# Pharmacokinetic Properties and Bioequivalence of 2 Formulations of Valsartan 160-mg Tablets: A Randomized, Single-Dose, 2-Period Crossover Study in Healthy Korean Male Volunteers

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## ABSTRACT

**Background:** The solubility of valsartan is dependent on pH and thus may cause patient variability in drug absorption and failure in bioequivalence studies; thus, increasing the solubility and release of valsartan at low pH has been suggested for a more favorable pharmacokinetic profile. However, due to this pH dependence, the change in the formulation process could alter the disintegration and/or dissolution profile of the drug, possibly making the results of bioequivalence studies misleading.

**Objective:** The aim of this study was to assess the bioavailability and tolerability of a newly developed oral formulation of valsartan 160 mg (wet-granulation tablet) in healthy Korean male volunteers.

**Method:** This study was performed with the subjects under fasted conditions, using a randomized, single-dose, 2-period crossover design. Subjects were assigned to receive, in randomized order, a single dose of the test formulation and a reference formulation (valsartan 160-mg dry-granulation tablet), with a washout period of 7 days between the administrations. Blood samples were collected up to 24 hours after dosing, and pharmacokinetic parameters were determined after the plasma valsartan concentration was analyzed using UPLC-MS/MS. The dissolution studies of both formulations were conducted using USP apparatus 2 at 50 rpm with 1000 mL of phosphate buffer solution (pH, 6.8) at 37°C ± 0.5°C. Bioequivalence was defined per Korean Food and Drug Administration's regulatory criteria as 90% CIs of the geometric mean test/reference ratios of $AUC_{0-t}$ and $C_{max}$ within the range of 0.8 to 1.25. Tolerability was assessed using physical examination and subject interviews.

**Results:** Sixty subjects were enrolled (mean [SD] age [range], 23.6 [2.4] years [21–31]; height, 173.7 [6.6] cm [161–190]; and weight, 68.0 [8.7] kg [54–85]). The mean $AUC_{0-\infty}$ values with the test and reference tablets were 31,784 (13,844) and 32,714 (14,512) ng · h/mL, respectively; $C_{max}$, 5094 (2061) and 5064 (1864) ng/mL; $T_{max}$, 2.92 (1.04) and 3.08 (1.01) hours. The 90% CIs for the geometric mean test/reference ratios of $AUC_{0-t}$ and $C_{max}$ were 0.9295 to 1.0546 and 0.9190 to 1.0848, respectively, which met the criteria for bioequivalence. The most frequently reported adverse event was dizziness after blank blood sampling, recorded in 4 subjects, 2 cases each with the test and reference formulations.

**Conclusions:** In this study in healthy Korean male volunteers, the test and reference formulations of 160-mg valsartan met the Korean Food and Drug Administration's regulatory criteria for bioequivalence despite the difference in formulation (wet granulation vs dry granulation). Both formulations were well tolerated, with no serious adverse events reported. (*Clin Ther*. 2014;36:273–279) 

**Key words:** bioequivalence, Korean male volunteer, pharmacokinetic, valsartan, wet granulation.

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## INTRODUCTION

Valsartan is a highly selective angiotensin II type 1 receptor antagonist and is widely used for the treatment of hypertension.[1] Valsartan has a half-life of 6 to 9 hours and is administered at a dose of 80 or 160 mg/d.[2] Valsartan has rapid absorption after oral administration but has low bioavailability of ~25% due to its poor solubility in the acidic environment of the gastrointestinal tract.[3] Orally administered valsartan is primarily eliminated in the feces (~83% of dose) and urine (~13% of dose).[4] The solubility of valsartan is dependent on pH and thus may cause subject variability in drug absorption and failure in bioequivalence studies.[5] Thus, increasing the solubility and release of valsartan at low pH has been suggested to be helpful for a more favorable pharmacokinetic profile.[6] However, due to this pH dependence, the change in the formulation process could alter the disintegration and/or dissolution profile of the drug, possibly making the results of bioequivalence studies misleading. The aim of the present study was to compare the pharmacokinetic properties and bioavailability of a newly formulated generic tablet with that of the branded tablet in healthy Korean male volunteers.

## PATIENTS AND METHODS

### Inclusion and Exclusion Criteria

This bioequivalence study was conducted at Metro Hospital (Anyang, Gyeonggi-do, Republic of Korea) in healthy Korean male volunteers selected from a pool of volunteers aged 20 to 55 years based on the results of physical and clinical pathology examinations and medical history. Subjects were excluded if they had hypersensitivity to any ingredient in the valsartan tablets; were receiving any other medicine that could have interfered with the study results within 10 days before the start of the trial; had taken a metabolic enzyme inducer or inhibitor (eg, barbiturates) within 1 month before study initiation; had excessive alcohol intake; or had severe renal, hepatic, or biliary obstruction. In addition, subjects were considered as unsuitable for the bioequivalence test by the medical physician if they had been previously involved in another bioequivalence study or clinical trial within 3 months before the test initiation. Before the study, the principal investigator explained the purpose, the methods, and the possible adverse drug reactions of this study to the subjects and received a signed informed-consent form, which was preapproved by the committee of the hospital, according to the Korean Food and Drug Administration (KFDA) guidelines.[7]

### Study Design

This study was performed with subjects under fasted conditions using a randomized, single-dose, 2-period crossover design and 2 × 2 Latin square method.[8] The protocol was approved by the Metro Hospital institutional review board and complies with the Declaration of Helsinki.[9]

The volunteers were assigned to receive the 2 formulations in randomized order. One group was administered with the test tablet* first, followed by the reference tablet,† with a washout period of 7 days between the 2 administrations; the other group received the drugs in reverse order.

Subjects were hospitalized at 5 PM on the day before administration and underwent blood draw for blood chemistry testing. Subjects received the evening meal at 7 PM on the day before administration, fasted for 12 hours before dosing, and continued to fast for up to 4 hours after drug administration.

At 8 AM on the morning of study drug administration, subjects were administered a single 160-mg dose of the test or reference tablet orally with 240 mL of water. Subjects were not allowed to drink water for 1 hour before and after drug administration and received standard afternoon and evening meals at 4 and 10 hours after dosing, respectively. Alcohol, xanthine-containing foods or beverages (eg, coffee, green tea, cola), illicit drugs, and intense exercise were not allowed during the study.

### Sample Collection

Before administration, a heparin-locked catheter was inserted into each subject's arm or back of the hand. After 1 mL of blood was drawn and discarded, 5 mL of blood was collected into an EDTA (K2)-containing heparinized tube (Vacutainer, Becton, Dickinson, and Company, Franklin Lakes, New Jersey) from the catheter as blank, and then 1 mL of heparinized normal saline was injected into the

*Trademark: Valsa V® (lot no. PVA13501; expiration date, January 2016; LG Life Sciences Ltd, Seoul, Republic of Korea).

†Trademark: Diovan® (lot no. B0005; expiration date, September 2014; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey).