A Physiological-based Pharmacokinetic (PBPK) Modeling Approach to Quantifying Drug-Drug Interactions: Applications to the Development of Fenfluramine (ZX008) for Treatment of Seizures in Dravet Syndrome (DS)

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Objectives: DS is a severe form of childhood epilepsy in which seizures are often refractory to traditional antiepileptic drugs (AEDs). Low dose fenfluramine (ZX008; Zogenix, Inc.) has shown promise in DS patients and is currently under development worldwide. Treatment of DS patients often requires a regimen of several AEDs that are metabolized via CYP450. The objective of this analysis was to construct a PBPK model system to quantify potential drug-drug interactions and facilitate dose justification for clinical trials of ZX008.

Methods: The PBPK model for fenfluramine was comprised of ten perfusion-limited tissues with tissue-to-plasma partition coefficients calculated by integrating physiochemical and in vitro properties based upon tissue composition-based equations. Fenfluramine was eliminated by renal excretion and hepatic metabolism; 76% of hepatic intrinsic clearance (CL\text{int}) went to norfenfluramine. The PBPK model was employed to predict the joint disposition of fenfluramine and norfenfluramine in Berkeley Madonna. The joint PBPK model was qualified using plasma PK profiles of d-fenfluramine and d-norfenfluramine from healthy adults. The remainder of the PBPK model system is comprised of models for concomitant AEDs (stiripentol, clobazam, valproic acid) constructed from literature sources.

Results: Model simulations adequately replicated the mean plasma PK profiles of d-fenfluramine and d-norfenfluramine in adults (Figure 1). Predicted mean AUC\text{0-24,ss} and C\text{max,ss} were within 1.25-fold of observed fenfluramine and norfenfluramine data in adults, supporting model robustness. Sensitivity analyses demonstrated that fenfluramine AUC\text{0-24,ss} is highly sensitive to changes in liver partition coefficient and CL\text{int}, where 30% decrease in CL\text{int} resulted in 1.5-fold increase of fenfluramine AUC\text{0-24,ss} in healthy adults. PBPK models for other AEDs showed similar robustness when evaluated using published data.

Conclusions: The developed joint fenfluramine PBPK model well characterized d-fenfluramine and d-norfenfluramine PK profiles in healthy adults. Data from an ongoing adult drug-drug interaction study will be used to qualify the PBPK model system for use in pediatric studies.

Figure 1: A) Scheme of joint PBPK model for fenfluramine and norfenfluramine after fenfluramine oral dosing in healthy adults; B) Model simulated versus observed PK plasma profiles of d-fenfluramine and d-norfenfluramine after administration of d-fenfluramine 15 mg twice daily orally for 15 days in healthy adults

Note: Solid line/grey shaded area represented median/90% confidence interval of model simulations for 1,000 virtual healthy adults; solid dots represented observed d-fenfluramine or d-norfenfluramine mean plasma PK data from healthy adults (Caccia, et al. Eur J Clin Pharmacol. 1985; 29: 221-4)