PII-49

LACK OF CLINICALLY SIGNIFICANT EFFECT OF MODERATE HEPATIC INSUFFICIENCY ON THE PHARMACOKINETICS OF MK-0431 (SITAGLIPTIN), A DIPEPTIDYL-PEPTIDASE-IV (DPP-IV) INHIBITOR. C. Stevens, BSN, A. J. Bergman, PhD, Q. Liu, PhD, W. Luo, PhD, A. Q. Wang, PhD, W. Zeng, MS, K. C. Lasseter, MD, S. Dilzer, RN, J. A. Wagner, MD, PhD, G. A. Herman, MD, E. Migoya, PharmD, Merck & Co., Inc., SFBC International, Rahway, NJ.

BACKGROUND: This study was conducted to evaluate the influence of hepatic insufficiency (HI) on the pharmacokinetics of MK-0431 (sitagliptin), an orally active, highly selective DPP-IV inhibitor currently in Phase III development for the treatment of patients with type 2 diabetes.

METHODS: This was an open-label study during which a single 100-mg oral dose of sitagliptin was administered to 10 patients with moderate HI (Child-Pugh's scores ranged from 7 to 9) and 10 healthy control subjects matched to each patient for race, gender, age (±5 yrs), and body mass index (±5%). Following each dose, blood and urine samples were collected to assess sitagliptin pharmacokinetics. Prespecified bounds for non-clinical significance for the AUC were [0.5, 2.00].

RESULTS: Mean sitagliptin plasma $AUC_{0-\infty}$ and C_{max} were approximately 21% and 13% higher, respectively, than matched control subjects; both parameters fell within the prespecified bounds. Moderate HI had no statistically significant effect on T_{max}, apparent terminal $t_{1/2}$, fraction of the oral dose excreted into urine ($f_{e,0-\infty}$) and renal clearance ($p>0.100$) of sitagliptin. Sitagliptin was generally well tolerated by patients and subjects.

CONCLUSIONS: Moderate HI has no clinically meaningful effect on the pharmacokinetics of sitagliptin and no dosage adjustment will be necessary for patients with moderate HI.

PII-50

EFFECTS OF P-GLYCOPROTEIN (P-GP) INHIBITION ON THE DISTRIBUTION OF DOMPERIDONE TO CARDIAC TISSUE: DEVELOPMENT OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL IN MDR1A/B(-/-) AND WILD TYPE MICE. F. Fenneteau, MScA, L. Couture, MSc, J. A. Nash, PhD, J. Turgeon, PhD, F. Nekka, PhD, University of Montreal, Charles River Laboratories, Preclinical Services - CTBR, Montreal, PQ, Canada.

BACKGROUND/AIMS: Domperidone, a peripheral dopamine-2 receptor antagonist, can exhibit block of cardiac K+ channel and has been associated with drug-induced long QT syndrome. This drug is also a P-gp substrate and inhibition of this transporter due to drug-drug interaction may lead to an increase in intracellular levels of domperidone and an increased risk of drug-associated toxicity. Our objective was to predict intracardiac concentrations of domperidone under conditions of variable P-gp activity.

METHODS: A physiologically based pharmacokinetic (PBPK) model was developed on Matlab® software to predict domperidone disposition in mice. Mainly based on in vitro parameters, this mechanistic model estimates a priori the overall plasma and tissue behaviour under in vivo conditions. Plasma and tissue samples collected at selected time points up to 120 min postdose are obtained after a single i.v injection of 5 mg/kg of H3-domperidone to male mdr1a/b(-/-) and wild type mice.

RESULTS: PBPK model predictions were in good agreement with experimental results for all tissues and organs considered. Predicted intracardiac domperidone concentrations were higher for mdr1a/b(-/-) mice compared to wild type mice suggesting the relevance of the protective function of P-gp in cardiac tissue.

CONCLUSIONS: This PBPK model succeeds in the prediction of domperidone disposition in both mice strains. This model can be scaled up to human to predict domperidone distribution behaviour when P-gp activity is decreased.

PII-51

EFFECT OF KETOCONAZOLE AND RIFAMPIN ON THE SINGLE DOSE PHARMACOKINETICS OF ASOPRISNIL AND ITS METABOLITE IN HEALTHY FEMALE SUBJECTS. R. D. Lee, PhD, G. Witt, MS, K. Chwalisz, MD, PhD, TAP Pharmaceutical Products Inc., Lake Forest, IL.

BACKGROUND: Asoprisnil (J867) is a novel selective progesterone receptor modulator (SPRM) with partial or mixed agonist/antagonist effects depending on the biological action studied. Previous studies using human liver microsomes have shown that the metabolism of asoprisnil to its J912 metabolite involves CYP2C8 and CYP3A. The objective of this study was to evaluate the effect of a potent inhibitor and inducer of CYP3A/CYP on the pharmacokinetics (PK) of asoprisnil.

METHOD: In these open-label sequential drug-drug interaction studies, two groups of 24 female subjects received a single 25 mg oral dose of asoprisnil before and after multiple oral doses of 400 mg ketoconazole or 600 mg rifampin for 5 or 6 days, respectively. Serial blood samples on asoprisnil dosing days were obtained over 30 hours to determine the PK of asoprisnil and J912. Plasma concentrations of asoprisnil and J912 were determined using a validated LC/MS/MS assay.

RESULTS: The 90% confidence intervals (CI) for the ratios of the central values of asoprisnil or J912 C_{max} and AUC were not contained within the *no effect* boundaries of 0.80-1.25 when asoprisnil was coadministered with either ketoconazole or rifampin. All treatments were safe and generally well tolerated.

	C_{max}		$AUC_{0-\infty}$	
Treatment	**Ratio**	**90% CI**	**Ratio**	**90% CI**
Ketoconazole				
Asoprisnil	6.552	5.649 - 7.601	8.973	7.829 - 10.284
J912	1.740	1.562 - 1.938	3.975	3.685 - 4.288
Rifampin				
Asoprisnil	0.078	0.0652 - 0.0936	0.086	0.0669 - 0.1096
J912	0.128	0.1105 - 0.1485	0.086	0.0764 - 0.0960

CONCLUSION: Concomitant administration of 25 mg asoprisnil after multiple daily doses of ketoconazole or rifampin significantly affect the PK of asoprisnil and its J912 metabolite, and therefore, coadministration is not recommended without appropriate dose adjustments.