CLINICAL STUDY REPORT SYNOPSIS

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NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Paliperidone extended release (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-SCH-1017 CR012085 **Title of Study:** A Single-Dose, Open-Label, Randomized, 2-Way Crossover Pivotal Bioequivalence Study of 12 mg Paliperidone Extended Release Tablets Manufactured at Gurabo and Vacaville Under Fasted Condition in Healthy Subjects.		
Investigators: Dr. Wouter Haazen, SGS Biopharma Research Unit Stuivenberg, Lange Beeldekensstraat 267, 2060 Antwerpen, Belgium		
Publication (Reference): None.		
Studied Period (years): 27 March 2007 to 14 May 2007 **Sample Analysis:** 15 May 2007 to 28 June 2007		**Phase of development:** 1
Objectives: The primary objective of this study was to establish bioequivalence of paliperidone ER tablets manufactured at Gurabo compared with paliperidone ER tablets manufactured at Vacaville in healthy subjects, administered as a single dose of 12 mg under fasted conditions. In addition, the safety and tolerability of both formulations were assessed.		
Methodology: This was a randomized, open-label, 2-way crossover study in healthy male adults. The study consisted of a screening phase and an open label treatment phase during which each subject received the 2 treatments of the study separated by a washout period of 7 to 14 days. Treatment A consisted of a single oral dose of 12-mg paliperidone ER tablets manufactured at Gurabo, administered under fasted condition. Treatment B consisted of a single dose 12-mg paliperidone ER tablets manufactured at Vacaville, administered under fasted condition. Blood samples for pharmacokinetic analysis were collected at pre-dose and for 96 hours post-dose for each period		
Number of Subjects (planned and analyzed): 72 planned; 72 analyzed for safety; 71 analyzed for pharmacokinetics.		
Diagnosis and Main Criteria for Inclusion: Healthy, non-smoking, males between 18 to 55 years of age with a body mass index between 18 and 30 kg/m^2 and body weight not less than 50 kg. Subjects were also to have blood pressure (after the subject is supine for 5 minutes) between 100 and 140 mmHg systolic, and between 50 and 90 mmHg diastolic.		
Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER 12 mg tablets, manufactured at Gurabo, batch number 7Ag1026-X		
Reference Therapy, Dose and Mode of Administration, Batch No.: Paliperidone ER 12 mg tablets, manufactured at Vacaville, batch number 0602596		
Duration of Treatment: 13 to 40 days		
Criteria for Evaluation: Pharmacokinetics: For the determination of the plasma concentration of paliperidone, venous blood samples of 3 mL were taken predose, and during the 96 hours following dosing with paliperidone ER. 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_{max}, t_{max}, t_{last} AUC_{last}, AUC_{∞}, $t_{1/2}$, λ_z, F_{rel} (for C_{max} and AUC_{∞}), and CL/F. Safety: Safety was evaluated by examining incidence, severity, and type of adverse events, and changes in clinical laboratory results, 12 lead electrocardiogram (ECG), vital sign measurements, physical examination, and concomitant medications/therapy.		

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)

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the plasma paliperidone concentrations at each sampling time and for all derived plasma pharmacokinetic parameters of paliperidone for both treatments. For inferential statistics, the pharmacokinetic parameters C_{max}, AUC_{last}, and AUC_{∞} of paliperidone were compared between both study treatments. The natural logarithm-transformed estimated primary pharmacokinetic parameters were fitted in a mixed-effect model that included treatment, period, and treatment sequence as fixed effects, and subject (nested to sequence) as a random effect. The least-square means and intrasubject variability estimated from the mixed-effect model were used to construct 90% confidence intervals (CIs) to the difference in means on the natural logarithm scale between the 2 treatments.

Safety: Safety results were summarized and presented in tables and listings. No statistical analysis was performed.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

- The peak concentration and the total exposure of paliperidone were bioequivalent for 12 mg paliperidone ER tablets manufactured at Gurabo and Vacaville (90% confidence intervals for the treatment ratios: 86.85% to 101.76% for C_{max}, 88.73% to 105.01% for AUC_{last}, and 89.16% to 105.40% for AUC_{∞}).
- The time to reach peak concentrations and the terminal half-life were similar for both treatments.

SAFETY RESULTS:

- There were no serious adverse events or withdrawals due to adverse events during the study.
- A total of 61 of the 72 subjects (85%) reported at least one adverse event. Percent of subjects with adverse events during 12 mg paliperidone ER tablets manufactured at Gurabo and 12-mg paliperidone ER tablets manufactured at Vacaville were 67% and 68% respectively.
- Overall, the most common adverse events were somnolence (40%), dry mouth (21%), dizziness (18%), insomnia (18%) and headache (14%). Most of the adverse events were considered by the investigator as possibly and probably related to study drug.
- Most of the treatment-associated adverse events were mild in intensity, except one case of joint sprain, and two cases of syncope, which were considered as moderate and severe, respectively.
- No clinical significant laboratory values were noted during the study with the exception of markedly abnormal lactic acid dehydrogenase (LDH) values in 3 subjects. Most of these LDH values were with the normal reference range (231 to 631 U/L) but exceeded the predefined upper limit of normal for paliperidone (500 U/L).
- There were no clinically relevant changes in vital signs or ECG parameters.

CONCLUSION:

- When administered as a single dose of 12 mg under fasted conditions, paliperidone ER tablets manufactured at Gurabo and Vacaville were bioequivalent with respect to peak exposure (C_{max}) and total exposure (AUC).
- Paliperidone ER was well tolerated in this study, and there were no unexpected safety findings.
- The incidence of treatment-emergent adverse events did not show any relevant differences between 12 mg paliperidone ER tablets manufactured at Gurabo (48 of 72 subjects, 67%) and 12 mg paliperidone ER tablets manufactured at Vacaville (49 of 72 subjects, 68%).
- No subjects experienced any serious adverse events. One subject withdrew his consent.

Date of the report: 30 January 2008

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