SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ER OROS Paliperidone NAME OF ACTIVE INGREDIENT(S): Paliperidone/R076477	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: R076477-P01-1007, CR004216 **Title of Study:** Disposition of Paliperidone Enantiomers After Treatment With Different Formulations of the Racemate and the Separate Enantiomers and the Determination of the Absolute Bioavailability of IR and ER OROS Paliperidone		
Principal Investigator: A. Mertens, M.D. - Clinical Pharmacology Unit, A.Z. Jan Palfijn, Antwerp; Belgium		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 28 June 2004 - 27 August 2004 Sample Analysis: plasma samples: 24 August 2004 - 28 September 2004; urine samples: 7 September 2004 - 4 October 2004		**Phase of development:** 1
Objectives: 1) to characterize the pharmacokinetics of paliperidone in plasma and urine after i.v. administration of the racemate, administration of the IR racemate oral solution, administration of the ER OROS tablet, and administration of the oral solutions of the individual enantiomers R078543 (+) and R078544 (–) ; 2) to determine the absolute oral bioavailability of IR and ER OROS paliperidone; 3) to document the (+)/(–) paliperidone enantiomer ratio after i.v. and oral administration (IR and ER OROS paliperidone); 4) to document the possible interconversion between the (+) and (–) enantiomers of paliperidone after oral treatment with the separate enantiomers; 5) to document the possible relationship between the subject's CYP2D6 phenotype and the (+)/(–) enantiomer disposition of paliperidone (*CYP2D6* genotyping was used to corroborate the phenotype). In addition, the safety and tolerability of all treatments were evaluated.		
Methodology: This was a single-center, single-dose, open-label, randomized, crossover study in healthy adults, following a 5-sequence, 5-treatment, 5-period Latin square design. The study consisted of a screening phase (within 21 days before the first administration of study drug), and a treatment phase consisting of 5 periods during which subjects received a single dose of study drug under fasting conditions (orally with 240 mL of water or i.v.) in a random order. Pharmacokinetic blood and urine samples were collected over a 96-hour period following study drug administration during each treatment period. Subjects were confined to the testing facility from at least 10 hours before dosing until 72 hours after dosing in each treatment period and returned for additional assessments. Each administration of study drug was separated by a washout period of at least 7 to a maximum of 14 days. The duration of subject participation was maximally 12 weeks, including the 3-week-screening period. CYP2D6 metabolizer status was assessed by phenotyping and corroborated by genotyping of a DNA sample collected from subjects who consented to this part of the study.		
Number of Subjects (planned and analyzed): 20 planned, 20 analyzed for PK and Safety, 19 analyzed for PG.		
Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18 to 55, inclusive; with a body mass index of 18 to 28 kg/m^2, inclusive; with a known dextromethorphan metabolic ratio of <0.02 or >0.35; and being normotensive.		
Test Product, Dose and Mode of Administration, Batch No.: 1 mg IR paliperidone as an oral solution (batch no: 04C29/F044), 3 mg ER OROS paliperidone oral tablet (batch no: MV0307085), 1 mg paliperidone as a 30-min i.v. infusion (batch no: 04C29/F044), 1 mg (+)-paliperidone (R078543) as an oral solution (batch no: 04D19/F001), and 1 mg (–)-paliperidone (R078544) as an oral solution (batch no: 04D22/F001).		
Reference Therapy, Dose and Mode of Administration, Batch No.: None		
Duration of Treatment: 5 single doses		

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Criteria for Evaluation:

Pharmacokinetics:

Plasma and urine concentrations of the paliperidone enantiomers were determined using an LC-MS/MS method. Concentrations of paliperidone were calculated as the sum of the enantiomer concentrations. In addition, serum and urine concentrations of creatinine were determined for the calculation of CL_{CR}. The protein binding and unbound fraction were determined for the 2 paliperidone enantiomers. The unbound fraction for paliperidone was calculated.

Based on the actual pharmacokinetic blood sampling times and actual urine collection periods, the following plasma and urinary pharmacokinetic parameters were determined for paliperidone and its enantiomers: C_{max}, t_{max}, t_{last}, AUC_{last}, λ_z, $t_{1/2}$, AUC_∞, $\%AUC_{\infty,ex}$, CL/F, F_{abs}, CL (if relevant), AUC_∞ +/– ratio, C_t +/– ratio per time point, unbound AUC_∞, unbound CL/F or unbound CL (if relevant), Ae (per collection interval and overall), Ae%dose, Excr. Rate, CL_R, CL_{GFR}, CL_{act}, CL_{CR}, and CL_{NR}.

A compartmental pharmacokinetic analysis of both enantiomers for the five different treatments was performed.

Pharmacogenomics: During Period 1, a 10-mL blood sample was collected of subjects who gave informed consent for this part of the study for genotyping of *CYP2D6*, and to allow for genotyping of additional genes associated with paliperidone or schizophrenia, which may influence pharmacokinetics, safety, or tolerability.

Safety: Safety was evaluated by examining incidence, severity, and type of adverse events, changes in clinical laboratory and physical examination results, vital sign measurements (including body temperature, blood pressure, and pulse rate), and 12-lead electrocardiograms (ECGs).

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the plasma concentrations at each sampling time, and for all pharmacokinetic parameters of paliperidone and its enantiomers, with differentiation between PM and EM for CYP2D6. Graphical exploration of the paliperidone and enantiomer plasma concentrations and urine data, and the derived pharmacokinetic parameters was performed.

The primary objective of the statistical analysis was to estimate the AUC_∞ ratio of (+)/(–) paliperidone in all 5 treatments. Interconversion was characterized on (+)/(–) paliperidone ratios of AUC_∞, and C_t for the different treatments.

The absolute bioavailability of IR paliperidone as an oral solution and ER OROS paliperidone was determined using the respective ratios of the mean pharmacokinetic parameters (primarily AUC_∞) for IR paliperidone as an oral solution racemate and ER OROS paliperidone versus paliperidone i.v. The analysis was carried out on dose-normalized, log-transformed data.

For compartmental pharmacokinetic analysis, descriptive statistics was calculated for all pharmacokinetic parameters of both enantiomers.

Pharmacogenomics: The predicted phenotype based on *CYP2D6* genotyping was cross-checked against the phenotypically-determined CYP2D6 metabolizer status and the relationship between genotype and pharmacokinetic parameters was examined graphically.

Safety: Treatment-emergent adverse events were summarized by body system and preferred term, by severity, and by relationship to study drug. Descriptive statistics and changes from baseline were used to summarize clinical laboratory data, vital signs, and ECGs at each scheduled time point. Physical examination abnormalities were listed.

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SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

The absolute bioavailability (log-transformed paliperidone AUC_{∞}) of 1 mg IR paliperidone oral solution is 106.11% (90% CI: 89.59% - 125.69%) and the absolute bioavailability of 3 mg ER OROS (dose-normalized to 1 mg) is 27.69% (90% CI of 23.38% - 32.80%).

On average, the unbound fraction in plasma was 18% for R078543 (+), 35% for R078544 (–) and around 24% for paliperidone.

Pharmacokinetic parameters of paliperidone and its enantiomers for all 5 treatments are summarized in Table A.

The C_{max} for paliperidone after the various treatments decreased in the following order: i.v. administration > R078543 (+) oral solution > IR paliperidone oral solution > R078544 (–) oral solution > ER OROS paliperidone. The reverse order was applicable for t_{max}. The terminal half-live of all substances is about 24 hours and consistent among the 5 treatments.

There was consistency in the exposure (AUC_{∞}) to both total and unbound paliperidone and its enantiomers across all the 5 treatments. Also the total and unbound clearance of paliperidone was comparable for all the treatments, including the ER OROS treatment when taking into account the bioavailability of 27.69%. The amount of paliperidone excreted in the urine was about 45% of the total administered dose for all the treatments, except the ER OROS formulation for which 13% of the dose was urinary excreted, reflecting the lower bioavailability for ER OROS.

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Table A: Pharmacokinetic Parameters (Mean ± SD) of Paliperidone and its Enantiomers (N=20)

	Treatment				
	Racemic paliperidone			Paliperidone enantiomers	
PK parameter	IR paliperidone oral solution 1 mg	ER OROS, oral 3 mg	30 min. i.v. infusion 1 mg	R078543 (+) oral solution 1 mg	R078544 (–) oral solution 1 mg
Substance: Paliperidone					
t_{max}, h	1.80 ± 0.91	23.46 ± 4.89	0.50 ± 0.00	1.80 ± 1.53	3.30 ± 1.91
C_{max}, ng/mL	9.38 ± 2.32	4.90 ± 2.14	17.8 ± 4.46	13.1 ± 5.34	6.14 ± 1.88
AUC_{∞}, ng.h/mL	241 ± 73.1	210 ± 100	233 ± 89.0	275 ± 109	219 ± 77.9
$AUC_{\infty,u}$ ng.h/mL	58.1 ± 12.5	53.8 ± 16.3 [b]	56.7 ± 16.9 [c]	63.8 ± 16.6 [b]	59.2 ± 13.0 [b]
$t_{1/2}$, h	25.2 ± 4.3	25.2 ± 4.2	24.6 ± 4.8	24.0 ± 4.2	26.3 ± 5.0
CL/F mL/min [a]	76.5 ± 26.8	356 ± 340	83.2 ± 34.7	71.1 ± 31.3	86.9 ± 36.2
CL_u/F mL/min [a]	301 ± 70.5	1060 ± 538 [b]	319 ± 97.7 [c]	276 ± 63.9 [b]	296 ± 71.2 [b]
CL_R mL/min	33.3 ± 12.6	35.5 ± 13.5 [b]	36.0 ± 14.1	30.8 ± 12.8 [c]	37.6 ± 15.0
Substance: R078543 (+)					
t_{max}, h	1.53 ± 0.82	23.56 ± 4.88	0.50 ± 0.00	1.55 ± 0.58	10.00 ± 5.19
C_{max}, ng/mL	6.51 ± 1.75	3.16 ± 1.45	11.5 ± 2.94	12.2 ± 4.98	2.35 ± 1.64
AUC_{∞}, ng.h/mL	153 ± 48.5	133 ± 64.7	148 ± 60.5	205 ± 84.0	118 ± 43.5 [b]
$AUC_{\infty,u}$ ng.h/mL	26.7 ± 6.16	23.0 ± 9.64	25.7 ± 9.16	35.4 ± 11.2	20.1 ± 5.20 [b]
$t_{1/2}$, h	25.7 ± 4.1	25.3 ± 5.0	25.0 ± 4.7	24.4 ± 4.9	29.5 ± 5.0 [c]
CL/F mL/min [a]	60.9 ± 23.3	277 ± 252	67.2 ± 30.8	96.9 ±46.6	ND
CL_u/F mL/min [a]	332 ± 90.0	1502 ± 1347	365 ± 134	523 ± 196	ND
CL_R mL/min	21.4 ± 8.74	23.0 ± 8.85 [b]	23.7 ± 9.83	22.5 ± 9.37 [c]	19.3 ± 7.81 [b]
Substance: R078544 (–)					
t_{max}, h	2.38 ± 1.59	23.56 ± 4.97	0.50 ± 0.00	9.40 ± 5.28	1.88 ± 0.48
C_{max}, ng/mL	3.07 ± 0.705	1.74 ± 0.712	6.34 ± 1.57	1.49 ± 0.500	4.88 ± 1.32
AUC_{∞}, ng.h/mL	91.3 ± 23.3	85.3 ± 29.0 [b]	89.4 ± 26.7 [c]	79.2 ± 23.3 [d]	110 ± 32.8
$AUC_{\infty,u}$ ng.h/mL	31.4 ± 6.77	28.9 ± 8.59 [b]	30.5 ± 8.06 [c]	26.4 ± 7.28 [b]	37.8 ± 9.13
$t_{1/2}$, h	25.9 ± 4.2	25.5 ± 3.8	25.4 ± 4.7	27.6 ± 3.6 [c]	24.1 ± 5.6
CL/F mL/min [a]	97.7 ± 27.6	339 ± 166 [b]	102 ± 32.5 [c]	ND	167 ± 59.8
CL_u/F mL/min [a]	277 ± 60.3	981 ± 498 [b]	291 ± 78.2 [c]	ND	471 ± 137
CL_R mL/min	50.5 ± 16.1	50.8 ± 16.2 [b]	52.4 ± 16.4 [c]	45.5 ± 16.5 [e]	52.3 ± 18.8

