Physiologically Based Pharmacokinetic Modeling and Simulation Using Simcyp® to Predict Drug-Drug Interaction When Mirabegron Is Coadministered With Fesoterodine

1 Objectives

This was a physiologically based pharmacokinetic (PBPK) modeling and simulation study to predict the drug-drug interactions (DDIs) between mirabegron and fesoterodine. The specific objectives of this study were:

- Model development and verification for mirabegron
- Build a Simcyp® model to simulate the observed steady-state plasma concentration-time profiles of mirabegron after 50 and 100 mg once-daily (QD)
- Add in vivo intravenous (IV-IVP) inhibition data (competitive DDI and time-dependent inhibition data for mirabegron) to the model to verify the observed DDI of mirabegron coadministered with fesoterodine (CYP2D6 substrate) as part of model validation
- Model development and verification for fesoterodine
- Build a Simcyp® model to simulate the observed concentration-time profiles of fesoterodine after 8 and 100 mg once-daily (QD) and without fesoterodine 200 mg (in CYP2D6 extensive [EM]) and poor metabolizers [PM]).
- Perform Simcyp® simulation to predict the extent of DDI when mirabegron is coadministered with fesoterodine (substrate).

2 Methods

- Simcyp® (version 14.1) input parameters for mirabegron
- The simulations based on Simcyp® model for mirabegron accurately described the plasma concentration-time profiles of mirabegron after 50 and 100 mg once-daily (QD)
- In addition to intravenous (IV-IVP) inhibition data (competitive DDI and time-dependent inhibition data for mirabegron) to the model to verify the observed DDI of mirabegron coadministered with fesoterodine (CYP2D6 substrate) as part of model validation
- The Simcyp® model accurately predicted the CYP2D6 inhibitory effect of mirabegron.
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3 Results

- The simulations based on Simcyp® model for mirabegron accurately described the plasma concentration-time profiles and PK parameters of mirabegron after oral administration of 50 or 100 mg QD and observed AUC values.
- Simulated plasma concentration-time profiles following oral administration of 50 mg desipramine, a CYP2D6 substrate, with and without coadministration of mirabegron (inhibitor) 50 mg QD (Table 4)
- Application of Simcyp® accurately predicted 68% increase in 5-HMT Cmax and AUC, respectively, due to coadministration of mirabegron with fesoterodine is predicted to result in approximately 17% and 23% increases in desipramine Cmax and AUC, respectively.

4 Summary and Conclusions

- Mirabegron and 5-HMT PK were accurately described with the PBPK models developed using Simcyp®.
- Application of Simcyp® accurately predicted 68% and 23% increases in desipramine Cmax and AUC, respectively, following coadministration with mirabegron, consistent with the observed clinical study results.
- The Simcyp® model accurately predicted the observed 2-fold higher AUC of 5-HMT either in CYP2D6 PMs or due to coadministration of ketoconazole, a potent CYP3A4 inhibitor.
- Based on Simcyp® modeling and simulations, coadministration of mirabegron and fesoterodine is predicted to result in approximately 17% and 23% increase in 5-HMT Cmax and AUC, respectively, which is not considered a clinically relevant DDI for fesoterodine.