cell count and platelet), and fasting blood glucose test. All participants had demonstrated ability to read, understand, and sign the informed consent form.

The exclusion criteria included significant clinical deviation from normal as determined by investigators, a history or suspicion of drug dependence and/or alcohol abuse, requirement of tranquilizers, sedatives, chronic medications (for hypertension and diabetes, anti-platelet agents, anti-epileptics, analgesics, opioids, psychotropics, antibiotics, monoamine oxidase inhibitors), a history or presence of organ dysfunction, history or presence of bone-marrow depression, serious blood disorders, cardiac arrhythmias, cardiovascular disease, stroke, bronchospasm, diabetes mellitus, renal diseases, liver diseases, thyrotoxicosis, parkinsonism, benign prostatic hypertrophy, epilepsy or migraine, and malignancy. Volunteers were excluded if they had hypersensitivity to valsartan or any other angiotensin II antagonists, participated in any bioequivalence study or donated blood for the past 8 weeks, who were heavy smokers (more than 10 cigarettes a day), or unable to understand and/or comply to the study protocol or to give consent.

Vital signs of all participants were taken during screening and throughout the study period. These included blood pressure, heart rate, respiratory rate, and body temperature taken in sitting position.

Study design

The study was an open-label, randomized-sequence, single-dose, two-way crossover study in healthy volunteers under fasting conditions. In accordance to FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations [7], it was recommended that bioequivalence studies for immediate-release products should be conducted under fasting conditions. Similarly, for EMA Guideline on the Investigation of Bioequivalence [8], it was also recommended to conduct bioequivalence studies under fasting conditions when the Summary of Product Characteristics of Valsartan recommended administration of the medicine irrespective of food intake.

The participants were divided into two groups where the first group received the test formulation during phase I of the study and the reference formulation during phase II. Second group of participants received the reverse order of test/reference formulation. There was a minimum 7 days washout period between the two phases of the study. To maintain consistency of the formulation, both test and reference formulations were taken from the same manufacturing batch (test formulation: batch number BE05598, expiry date: May 2017; reference formulation: batch number B8324, expiry date: September 2014). The excipients used to formulate the test products were general excipients used in tablet formulation, which included fillers, binders, disintegrant and lubricant, in similar quantity and quality to that of the reference products. There was no expected interaction with the pharmacokinetic of the active substance.

The clinical study was initiated on the 24th May 2014 and completed on 1st June 2014. Subsequent analysis of plasma samples, statistical analysis and report preparation were completed on the 4th July 2014.

All participants were confined in the clinical facility and were required to undergo a 10-hour fasting prior to dosing. One dose of

either the test or reference formulation was administered by a qualified pharmacist with 240 ml of plain water. Participants were not allowed any water for 1 hour before and 1 hour after dosing, except the water used for drug administration. Food was withheld for at least 4 hours post dosing. Standardized, calorie-counted meals were provided at 4 and 10 hours after dosing, while standardized snacks were provided at 8 and 13 hour post dosing. Based on the T_{max} and $t_{1/2}$ of valsartan, the blood samples were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after drug administration. 5% deviation from the scheduled blood sampling time was allowed before being considered as protocol deviation.

A total volume of 157 ml of blood (75 ml during each phase, and 7 ml for blood chemistry analysis) were taken from each participants. The collected blood samples were subsequently centrifuged at 3500 rpm for 15 minutes. Plasma samples were transferred to separate glass containers where they were kept frozen at -20°C until analysis.

The sample size of participants was estimated by using the intrasubject coefficient of variation (CV) [9]. However due to the lack of data on intrasubject CV of valsartan, the number of required participants was estimated from previous bioequivalence studies as well as the bioavailability of valsartan. A recent study by Sioufi et al. which investigated the effect of age on valsartan pharmacokinetic reported a high coefficient of variation, ranging from 41-66% [10]. In addition, valsartan had low absolute bioavailability of approximately 25% [11] which may result in high intersubject variability. It was estimated that the study conducted with 24 participants would be able to achieve a statistical power of at least 80%, assuming the $\mu T/\mu R$ would not deviate by more than 5% and the CV would not exceed 20%.

Randomization and blinding

The participants were randomised into the test and reference group by using the randomisation program named Random Allocation Software developed by Sagnaie (2004).

The study was an open-label trial, where the investigators and participants knew the type of the formulations administered at each study phase. However, the randomisation list was not available to the bioanalytical team at the University Sains Malaysia until the analysis was completed.

Drug analysis

High performance liquid chromatography (HPLC) with Fluorescence Detector were used to analyse the plasma valsartan concentration. The system comprised of a Waters 600E Multisolvant Delivery System (Waters, Maple Street Milford, USA), a Waters 717 Plus Autosampler (Waters, Maple Street Milford, USA), and a Waters 2475 Multi λ Fluorescence Detector (Waters, Maple Street Milford, USA). Data acquisition and analysis were performed with EmpowerTM2 software (Waters, Maple Street Milford, USA).

