Population Pharmacokinetic Analysis of Dabigatran in Bioequivalence Studies

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Objectives: To characterize the population pharmacokinetics (PK) of dabigatran following oral administration of 150 mg Pradaxa® (dabigatran etexilate) tablet and to quantify its sources of PK variability.

Methods: A total of 702 healthy volunteers who received repeated administration of Pradaxa® in fourteen replicated cross-over PK bioequivalence studies were included in this analysis. Only the PK data from the reference formulation were used for the population PK modeling. PK data was analyzed with non-linear mixed effect model using NONMEM 7.3 software. The effect of selected subject’s covariates on dabigatran’s PK was investigated. Model evaluation was performed using predictive checks and non-parametric bootstrap.

Results: A two compartment model with a time-dependent absorption process, linear distribution and linear elimination was developed to best describe the PK data. Residual variability (RV) was modeled using additive error model after natural logarithmic transformation of measured concentrations and model predictions. Oral clearance (CL) and apparent volume of distribution at steady state were computed to be 109 L/h and 786.9 L, respectively. Inter-individual variability was estimated in CL (23.3%), apparent volume of distribution (121.6%), the time at which the absorption rate constant assumes to be half of its maximum value ($t_{50}$) (21.2%) and RV (37.1%). Inter-occasion variability in the fraction of drug absorbed and $t_{50}$ were quantified to be 65% and 24.4%, respectively. The data did not suggest the inclusion of inter-study variability on PK parameters. Among the covariates evaluated, age, sex, body weight, height, body mass index, race, ethnicity and region did not modified drug exposure more than 20% and were not included in the best model. Bootstrap and visual predictive check evidenced that the model was appropriate to describe the time course of dabigatran plasma concentrations.

Conclusions: The integration of bioequivalence PK data demonstrated dabigatran has time dependent absorption, linear elimination from plasma and large inter-individual and inter-occasion variability.