SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, a division of Janssen Pharmaceutica N.V. NAME OF FINISHED PRODUCT: NA - OROS® NAME OF ACTIVE INGREDIENT: R076477 (paliperidone)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No: R076477-P01-101, CR004282

Title of Study: A Comparative Evaluation of the Pharmacokinetics and Pharmacodynamics Under Fasting and Fed Conditions of 2 Paliperidone Extended-Release Formulations With Paliperidone Oral Solution in Healthy Adults

Principal Investigator: F. Vanhoutte, M.D. - Clinical Pharmacology Unit, Merksem; Belgium

Publication (Reference): None

Studied Period (years): Clinical Conduct: 26 June 2003 – 12 August 2003 Sample Analysis: 16 July 2003 - 18 September 2003	**Phase of development:** 1

Objectives: The primary objectives of the study were to evaluate the pharmacokinetics (PK) of 2 extended-release (ER) formulations of 2 mg-eq paliperidone in comparison with 2 mg immediate-release (IR) paliperidone oral solution, and to evaluate the effect of food on the PK of these ER formulations. Additional objectives were to compare the pharmacodynamic effects (postural changes in blood pressure and heart rate), to evaluate the safety and tolerability of all treatments, and to explore the relationship between CYP2D6 and CYP3A4/5genotype and paliperidone exposure.

Methodology: This was a single-center, open-label, randomized, 5 treatment-period, crossover study in healthy adults. The study consisted of a screening phase and a treatment phase during which each subject received 5 treatments of study drug in a random order and separated by a washout period of at least 7 to 14 days. Treatments consisted of a single oral dose of: A) paliperidone ER pellet formulation, (2 mg-eq) as 1 capsule of 2.5 mg, fasted; B) the same formulation as A but with food; C) paliperidone-coated ER OROS® formulation (2 mg-eq) as 2 tablets of 2 mg, fasted; D) the same formulation as C but with food; E) IR paliperidone oral solution, 2 mg (2 mL) of a 1 mg/mL solution, fasted.

Number of Subjects (planned and analyzed): 35 planned; 35 analyzed.

Diagnosis and Main Criteria for Inclusion: Men or women; aged 18 to 55 years, inclusive; acceptable weight; normotensive; healthy on the basis of a prestudy physical examination, medical history, ECG, and the laboratory results of blood biochemistry, hematology and urinalysis performed within 21 days before the first dose; women had to be postmenopausal for at least 1 year, surgically sterile, or practicing an effective method of birth control; informed consent documents (also for genetic testing) signed.

Test Product, Dose and Mode of Administration, Batch No.: paliperidone ER pellet formulation, 2 mg-eq, as 1 oral 2.5-mg capsule, 03E26/F025; paliperidone-coated OROS ER formulation, 2 mg-eq, as 2 oral 2-mg tablets, MV0311255; paliperidone IR oral solution, 2 mg (2 mL) of a 1-mg/mL oral solution, 03E27/F021.

Duration of Treatment: 5 times 1 day separated by a washout period of at least 7 to 14 days

Criteria for Evaluation:

Pharmacokinetics: blood samples were collected predose and at predefined time points up to 96 hours after each study drug administration. Paliperidone plasma concentrations were determined using a validated LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.100 ng/mL (most samples), and 0.200 ng/mL (8 samples). Times of defecation were recorded for all treatments until 48 hours postdose. For Treatment C and D, stools were collected until the OROS systems had been retrieved or until 48 hours postdose.

Pharmacogenomics: A single blood sample was collected at any time during the study, after randomization.

Pharmacodynamics: Postural changes in heart rate and blood pressure were assessed at screening, predose, and predefined time points up to 48 hours after each study drug administration, and at the end of study.

Safety: *Adverse events*: reported by the subjects for the duration of the study. *Laboratory tests*: hematology, serum chemistry, and urinalysis (screening, predose on Day 1 of Period 1, end of the study), serology (screening), β-hCG (screening, end of study) and urine (before each drug administration) pregnancy test, urine drug screen (screening, before each drug administration), alcohol breath test (before each drug administration). *Physical examination*: screening, end of study. *Body temperature*: screening, predose for each study drug administration, end of study. *ECG*: screening, Day -1 of Period 1, end of study.

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Statistical Methods:

Pharmacokinetics: For each treatment, descriptive statistics were calculated for plasma concentrations at each time point, and for all PK parameters of paliperidone. Individual plasma concentration versus time profiles, and mean profiles per treatment were plotted. Calculation of point estimates and 90% confidence intervals (CIs) for the ratios of AUC_{last}, AUC_{∞}, and C_{max} (log-transformed data) for Treatments A vs. E, C vs. E, B vs. A, D vs. C.

Pharmacodynamics: Descriptive statistics were calculated; changes from baseline were summarized and graphically displayed. Symptoms of orthostatic hypotension were listed.

Safety: Adverse events were summarized. Descriptive statistics were calculated and changes from baseline were summarized for laboratory test results, and ECG findings. Physical examination, body temperature, and concomitant therapies were listed.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

One subject with missing data and 2 other subjects who vomited were excluded from the statistical analysis of the PK parameters.

Both ER formulations had lower mean C_{max} and lower mean AUC_{last} and AUC_{∞} values compared to the IR paliperidone oral solution, all in the fasted state. The relative, dose-normalized, bioavailability compared to IR paliperidone oral solution is shown in the table below. The 90% CIs were rather small.

	N	Mean Test Treatment		Mean Reference Treatment		Ratio % 90% CI[a]
C_{max}, ng/mL	32	A:	8.86	—E:	19.0	38.22 (35.49; 41.15)
	32	C:	8.41	—E:	19.0	21.55 (20.01; 23.20)
AUC_{last}, ng.h/mL	32	A:	258	—E:	380	55.38 (51.78; 59.22)
	32	C:	353	—E:	380	45.06 (42.13; 48.19)
AUC_{∞}, ng.h/mL	32	A:	281	—E:	407	56.05 (52.36; 59.99)
	32	C:	382	—E:	407	45.46 (42.47; 48.67)

[a)] Ratios and 90% CI corrected to 2-mg dose

Treatment A: ER pellet formulation (2.5 mg capsule) /fasted; Treatment C: coated ER OROS formulation (2x2 mg tablets)/fasted; Treatment E: 2.0 mg IR oral solution/fasted.

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The effect of food on the PK parameters of both ER formulations is summarized in the table below. The mean bioavailability was increased in the presence of food with circa 24% for the coated OROS formulation and 17% for the ER pellet formulation. The upper limit of the 90% CI for AUC_{last} and AUC_{∞} values for both ER formulations were above the bioequivalence interval of 80% to 125%. The 90% CI for C_{max} for the ER pellet formulation was 100-116%, which is within the 80-125% bioequivalence limits, while for the coated ER OROS formulation the upper limit of the 90% CI was above the 80-125% bioequivalence interval.

	N	Mean Test Treatment	Mean Reference Treatment	Ratio %	90% CI
C_{max}, ng/mL	32	B: 9.67	—A: 8.86	107.77	(100.07; 116.05)
	32	D: 10.4	—C: 8.41	117.57	(109.18; 126.62)
AUC_{last}, ng.h/mL	32	B: 306	—A: 258	117.94	(110.28; 126.13)
	32	D: 435	—C: 353	120.17	(112.37; 128.52)
AUC_{∞}, ng.h/mL	32	B: 330	—A: 281	117.47	(109.73; 125.74)
	32	D: 474	—C: 382	120.48	(112.55; 128.97)

Treatment A: ER pellet formulation (2.5 mg capsule) /fasted; Treatment B: ER pellet formulation (2.5 mg capsule) /fed;
Treatment C: ER OROS formulation (2x2 mg tablets)/fasted; Treatment D: ER OROS formulation (2x2 mg tablets)/fed.

OROS SYSTEM RECOVERY: Fifty-one systems were retrieved. The mean residual paliperidone content per system was 0.080 mg/RD (4.0%), suggesting almost complete delivery of the drug from the systems..

PHARMACOGENOMIC RESULTS: There was no apparent relationship between *CYP2D6* genotype and paliperidone exposure (C_{max}, AUC_{∞}). It should be noted that the exposure of 1 of the CYP2D6 poor metabolizers (Subject 109) was higher than that of the intermediate and extensive metabolizers for treatment B (C_{max} only), C, D and E (C_{max} and AUC). The relationship between *CYP3A4/5* genotypes and paliperidone exposure was not assessed.

PHARMACODYNAMIC RESULTS: Orthostatic intolerance was more pronounced with the solution fasted treatment than with the ER treatments and the orthostatic effect on SBP and DBP was less pronounced for the OROS treatments than for the other treatments.

SAFETY RESULTS: Overall, 34 of 35 subjects experienced at least one adverse event during the study. Somnolence and dizziness were the most frequently reported adverse events. Incidence of adverse events was higher for the IR oral solution treatment than for the ER pellet or coated ER OROS treatments. Most treatment emergent adverse events reported during this study were assessed by the investigator mild or moderate in severity and were considered at least possibly related to study drug. There were no deaths or other serious adverse events during this study, and no subjects withdrew due to an adverse event.

CONCLUSION:

The relative bioavailability based on AUC was approximately 56% for the ER pellet formulation, and around 45% for the paliperidone coated ER OROS formulation.
The mean bioavailability was increased in the presence of food by approximately 24% for the paliperidone coated ER OROS formulation and 17% for the ER pellet formulation.
There was no apparent relationship between the *CYP2D6* genotype and paliperidone exposure.
Paliperidone given as a single oral dose as ER pellet formulation, paliperidone-coated ER OROS formulation under fasted or fed conditions or as an IR oral solution under fasted conditions is safe and relatively well tolerated. The ER formulations seemed to cause fewer adverse events and less orthostatic hypotension than the IR paliperidone oral solution formulation (fasted).

Date of the report: 21 January 2005

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