Modeling and Simulation of Pyronaridine in Pediatric Malaria-Infected Patients: Support for Proposed Labeling of Weight-Based Dosing for Pyramax® Granules

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Purpose

Pyramax® is a pyronaridine/artesunate fixed-dose combination for the treatment of uncomplicated P. falciparum and P. vivax malaria in adult and pediatric patients. A granule formulation of this combination has been developed for the treatment of uncomplicated malaria in pediatric patients weighing less than 20 kg. Simulations of pyronaridine (PYR) systemic exposure in pediatric malaria-infected patients based on population pharmacokinetic modeling were performed to confirm the weight-based dosing of Pyramax® granules in children.

Methods

The population pharmacokinetics of PYR were evaluated in pediatric malaria-infected patients participating in six Pyramax® clinical trials. A total of 1085 blood PYR concentrations were available from 349 malaria patients between 0.5 and 16 years of age with mild to moderate uncomplicated malaria. Non-linear mixed effects modeling was used to obtain the pharmacokinetic and variability parameter estimates. PYR concentrations were well described by a two-compartment model with first order absorption and elimination. Allometric scaling was implemented to address the effect of body weight on clearance and volume parameters. 500 simulations of PYR exposure (AUC0-inf) levels corresponding to the administration of a regimen of three once daily doses of both the granule and tablet formulations were performed in NONMEM utilizing the final population pharmacokinetic model. The simulations were conducted in order to first, illustrate the consistent exposure levels of PYR in pediatric patients with weights ranging from 5 Kg to 19 Kg and second, to compare PYR exposure between the granule dosage administration for subjects weighing < 20 Kg and the tablet dosage administration for subjects weighing ≥ 20 Kg.

Results

The final parameter estimates of PYR apparent clearance (CL/F), central volume of distribution (V2/F), peripheral volume of distribution (V3/F), inter-compartmental clearance (Q/F) and absorption rate constant (Ka) were 377 L/day, 2230 L, 3230 L, 804 L/day and 17.9 day-1, respectively. The corresponding percent coefficient of variation of inter-individual variability for CL/F, V2/F, V3/F and Ka were 40.7%, 99.6%, 50.6% and 65.8%, respectively. Covariate model building conducted using forward addition ($p<0.05$) followed by backward elimination ($P<0.001$) yielded two significant covariate-parameter relationships: age on V2/F and formulation on Ka. Median simulated Ln AUC (mg.d/L) values in pediatric malaria infected patients weighing < 20 Kg after the administration of the granule dosage form were 0.255, 0.385, 0.334 and 0.281 mg.d/L for the corresponding dosing cutoff weights of 5, 8, 15 and 19 Kg, respectively. Furthermore, median simulated Ln AUC (mg.d/L) values in subjects weighing ≥ 20 Kg after the administration of the tablet dosage form were 0.274, 0.392, 0.331, 0.423 and 0.364 for the corresponding body weights of 20, 30, 40, 50 and 60 Kg, respectively.

Conclusion

Evaluation of bootstrapping, visual predictive check, and condition number indicated that the final model displayed satisfactory robustness, predictive power, and stability. Simulations of PYR Ln AUC levels generated from the final model show consistent exposure levels across the pediatric weight ranges. They also confirm uniform PYR exposure between the granule dosage administration for subjects weighing < 20 Kg and the tablet dosage administration for subjects weighing ≥ 20 Kg, supporting the proposed labeling for weight-based dosing of Pyramax® granules.