The separation was performed on a Genesis C_{18} analytical column (150 \times 4.6 mm, 4 μ m; Grace Davison Discovery Sciences, Illinois, USA), with refillable guard column (2 mm \times 2 mm; Upchurch Scientific, Oak Harbor, USA) packed with Perisorb RP-18 (30-40 μ m, pellicular). The column was maintained at 23°C. The mobile phase was a mixture of 50.0% acetonitrile in 0.01M disodium hydrogen phosphate buffer, adjusted to pH3.5 with 85% phosphoric acid. The chromatographic separation was performed isocratically with a flow rate of 1.0ml/min. The fluorescence detector was operated at excitation wavelength of 234nm and emission wavelength of 374nm, with sensitivity set at 10000

EUFS. Injection volume was 20ml and samples were quantified using peak area.

Tolerability

Vital signs, i.e. blood pressure, pulse rate, respiratory rate and temperature were measured at pre-dose and 4h, 10h, and 24h post-dose. Subjects were asked to report any discomfort or adverse events at any time during the study period and at discharge.

Pharmacokinetic analysis

The pharmacokinetic analysis of valsartan involved the interpretation derivation of several parameters, namely, maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}) and the total area under the plasma concentration-time curve ($AUC_{0-\infty}$). These parameters were derived from the plasma concentration-time data. C_{max} and T_{max} were obtained directly from the plasma values, while AUC_{0-t} was calculated using the trapezoidal formula and $AUC_{t-\infty}$ was obtained by dividing the last measurable plasma drug concentration with the elimination rate constant (k_e). $AUC_{0-\infty}$ was obtained by summing both values of AUC_{0-t} and $AUC_{t-\infty}$.

The elimination rate constant, k_e , was derived from the terminal slope of the individual, logarithmic (ln) transformed, plasma concentration values (at least three concentration values were used) and the application of linear regression. The half-life of valsartan ($t_{1/2}$) was calculated with the following equation: $t_{1/2} = \ln 2/k_e$ [12].

Statistical analysis

Commercial statistical software, EquivTestPK, was used to perform analysis of the pharmacokinetic parameter (Statistical Solution, Cork, Ireland). Analysis of variance (ANOVA) was used to analyse C_{max} , AUC_{0-t} , $AUC_{0-\infty}$ and k_e because it can distinguish the effects due to participants, periods, and treatment [13]. Wilcoxon Signed Rank Test for paired samples was used for analysis of T_{max} .

Bioequivalence was assessed based on the ratio of the C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ values of test-versus-reference formulation. The 90% confidence intervals were calculated using the two one-sided test procedure where $\alpha = 5\%$ level of significance [14]. The 90% confidence interval of the ratio of C_{max} , AUC_{0-t} and $AUC_{t-\infty}$ should fall between 80.00-125.00% (transformed values) [8]. The Malaysian Guideline for Conduct of Bioavailability and Bioequivalence Studies stipulated a similar range for AUC_{0-t} and $AUC_{t-\infty}$, but allow a wider range for C_{max} when it was appropriately justified [15].

Results

Study participants

The demographic characteristics of study participants were evaluated as shown in Table 1.

All 24 participants successfully completed both phases of the study and plasma samples were used for pharmacokinetic analysis. A total of two minor protocol deviations were observed: (1) minor delay of more than 5% in the blood sampling time for subject S6 at 0.5 hour during phase I (2) omission of blood sampling for subject S23 at 5 hour during phase I. For the first deviation, the actual sampling time was used for the calculation of pharmacokinetic parameter and for the second deviation, the AUC_{4h-6h} was calculated using the trapezoidal formula with the plasma concentration obtained from 4 hour to 6

hour. All deviation were deemed unlikely to adversely affect the study results and conclusion of the study. There was no deviation during the bioanalysis procedure. No serious adverse drug reaction or side effects were reported by the participants nor observed by investigators during the study periods.

Pharmacokinetic and bioequivalence analysis

Mean plasma valsartan concentration versus time profile for both test and reference formulation were shown in Figure 1; the pharmacokinetic parameter were listed in Table 2.

Both formulations displayed similar concentration-time profile with comparable T_{max} and C_{max} , when both profiles were superimposed. No statistical difference was observed between the logarithmic transformed values of AUC_{0-t} ($p=0.9488$), $AUC_{0-\infty}$ ($p=0.7863$) and C_{max} ($p=0.4695$) when analysed with ANOVA procedure appropriate for the study design. For parameter T_{max} , no statistically significant difference was observed as well ($p=0.5781$).

