Background & Objectives

- Quetiapine is an atypical antipsychotic drug with efficacy demonstrated in clinical trials for the treatment of schizophrenia, bipolar disorder, major depressive disorder, and generalized anxiety disorder in adult patients.
- The clinical utility of the quetiapine formulations has also been evaluated in pediatric patients for the treatment of schizophrenia, bipolar mania, and bipolar depression.
- Quetiapine has a short half-life (-7 h) and twice daily administration is recommended for the immediate-release (IR) formulation. An extended-release (XR) formulation has been developed to allow once-daily dosing.
- Quetiapine is mainly metabolized by CYP3A, with minor contribution from CYP2C9 and CYP2D6.
- The pharmacokinetics of the quetiapine IR formulation has been studied in children and adolescents. However, a formal pharmacokinetic study of the XR formulation has not been conducted in similar age groups.

Methods

- The strategy for building and validating the PBPK and projecting the PK of the XR formulation in children and adolescents is illustrated in scheme on right. The in vitro data, in vivo drug-drug interaction and induction data in human, clinical PK data from the pediatric PK study with IR formulation, and PK data from bioavailability studies with the IR and XR formulation in adults were used to build and validate the quetiapine PBPK model (Table 1).
- The PBPK model was constructed for quetiapine using a population-based ADME simulator, Simcyp v11 (Sheffield, UK). Default parameter values for creating a virtual North European Caucasian population (demography, physiological parameters including liver volume and blood flows, enzyme abundances) have been applied for adults.
- The Simcyp pediatric module that includes PBPK model together with extensive libraries on pediatric demography (age, height, weight, body surface area), developmental physiology (liver size, renal function, liver blood flow) and biochemistry (albumin, CYP ontogeny) was used to construct PBPK model in pediatrics (1).
- The advanced dissolution absorption metabolism (ADAM) model contains information on how the size of the GI tract changes with age from birth onwards; other parameters such as gastric emptying and intestinal transit times are assumed to be at adult values.

Results

- Results from ketoconazole and carbamazepine DDI studies were integrated to develop a retrograde model
- The model can reasonably predict the quetiapine plasma drug concentration-time profiles at steady state for both adults and children (Figure 1).
- The model can also reasonably predict the quetiapine plasma drug concentration-time profiles at steady state for both IR and XR formulation in adults (Figure 2).
- Inclusion of the colonic absorption component of the ADAM model improved the prediction of the plasma drug concentration-time profile for the quetiapine formulation (Figure 3).
- The model predicted that exposure to quetiapine after administration of 300mg daily as the XR formulation across the age ranges evaluated (10-12 yr, 13-17 yr and adults) (Figure 4 & Table 1).

Discussion and Conclusion

- The FDA has used information generated by PBPK to facilitate the decisions of (1) the need to conduct specific clinical pharmacology studies, (2) specific study designs and (3) appropriate labelling language. Thus, a SimCYP PBPK model for quetiapine was developed to predict the PK of quetiapine XR in children and adolescents.
- PBPK modeling can reasonably predict quetiapine exposure in IR and XR formulations in adults, children and adolescents by comparing with various clinical trials.
- The established PBPK model predicted that children XR and IR formulations would achieve similar quetiapine exposure in children and adolescents.

References