Modeling and Simulation of Piperaquine (PQ) After Administration of Eurartesim® (PQ Tetraphosphate/Dihydroartemisinin)

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Objectives: Develop a population pharmacokinetic (PK) model for PQ by pooling data from 5 studies and applying it to predict PQ PK in pediatric patients (6-12 months) infected with Plasmodium falciparum malaria after administration of a new dispersible formulation.

Methods: Subjects/patients with at least one measurable PQ concentration were included in the analysis for a total of 207 PQ profiles, 4636 samples (4422 measurable samples). The MLEM algorithm in ADAPT5 [1] was used to estimate the population parameters. The M3 method from Beal [2] was used for concentrations below the limit of quantification. The Bayesian Information Criteria (BIC) was used for model discrimination and covariate inclusion/exclusion. Internal model validation was done with visual predictive check plots created with R [3] version 3.1.2.

Results: A three-compartment model with lag-time, zero-order absorption, and enterohepatic circulation was the structural model that best fitted the PQ data. Dose-corrected body weight improved the BIC. Inter-occasion variability on the bioavailability parameter for the first dose improved the model. Body weight (WGT), health status, food, formulation, crushed, and sex were covariates included in the final model.

Two-hundred infants were simulated (gender balanced) receiving 80, 160, or 320mg PQ, depending of their WGT, once a day for 3 consecutive days. WGT was simulated according to the WHO training [4]. Day 3 AUC, Cmax and Tmax were calculated.

Conclusions: Simulated results for the new dispersible formulation under fasted condition suggest that the geometric mean of PQ AUC and Cmax would be 11,322ng/mL*h and 294ng/mL, respectively, with a median Tmax of 5.48h.

References: