SYNOPSIS

CR011440

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Paliperidone ER NAME OF ACTIVE INGREDIENT(S): (+)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-y1)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyridol[1,2-a]pyrimidin-4-one	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: R076477-BIM-1001, CR011440 **Title of Study:** Evaluation of the Effect of Carbamazepine on the Steady-State Pharmacokinetics of Paliperidone Extended Release in Clinically Stable Subjects with Schizophrenia or Bipolar I Disorder		
Principal Investigator: Igor Francetic, M.D. (Croatia)		
Publication (Reference): None.		
Studied Period (years): Clinical Conduct: 18 September 2006 – 15 March 2007 Sample Analysis: 12 March 2007 – 18 April 2007 (plasma); 4 June 2007 – 7 June 2007 (urine)		**Phase of development:** 1
Objectives: The primary objective of this study was to evaluate the effects of a potent metabolic enzyme inducer, carbamazepine, on the steady-state pharmacokinetics of orally administered paliperidone ER. The safety and tolerability of the treatments in clinically stable subjects with a diagnosis of schizophrenia or Bipolar I Disorder were also assessed.		
Methodology: This was an open-label, multiple-center, multiple-dose, 2-treatment, 2-period sequential drug interaction study. It consisted of 3 phases: a screening phase beginning within 21 days before the first study drug administration; an open-label treatment phase consisting of 2 treatment periods (Period 1 and Period 2), during which subjects received multiple oral doses of 6-mg paliperidone ER alone or in combination with multiple oral doses of carbamazepine, and end-of-study evaluations upon completion of all the study procedures in Period 2 or at early withdrawal. There was no washout period between treatment periods.		
Number of Subjects (planned and analyzed): Enrollment of 60 subjects was planned with the intention that at least 48 complete the study. Sixty-four subjects were enrolled and 57 completed the study.		
Diagnosis and Main Criteria for Inclusion: Subjects were clinically stable men and women between 18 and 55 years of age, inclusive, with a diagnosis of schizophrenia or Bipolar I Disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Apart from this diagnosis, they were to be healthy on the basis of physical examination, medical history, 12-lead ECG, and laboratory results of serum chemistry, hematology, and urinalysis performed within 21 days before the first dose, and were to have a CGI-S score of 3 or less at baseline and at screening and body mass index (BMI) of 18 to 35 kg/m2, inclusive. Supine blood pressure was between 100 and 140 mmHg systolic, inclusive, and 50 and 90 mmHg diastolic, inclusive. Women were required to be postmenopausal, surgically sterile, or practicing an effective method of birth control.		
Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone 6-mg tablets for oral use, batch no. 0500129, formulation no. F055. Carbamazepine (Tegretol CR, Novartis) 200-mg tablets commercially available, batch no. T5248, formulation no. F000. Treatment in Period 1: 6 mg paliperidone ER o.d. from Day 1 through Day 7. Treatment in Period 2: 6 mg paliperidone ER o.d. and carbamazepine 200 mg b.i.d. from Day 8 through Day 28.		
Reference Therapy, Dose and Mode of Administration, Batch No.: None		

SYNOPSIS (CONTINUED)

Duration of Treatment: Period 1: 7 days; Period 2: 21 days.

Criteria for Evaluation:

Pharmacokinetics: Paliperidone plasma concentrations were determined from 4 mL antecubital venous blood samples as follows: in Period 1, within 2 hours before paliperidone ER administration on Days 1, 3, 6, and 7, and at 1, 2, 4, 6, 8, 10, 12, 22, and 24 hours after paliperidone ER administration on Day 7; in Period 2, within 2 hours before paliperidone ER administration on Days 11, 15, 19, 23 (±1 day), and 28, and at 1, 2, 4, 6, 8, 10, 12, 22, and 24 hours after dosing on Day 28.

2-mL venous blood samples were taken 12 h post paliperidone administration on Day 7 and 28 to determine creatinine concentration. Urine was collected during the 0-12 hours and 12-24 hours postdose intervals on Days 7 and 28 to determine creatinine, paliperidone, and paliperidone enantiomers concentrations.

Based on the individual plasma concentration-time data, using the actual sampling times, the following pharmacokinetic parameters of paliperidone were estimated for each of the treatments: $C_{predose}$, $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $C_{avg,ss}$, AUC_{τ}, CL_{ss}/F, and FI.

Based on concentrations of paliperidone and its enantiomers derived from individual urine samples, the following pharmacokinetic parameters were estimated for each of the treatments: $Ae_{0\text{-}12h}$, $Ae_{12\text{-}24h}$, $Ae_{0\text{-}24h}$, Ae,%dose, Excr.Rate, CL_R, and CL_{NR}.

