Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Predict Desloratadine Pharmacokinetics in Children

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Objectives: Desloratadine, an active metabolite of loratadine, is a tricyclic H₁-antihistamine that is used to treat allergies. Desloratadine is extensively metabolized by CYP2C8 with fraction of metabolism value of ~80%. The objective of this study was to develop a PBPK model to predict desloratadine PK in pediatric patients across various age groups.

Methods: A minimal PBPK model with first order absorption was constructed for desloratadine in the Simcyp simulator V14.1 based on physicochemical properties and clinical observations. Following appropriate verification using 3 adult clinical studies, pediatric PK was predicted across various age groups with application of physiological-based ontogeny. The predicted clearance values were then compared with available clinical data in subjects for each age group.

Results: The developed PBPK model captured the AUC and C<sub>max</sub> of desloratadine (AUC ratios (predicted over observed) of 0.76, 1.18, 1.07 and C<sub>max</sub> ratios of 0.89, 0.85, 1.11) in 3 adult studies. The PBPK model then reasonably predicted the AUC values of desloratadine in school-aged children (6 - 11 years), young children (2 - 5 years) and infants (1~2 years), with AUC ratios of 1.45, 1.64 and 1.85, respectively. However, the prediction error was greater (AUC ratio of 2.50) in another infant study (0.5 to 1 year) when using the default Simcyp ontogeny profile for CYP2C8. The predictive performance could be improved for both infant studies (AUC ratios of 1.09 and 1.34 as compared to 1.85 and 2.50, respectively) by applying the ontogeny profile reported by Upreti and Wahlstrom¹.

Conclusions: Pediatric PK of desloratadine can be extrapolated using a developed PBPK model in adults by considering pediatric demography, developmental physiology and biochemistry as well as ontogeny profiles of CYP2C8 built in the Simcyp pediatric module. Improved predictive performance in younger age infants was observed using ontogeny profiles derived from an in-vivo approach¹.