Objectives: The objective of this study was to develop a physiologically based pharmacokinetic (PBPK) model of atazanavir following oral administrations. The predictive performance of the model for UGT1A1 inhibition was assessed using a validated raltegravir PBPK model.

Methods: A mechanistic absorption/PBPK model of atazanavir was developed using GastroPlus™ 9.0 (Simulations Plus, Inc.). The program’s Advanced Compartmental Absorption and Transit™ (ACAT™) model was used in conjunction with the PBPKPlus™ module to describe the absorption and pharmacokinetics of atazanavir. Human physiologies were generated by the program’s internal Population Estimates for Age-Related (PEAR™) Physiology™ module. Data describing the drug’s physicochemical properties, enzyme kinetic inputs, and plasma concentration-time profiles were obtained from literature. All tissues were modeled as perfusion-limited tissues. The Lukacova method was used for tissue/plasma partition coefficient estimation. The model was validated by comparing simulated and observed plasma concentration-time profiles for atazanavir across different dose levels following single and multiple oral administrations. The drug-drug interactions mediated via UGT1A1 inhibition [1] were predicted with the GastroPlus DDI module through dynamic simulations using the validated atazanavir and raltegravir PBPK models.

Results: The PBPK model correctly described observed plasma concentration-time profiles of atazanavir for different doses in healthy subjects after single and multiple oral administrations. Dynamic simulations adequately predicted the effect of UGT1A1 inhibition by atazanavir on raltegravir PK. The predicted increase in AUC$_{0-t}$ and C$_{max}$ of raltegravir in the presence of atazanavir was approximately 2-fold, which was in close agreement with observed values.

Conclusions: The absorption and pharmacokinetics of atazanavir were accurately predicted using the proposed PBPK model. The model demonstrated excellent performance for the prediction of drug-drug interactions related to inhibition of UGT1A1-mediated raltegravir metabolism by atazanavir. New guidance issued by the US-FDA recommends assessing drug interactions for UGT substrates. This model can be successfully used to predict quantitative drug interactions for UGT1A1 substrates.

References: