Population Pharmacokinetics of Levonadifloxacin Administered as WCK 2349, a Novel Oral Benzoquinolizine Quinolone Prodrug

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Background: WCK 2349 is a novel L-alanine ester prodrug of levonadifloxacin being developed as an oral broad spectrum, anti-methicillin resistant Staphylococcus aureus (MRSA) agent. WCK 2349 is being developed for the treatment of patients with hospital acquired bacterial pneumonia (HABP) and acute bacterial skin and skin structure infections (ABSSSI). The objective of this work was to describe the population pharmacokinetics of levonadifloxacin administered as oral WCK 2349. Methods: A population PK model was developed using PK data from three Phase I studies in healthy volunteers - one Phase 1 single ascending study (200 mg - 1500 mg) in India, and two multiple dose studies in India and the US. All modeling was performed using the population program Phoenix NLME (Nonlinear Mixed Effects v 1.4). The levonadifloxacin concentrations were analyzed using a 2-compartment model first order elimination model. The absorption of WCK 2349 after oral dosing leading to rapid appearance of levonadifloxacin in plasma was described using a zero-order infusion process where the duration of infusion (D1) was estimated. The systemic clearance was estimated as CL and the distribution clearance as Q. The apparent volumes of distribution of the central compartment (VC) and tissue compartment (VT) were also estimated. Body weight was the main covariate that was tested. Results: The 2-compartment model where all clearance and volume parameters were allometrically scaled, adequately described the typical and individual PK profiles. The population parameter estimates for the duration of absorption (D1), standardized clearance (CL/F) and volume of distribution (V/F) were 1.13 hours, 7.2 liters/hour and 54.5 liters, respectively. Inter-individual variability estimates in D1, CL/F, and V/F were 0.4%, 20%, and 18%, respectively. Aside from weight, no other covariates resulted in statistically significant improvements in the data fit. Conclusions: This is the first model describing the pharmacokinetics of WCK 2349. The model accounted for differences in body weight between the US and Indian subjects. The results of this model were utilized for Phase 3 dose selection.

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