Physiologically-Based Pharmacokinetic Modeling Prediction of CYP3A4 and CYP1A2 Inhibition or Induction on Exposure of Olanzapine and Samidorphan Given in Combination as ALKS 3831

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Objectives: ALKS 3831 is a fixed-dose combination of olanzapine and samidorphan (a μ-opioid receptor antagonist), designed to combine the antipsychotic efficacy of olanzapine with a reduced risk of weight gain and associated metabolic deficits. As CYP3A4- and CYP1A2-mediated oxidation are primary metabolic pathways for samidorphan and olanzapine, respectively, physiologically-based pharmacokinetic (PBPK) modeling was applied to predict the drug-drug interaction (DDI) potential between ALKS 3831 and CYP3A4/CYP1A2 inhibitors/inducers.

Methods: Separate PBPK models were constructed for olanzapine and samidorphan in the Simcyp Simulator and refined by leveraging in vitro metabolism and in vivo clinical data. The two models were combined to represent administration as ALKS 3831 and verified by comparing simulated and observed clinical data. The final models were used to predict the change in olanzapine and samidorphan exposure following co-administration of ALKS 3831 with CYP3A4 and CYP1A2 inhibitors or inducers.

Results: Applying the PBPK models to assess the DDI potential indicates there is likely to be a 1.4 to 1.6-fold increase in samidorphan exposure and negligible change in olanzapine exposure after coadministration with moderate/strong CYP3A4 inhibitors. A 42% reduction in samidorphan exposure and 14% reduction in olanzapine exposure is predicted after coadministration with a moderate CYP3A4 inducer. Coadministration with a strong CYP1A2 inhibitor is predicted to cause a 1.6- and 2.1-fold increase in olanzapine exposure in non-smokers and smokers, respectively, with no impact on samidorphan exposure. Smoking (associated with increasing CYP1A2 abundance) is predicted to cause a 20% to 40% reduction in olanzapine exposure with no impact on samidorphan exposure.

Conclusions: Application of robust PBPK modeling allowed prediction of untested DDI scenarios. Coadministration with a moderate CYP3A4 inhibitor is predicted to have a weak effect on samidorphan exposure and negligible effect on olanzapine exposure. CYP3A4 induction is predicted to reduce both samidorphan and olanzapine exposure. CYP1A2 inhibition or induction is predicted to have an effect on olanzapine exposure only.