Population Pharmacokinetics of intravenous Levonadifloxacin Administered as WCK 771, a Novel Benzoquinolizine Quinolone

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Background: WCK 771 is an L-arginine salt of Benzoquinolizine quinolone levonadifloxacin with enhanced activity against methicillin resistant Staphylococcus aureus (MRSA) and quinolone-resistant staphylococci. It is being developed as a parenteral anti- MRSA agent for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and hospital acquired bacterial pneumonia (HABP). The objective of this work was to describe the pharmacokinetics (PK) of WCK 771. Methods: A population PK model was developed from plasma concentration-time data obtained from 54 Indian subjects in various Phase I clinical trials given either single dose (range of 600-1200 mg) or multiple dose (range 600-1200 mg BID or TID for 5 days), as well as 30 Caucasian subjects in a single US trial (600, 800, 1000 mg BID for 5 days). The levonadifloxacin concentrations were analyzed in Phoenix NLME (v 1.4) using a 2-compartment IV-infusion style administration model. The appearance of levonadifloxacin after WCK 771 IV dosing was described using a zero-order infusion process where the duration of infusion (D1) was estimated. The systemic clearance CL, the distribution clearance Q, the central (Vc) and peripheral (Vp) volumes of distribution 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 hour (fixed), 5.40 liters/hour and 37.12 liters, respectively. Inter-individual variability estimates in CL/F, and V/F were 19.1%, and 29.1%, 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 levonadifloxacin following IV administration of WCK 771. The model accounted for differences in body weight between the US and Indian subjects. The results of this model would form the basis of dose selection for Phase 3 studies.

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