The 90% confidence interval of the ratio of test over reference formulation for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were 0.9089-1.1778, 0.9238-1.1819, and 0.9590-1.2436 respectively, which were within the acceptable bioequivalence limit of 0.8000-1.2500.

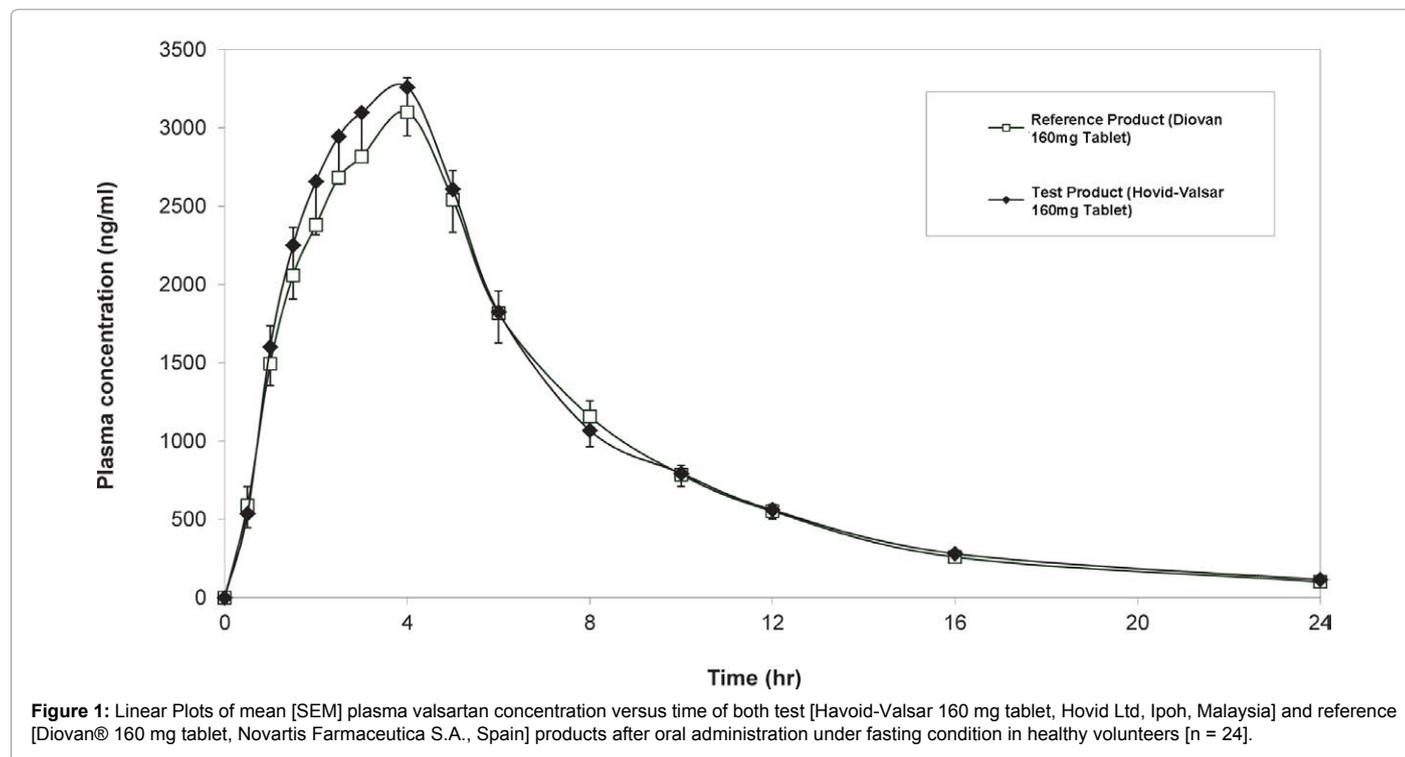
Analysis of plasma valsartan concentration

The analysts who performed the analysis were blinded to the treatment randomisation, and all analysis were performed under Good Laboratory Practice environment. Plasma samples were pre-treated with the following procedure prior to analysis: frozen plasma samples were thawed at room temperature. 250 ml aliquot of the plasma was measure accurately into a 1.5 ml micro centrifuge tube, with the addition of 500 μ l of acetonitrile. The mixture was then vortex-mixed for 30 seconds, then subjected to centrifugation for 10 minutes at 12800 g. Another 10 μ l of 70-72% perchloric acid was then added into the mixture, and the mixture was vortex-mixed for 15 seconds. After that the mixture was centrifuged for 5 minutes at 12800 g. 20 μ l of the supernatant layer was then injected into the column.

