PI-149

THE ABSOLUTE BIOAVAILABILITY OF AN ORAL SUSTAINED-RELEASE FORMULATION OF DESVENLAFAXINE SUCCINATE IN HEALTHY SUBJECTS. V. D. Parker, PhD, L. S. Richards, MA, A. I. Nichols, PhD, J. A. Behrle, MS, R. J. Fruncillo, MD, PhD, Wyeth Research, Collegeville, PA.

BACKGROUND/AIMS: To assess the absolute bioavailability of sustained-release desvenlafaxine succinate (DVS-SR) and pharmacokinetics of desvenlafaxine (DV) in healthy subjects.

METHODS: In this single-dose, open-label, 2-period crossover study, subjects were randomized to receive either a 1 × 100-mg oral tablet of DVS-SR or a single 50 mg/1 hr intravenous (IV) infusion of desvenlafaxine succinate (DVS) in each period. Plasma was assayed for the total racemic mixture (R+S) and ratio (R/S) of DV. The absolute bioavailability was calculated from oral and IV AUC values of the racemic mixture of DV.

RESULTS: A total of 14 subjects were enrolled and completed the study. DVS-SR was generally well tolerated. There were no clinically important changes in routine laboratory tests, vital signs measurements, and electrocardiograms (ECG). The 50-mg IV formulation had a higher C_{max} (232 ng/mL) than the 100-mg oral formulation (160 ng/mL). The half-lives were similar, ranging from 14 to 15 hours, and the 100-mg oral formulation of DVS-SR had a higher overall exposure (AUC_{oral} 3996 vs AUC_{IV} 2443 ng*h/mL). The absolute bioavailability of the oral formulation was 80.5%. The concentration profiles for R and S enantiomers were approximately equivalent to each other for both the IV and oral formulations.

CONCLUSION: DVS-SR provided good oral bioavailability (80.5%) and an evenly balanced enantiomeric ratio.

PI-150

A STUDY OF THE EFFECTS OF LASOFOXIFENE (LASO) ON THE PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) OF WARFARIN. D. Ouellet, PhD, C. Bramson, MD, S. Carvajal-Gonzalez, PhD, A. E. Remmers, PhD, D. Roman, MD, E. Randinitis, PhD, M. J. Gardner, PhD, Pfizer, Inc, Ann Arbor, MI.

BACKGROUND/AIMS: To determine the effects of steady-state LASO on the PK and PD of single-dose warfarin. Although no PK drug interaction was expected, these 2 compounds are likely to be coadministered in patients.

METHODS: Open-label, 2-period, fixed-sequence study in 12 healthy postmenopausal women with CYP2C9 genotypes of 1*/1* (wt, n=8), 1*/2* (n=2), or 1*/3* (n=2). Warfarin 20 mg was given on Day 1 and after 7 days of LASO 0.5 mg (after a loading dose of 4 mg). Blood was collected serially for up to 168 hr post-dose for determination of prothrombin time (PT)/INR and R- and S-warfarin. The 90% CI of the ratios with/without LASO for PK and PD parameters (Cmax and AUC) were calculated. LASO was considered to have no effect if the 90% CI was within the 80–125% range.

RESULTS: LASO had no effect on R- and S-warfarin PK. S-warfarin AUC was 1.3- and 1.8-fold larger in subjects with 1*/2*and 1*/3* genotypes, respectively, relative to 1*/1*. Coadministration of warfarin and LASO resulted in a small decrease in warfarin PTmax and PTAUC with ratios (90% CI) with/without LASO of 84.2 (80.6 - 87.8) and 91.9 (89.6 - 94.2) respectively. Results for INR were similar.

CONCLUSIONS: The decrease in PT/INR is not considered clinically meaningful, however, consistent with warfarin's label more frequent INR monitoring may be considered during LASO introduction and discontinuation.

PI-151

LACK OF EFFECT OF APREPITANT ON THE PHARMACOKINETICS OF HYDRODOLASETRON IN CYP2D6 EXTENSIVE AND POOR METABOLIZERS. X. Li, PhD, E. Pequignot, MS, D. Panebianco, MS, A. Majumdar, PhD, D. Selverian, L. Rosen, MD, PhD, K. Petty, MD, PhD, Merck & Co., Inc., Thomas Jefferson University, West Point, PA.

Aprepitant (APR) is the first neurokinin-1 (NK1) receptor antagonist approved for use with a corticosteroid and a 5-hydroxytryptamine3 (5HT3) receptor antagonist in the prevention of chemotherapy induced nausea and vomiting (CINV). Dolasetron (DOL) is a 5HT3 antagonist that is converted to the active metabolite hydrodolasetron (HDOL). Metabolism via CYP2D6 contributes significantly to the elimination of HDOL. Because APR may be coadministered with different 5HT3 antagonists including DOL, the purpose of this study was to determine if APR alters the pharmacokinetic profile of HDOL in CYP2D6 extensive metabolizers (EM) and poor metabolizers (PM). This was an open-label, 2-period, crossover study in which twelve healthy subjects (N=6 EM's and N=6 PM's) received 2 treatments. Treatment A consisted of a single oral dose of 100-mg DOL. In treatment B, subjects received simultaneously 100-mg oral DOL and 125-mg oral APR at 0 hours, followed by single oral doses of 80-mg APR 24 hours and 48 hours later. The pharmacokinetic data of HDOL are shown in the table below. The data suggest that APR does not affect the pharmacokinetics of HDOL in CYP2D6 extensive or poor metabolizers.

HDOL Variable (units)	CYP2D6 Metabolizer	Geometric Means†‡ DOL with APR	Geometric Means†‡ DOL Alone	Geometric Mean Ratio of DOL With APR/DOL Alone (90% CI)†	p-Value§
$AUC_{0-\infty}$ (ng · hr/mL)	Extensive	1132.9	1047.9	1.08 (0.96, 1.22)	>0.250
	Poor	3223.7	2913.3	1.11 (0.98, 1.25)	0.150
	All	1911.1	1747.2	1.09 (1.01, 1.18)	0.065
C_{max} (ng/mL)	Extensive	219.9	212.4	1.04 (0.84, 1.27)	>0.250
	Poor	401.1	356.1	1.13 (0.92, 1.38)	>0.250
	All	297.0	275.1	1.08 (0.94, 1.24)	>0.250
T_{max} (hr)	Extensive	1.7	2.0	NA	NA
	Poor	2.5	2.0		
	All	2.0	2.0		
$t_{1/2}$ (hr)	Extensive	9.0	11.4		
	Poor	12.1	11.9		
	All	10.3	11.7		