Population Pharmacokinetics of Eltrombopag in Patients with Cancer and Healthy Subjects

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Purpose: To develop a population pharmacokinetic (PK) model of eltrombopag in patients with cancer and healthy subjects (HVTs). Eltrombopag is an oral once-daily nonpeptide thrombopoietin receptor (TPO-R) agonist, approved in US for patients with chronic idiopathic thrombocytopenic purpura (ITP) and in development for chemotherapy induced thrombocytopenia.

Methods: 125 patients with advanced solid cancers receiving paclitaxel/carboplatin and 163 HVTs contributed 753 and 3991 plasma eltrombopag concentrations, respectively. Cancer patients received 50, 75 or 100 mg eltrombopag QD on days 2-11 of each 21-day cycle. HVTs received 5-200 mg eltrombopag as a single dose and/or as repeat QD doses for 5-10 days. A mixed-effects modeling approach was used with first-order conditional method of NONMEM. The model previously developed for patients with ITP was used as a starting point. The full model approach was implemented for covariate modeling, followed by elimination of insignificant or poorly estimated covariates.

Results: Eltrombopag PK in patients with cancer and HVTs was described by a 2-compartment linear model with dual sequential first-order absorption, absorption lag-time, and inter-occasion variability in absorption. Typical (95% CI) parameters of a 70 kg non-Asian ≤ 50 years old male with cancer were estimated as CL/F=0.839 (0.767, 0.911) L/hr, Vc/F=11.7 (10.6, 12.8) L, Vp/F=9.81 (9.19, 10.4) L, and Q/F=0.546 (0.501, 0.591) L/hr. Inter-individual variability was 44.4% and 38.6% in CL/F and Vc/F, respectively, (r=0.765). Inter-occasion variability in Ka was high, 120%. CL/F was 47% (34%, 61%) lower in Asians versus other races, 15% (8%, 23%) lower in females versus males, and decreased at age > 50 years, resulting in up to 43% decrease for the oldest age of 81 years. Vc/F was 34% (8%, 60%) lower in Asians, and 26% (18%, 34%) lower in HVTs compared to patients with cancer.

Conclusions: The model adequately described eltrombopag PK in patients with cancer and HVTs. CL/F in patients with cancer and HVTs was higher (17%) than in ITP patients. CL/F decreased in older patients with cancer (>50 years), and did not depend on weight. Female and Asian patients with cancer had lower CL/F, consistent with findings in ITP patients and HVTs.