Safety: Adverse events: subjects reported adverse events throughout the study. The occurrence of all adverse events was documented in the CRF with the following information, where appropriate: nature of adverse event, when the adverse event first occurred, intensity of the adverse event, seriousness, how long the adverse event persisted, countermeasures, outcome, and relationship to investigational product. Laboratory tests (hematology, serum chemistry, and urine) and 12-lead ECGs were performed at screening, Day 1, Day 8, and at end-of-study or at early withdrawal. Vital sign measurements and physical examination were performed at screening and at end-of-study/early withdrawal. In addition, pulse rate and blood pressure were measured on Days 1, 7, 8, 15, 23, 28, and end of study/early withdrawal. Clinical Global Impression of Severity of Illness (CGI-S) was determined at screening, Day 1, Day 8, Day 15, Day 23, and at end-of-study/early withdrawal

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the plasma paliperidone, carbamazepine, and carbamazepine 10,11-epoxide concentrations at each sampling time and for all derived plasma pharmacokinetic parameters of paliperidone for both treatments. The treatment ratios (with vs. without co-administration of carbamazepine) of $C_{max,ss}$ and AUC_{τ} of paliperidone were listed for all individuals and were summarized using descriptive statistics. 90% confidence intervals for the ratio of geometric mean paliperidone PK parameters $C_{max,ss}$ and AUC_{τ} with and without co-administration of carbamazepine were constructed using the estimated least square means and intrasubject variance from a mixed effects model. An additional analysis was performed to evaluate the percent amount excreted unchanged in urine and renal clearance of paliperidone with and without co-administration of carbamazepine.

Safety: The percentage of subjects with specific treatment-emergent adverse events was summarized for each treatment. Laboratory data were summarized by the type of laboratory test. Pulse rate, systolic and diastolic blood pressure, body temperature, ECGs, and CGI-S scores were descriptively summarized by parameter and time point. Abnormalities were listed.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Paliperidone ER NAME OF ACTIVE INGREDIENT(S): (+)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-y1)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyridol[1,2-a]pyrimidin-4-one	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: PK parameters were available from 58 subjects after administration of paliperidone ER alone and from 55 subjects after administration of paliperidone ER + carbamazepine. Overall, paliperidone plasma concentrations at steady-state were lower following administration of paliperidone ER and carbamazepine than after administration of paliperidone ER alone.

Summary of Pharmacokinetic Parameters (Mean ± SD) of Paliperidone ER

Treatment	$C_{min,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$C_{avg,ss}$ (ng/mL)	AUC_{τ} (ng.h/mL)	CL_R (mL/min)
Paliperidone ER alone (N=58)	17.6 ± 9.01	31.7 ± 15.2	23.8 ± 11.5	560 ± 273	44.2
Paliperidone ER + carbamazepine (N=55)	10.8 ± 5.22	19.6 ± 8.78	14.7 ± 6.20	351 ± 149	58.2

Difference in plasma exposure to paliperidone between the treatments was evaluated using an ANOVA mixed effects model. Co-administration of 200 mg carbamazepine b.i.d. with 6 mg paliperidone ER o.d. decreased $C_{max,ss}$ and AUC_{τ} of paliperidone on average by 37.5% and 36.6%, respectively (90% confidence interval for the treatment ratios of geometric means: 55.77-69.98% for $C_{max,ss}$ and 57.19-70.29% for AUC_{τ}). The relative amount of the administered dose of paliperidone excreted unchanged in urine decreased on average by 14% after co-administration with carbamazepine. Mean renal clearance of paliperidone was increased by 35.5% in the presence of carbamazepine.

SAFETY RESULTS: Paliperidone ER was well tolerated in this study. Incidence of AEs was similar after treatment with paliperidone ER alone (30%) and with paliperidone ER with carbamazepine (24%). The most frequent AEs observed were expected side effects of paliperidone (headache in 11% of subjects and weight increase in 5% of subjects) or expected consequence of increased load of antipsychotics (extrapyramidal syndrome in 6% of subjects). There were no deaths or other serious adverse events during the study. The mean increase by 7 bpm in supine pulse rate observed after administration of paliperidone ER is in line with observations from previous clinical studies. No relevant change in ECG parameters and CGI-S scores occurred.

CONCLUSION: In men and women with a diagnosis of schizophrenia or Bipolar I Disorder, co-administration of 200 mg carbamazepine b.i.d. with 6 mg paliperidone ER o.d. decreased steady-state exposure (AUC_{τ}) and peak plasma concentration ($C_{max,ss}$) of paliperidone by 36.6% and 37.5%, respectively.

Co-administration of paliperidone ER 6 mg o.d. with carbamazepine 200 mg b.i.d. was generally safe and well tolerated.

Date of the report: 08 November 2007

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.