Novel Mechanism-based Population Pharmacokinetic/Pharmacodynamic Model of Blood Pressure and the Antihypertensive Activity of Fimasartan

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Objectives: Fimasartan is a novel angiotensin II receptor blocker available in South Korea and Latin America. Our aim was to develop a novel population pharmacokinetic/pharmacodynamic model to describe the time-course of blood pressure and the antihypertensive activity of fimasartan to support human dose selection.

Methods: The population pharmacokinetic/pharmacodynamic model was developed by combining data from two previously published studies that contained no modeling analyses. These datasets included 56 healthy volunteers receiving placebo, a single oral dose of 20 to 480 mg fimasartan, or seven doses of placebo, 120, or 360 mg every 24h, and 39 patients with mild-to-moderate hypertension receiving placebo, 20, 60, or 180 mg every 24 h for 28 days. Fimasartan plasma concentrations were determined by LC-MS/MS and modelled simultaneously together with all systolic and diastolic blood pressure data. Population modeling was performed in S-ADAPT.

Results: The population pharmacokinetic model accounted for enterohepatic recirculation. Diastolic and systolic blood pressure were described by turnover models whose input rate followed a circadian rhythm. Fimasartan inhibited the input into the diastolic and systolic blood pressure compartments. The maximum extent of inhibition of diastolic blood pressure was 30.7% in patients and 19.2% in healthy volunteers. Half-maximal inhibition required 12.9 ng/mL (156% CV) fimasartan. The coefficients of correlation of the observations vs. individual (population) fits were 0.918 (0.788) for diastolic blood pressure, 0.891 (0.720) for systolic blood pressure, and 0.932 (0.801) for plasma concentrations. Visual predictive checks indicated adequate predictive performance.

Conclusions: The developed population PK/PD model successfully described and predicted the antihypertensive activity of fimasartan in Korean patients and can support optimal dose selection in patients.