Population Pharmacokinetics of Dolutegravir in HIV-Infected Pediatric Subjects

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Objective: Dolutegravir (DTG) is a once-daily integrase inhibitor, currently approved for use in treatment-naïve and treatment-experienced adults as well as adolescents and children weighing at least 30 kg. The main objectives of the analysis were to develop a population pharmacokinetic (Pop PK) model of DTG following oral administration, to evaluate subject covariates, and to obtain DTG exposure metrics via simulation to evaluate the appropriateness of the current pediatric weight based dosing regimens.

Methods: Data (n=41) from study P1093, an ongoing Phase I/II multicenter study in HIV-infected children and adolescents was used for the model development. On enrollment, DTG (dosed by weight bands) was started as monotherapy (if not on antiretrovirals) or added to a stable-failing regimen. Intensive PK evaluations were completed between days 5-10, after which background therapies were optimized. The Pop PK model was developed with NONMEM VII software (ICON, Ellicott City, MD) using the first-order conditional estimation with interaction method. The structural model was refined to incorporate separate absorption and bioavailability parameters for DTG tablet and granule formulations. Final model selection was based on evaluation of goodness-of-fit plots, biological plausibility and precision of parameter estimates. Further simulations were performed to evaluate appropriateness of weight-based dosing.

Results: DTG PK in HIV-1 infected treatment-experienced pediatric subjects was adequately described by a one-compartment model with first-order absorption, absorption lag time and first-order elimination. The estimated mean (95% CI) parameter values were clearance (CL/F)=1.02 (0.853, 1.19) L/hr and volume of distribution (V/F)=18.1 (15.7, 20.5) L. For the range of weights in the analysis (17.0-91.0 kg), CL/F ranged from 0.353-1.24 L/hr and V/F ranged from 4.40-23.5 L. Inter-individual variability (IVV) for CL/F was moderate at 32.4% whilst inter-occasion variability (IOV) for CL/F was slightly higher at 47.4%. Large IV (CV=204%) and IOV (CV=257%) for tablet Ka was observed. Simulation showed that the exposures from DTG tablets were comparable to the adult 50 mg dose across all weight bands.

Conclusion: Dosing of DTG tablets on a weight-band basis (20, 25, 35, 50 mg) in children provides comparable exposures to that observed in adults (50 mg) whilst higher PK variability in pediatric patients was observed.