The analytical method was validated in accordance to the US FDA guidance for industry on bioanalytical method validation [16]. The parameters assessed were (1) selectivity (2) linearity and range of calibration curve (3) accuracy, precision and recovery and (4) stability of analyte. The method was selective and had linearity over the concentration range of 100.0-7500.0 ng/ml (correlation of coefficient, $r \geq 0.9998$). Accuracy was expressed as the percentage of measured

Characteristic	Value (n=24)
Age, y	
Median	27
Interquartile Range	9.0
Race, no. (%)	
Malay	22 (91.6)
Indian	1 (4.2)
Other	1 (4.2)
Height, cm	
Median	169
Interquartile Range	8.5
Weight, kg	
Median	70
Interquartile Range	18.0
Body mass index, kg/m ²	
Median	24
Interquartile	7.2

Table 1: Baseline demographic characteristic of 24 volunteers.



Pharmacokinetic Parametre	Test Formulation	Reference Formulation
AUC _{0-t} , ng • h /ml Mean (SD)	23180 (9969.7)	22318 (7715.6)
AUC _{0-∞} , ng • h /ml Mean (SD)	24756 (10486.6)	23608 (8187.5)
C _{max} , ng/ml Mean (SD)	3911 (1637.1)	3567 (1259.0)
T _{max} , hr Mean (SD)	3.08 (1.007)	3.21 (1.343)
K _e , hr ⁻¹ Mean (SD)	0.13 (0.045)	0.15 (0.052)
t _{1/2} , hr Mean (SD)	5.71 (1.819)	5.11 (1.689)

SD, standard deviation, AUC_{0-t}, area under the plasma-concentration curve from dosing to last quantifiable time point; AUC_{0-∞}, area under the plasma-concentration curve from dosing to infinity; C_{max}, peak plasma concentration; T_{max}, time to reach peak plasma concentration; K_e, elimination rate constant; t_{1/2}, half-life

Table 2: Pharmacokinetic parametres of the test valsartan formulation versus the reference formulation after ingestion of one 160mg tablet under fasting condition.

concentration over that of the spiked value, and precision was denoted using coefficient of variation. For within-day validation, both the mean measured concentration and coefficient of variation did not exceed 15% for all concentration, and did not exceed 20% at LLOQ. The accuracy for within-day validation did not deviate by more than ± 6.5%, and at LLOQ deviated by 17.3%; for between-day validation, mean measured concentration did not deviate more than ± 4.8%, and at LLOQ only deviated by 14.9%. The coefficient of variation values were not more than 1.3% for all concentration for within-day validation, and not more than 4.2% for between-day validation. The limit of quantification was set at 100.0 ng/ml. The absolute recovery of valsartan ranged from 87.6-97.7%.

Tolerability analysis

There were no reported or observed adverse reactions throughout the study period.

Discussion

The study was designed and conducted in accordance to the European Medicines Agency Guideline on the Investigation of Bioequivalence and the Malaysian Guidelines for the Conduct of Bioavailability and Bioequivalence Studies. According to the guidelines, the design of the current study was fit for the purpose to distinguish the formulation effect from other effects [8]. Previous literature reports of valsartan half-life varied from approximately 6 hours to 11 hours [3,17,18], which correlated with the half-life found in this study. This had reinforced that the washout period had adequately separated the two treatment periods to allow the valsartan concentration in all participants to fall below the lower limit of bioanalytical quantification before the second phase of the study (> 28 half-lives). The sampling times were adequate to characterise the plasma concentration-time profile, providing reliable estimation of the rate (T_{max} and C_{max}) and extent of valsartan absorption (AUC_{0-t} covered at least 80% of AUC_{0-∞}).

High variability was reported in previous valsartan studies [17,19,20]. In this study the intra-subject variation for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were calculated as 29.7%, 27.5% and 33.2% respectively. A total of 24 subjects who participated in the study was sufficient to provide a power of approximately 70% for concluding that these two formulations are equivalent at a type 1 error rate of 0.05, if the true difference is equal or less than 20% [9].

The sample size of the study was deemed insufficient to generate > 80% power. However this power refers to the manufacturer's risk of erroneously concluding bioequivalence when the two formulations were indeed bioequivalent. The consumer's risk of erroneously accepting bioequivalence remained unchanged at 5% level (type I error) [9].

Conclusion

This study had concluded that the test formulation is bioequivalent to the reference formulation, and had met the Malaysian regulatory definition of bioequivalence based on the rate and extent of absorption of a single dose administered under fasting condition.

Acknowledgement

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Declaration of Personal Interest

Kah Hay Yuen was the advisor to the R&D department of Hovid Ltd, the manufacturer of the test formulation. Siew Siew Tan, Jia Woei Wong, Siaw Kuen Chin, Ai Boey Lim and Ean Peng Soon were employees to Hovid-Research Sdn Bdn, an independent research company which was affiliated with Hovid Ltd. Wen Yao Mak and Irene Looi did not have any conflict of interest to disclose.

Declaration of Funding Interest

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