PREDICTION OF DRUG-DRUG INTERACTIONS (DDI) WITH A MODERATE CYP3A INDUCER: DEVELOPMENT AND VALIDATION OF PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODEL OF RIFABUTIN

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Background: Rifabutin, a moderate CYP3A inducer, is a clinically relevant anti-infective agent for patients with B-cell malignancies. Many anti-cancer agents are metabolized by CYP3A and a validated rifabutin PBPK model to predict DDI would be a useful development tool. However, no rifabutin PBPK models have been published to date.

Methods: A PBPK model based on physiochemical, in vitro properties, and plasma concentration profiles of single- and multiple dose rifabutin 300 mg once daily was developed using Gastroplus 9.8. Rifabutin precipitation time and permeability were optimized to refine oral absorption. CYP3A mediated hepatic clearance and first pass gut metabolism were based on reported in vitro CYP3A enzymatic parameters. Esterase mediated clearance was incorporated as linear systemic clearance. CYP3A induction parameters were included to simulate 300 mg multiple dose (with CYP3A autoinduction) and confirm the fraction metabolized by esterase. The model was validated by comparing simulations of 1) rifabutin 150 mg single dose, 2) DDI of midazolam with rifabutin, and 3) DDI of rifabutin with fluconazole with the corresponding clinically reported data.

Results: The optimized model adequately described rifabutin 150 mg single dose plasma concentration profile. Predicted and observed (P/O) C_{max} and AUC_{0-24} ratio was <1.5. The ability of the model to predict rifabutin CYP3A induction potential was confirmed by good agreement between simulated and observed PK exposure of midazolam DDI with rifabutin. As a victim, rifabutin PK exposure with fluconazole was predicted well with a P/O ratio of <2 for C_{max} and AUC_{0-24}.

Conclusion: The validated model of rifabutin can be applied to predict the impact of moderate CYP3A inducers on CYP3A substrates.