ND: Not Determined

[a] For the i.v. treatment, CL/F and Cl_u/F equal CL and Cl_u respectively.

[b,c,d,e] descriptive statistics based on n=18, n=19, n=17 and n=16, respectively

The plasma concentration-time profiles for poor (n = 10) and extensive (n = 10) CYP2D6 metabolizers substantially overlap, and graphical exploration indicated no difference in pharmacokinetic parameters (C_{max} and AUC_{∞}) between poor and extensive CYP2D6 metabolizers in the various treatments. Also, these parameters were not related to the *CYP2D6* genotype.

The AUC_{∞} (+)/(–) ratio was 1.66 after administration of the racemic mixture, either as an i.v. infusion, IR oral solution or ER OROS formulation.

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To further characterize the in vivo interconversion between the (+) and (–) enantiomer of paliperidone, subjects were treated with oral solutions of the individual enantiomers. When R078544 (-) was administered, the (+)/(–) AUC_{∞} ratio was 1.01 based on total concentrations and 0.51 based on unbound concentrations. When R078543 (+) was administered, these ratios were 2.81 and 1.43 respectively. Based on $AUC_{\infty,u}$, 43% of the paliperidone exposure could be attributed to the R078544 (-) enantiomer after administration of R078543 (+), and 35% of the paliperidone exposure was attributable to R078543 (+) after administration of R078544 (-). The in vivo interconversion is thus similar from the (+) to the (–) enantiomer and from the (–) to the (+) enantiomer.

For the compartmental pharmacokinetic analysis, a low intersubject variability was observed for most predicted pharmacokinetic parameters and the obtained results were in good agreement with the results after non-compartmental pharmacokinetic analysis.

PHARMACOGENOMIC RESULTS: The genotyping data supported the dextromethorphan phenotyping data for CYP2D6 metabolizer status in all but 1 subject. Graphical exploration of the data indicated no relationships between the observed CYP2D6 phenotype or genotype and the pharmacokinetic parameters (C_{max} and AUC_{∞}).

SAFETY RESULTS: Overall, all treatments with paliperidone were well tolerated by the subjects.

The most frequently reported events were somnolence, postural hypotension, and headaches, which are known to occur with paliperidone, fatigue was also frequently reported.

Slightly more subjects reported adverse events during i.v. paliperidone treatment than during the 4 oral treatments. The most obvious difference was observed in the incidence of symptomatic postural hypotension. Most adverse events were mild or moderate, 6 were severe.

There were no clinically relevant changes in laboratory parameters and ECG findings. Mean values for vital signs did not change over the study period with any of the treatments.

CONCLUSIONS:

The absolute oral bioavailability was 106% for IR paliperidone and 28% for the ER OROS formulation.

The overall exposure and the clearance are comparable after i.v. treatment (1 mg), oral IR paliperidone (1mg) and ER OROS (3 mg).

The maximal plasma concentration after ER OROS paliperidone (3 mg) administration was approximately 2 times lower compared to the IR paliperidone oral administration (1 mg), and 3.5 times lower compared to the i.v. administration (1 mg).

The plasma-protein binding differs between the 2 paliperidone enantiomers and was 82% for R078543 (+), 65% for R078544 (–) and 76% for paliperidone.

There is about 40% in vivo interconversion from the R078543 (+) to the R078544 (–) enantiomer, and vice versa.

After administration of paliperidone as a racemate, the (+)/(–) paliperidone AUC∞ ratio is 1.66, irrespective of the route of administration and type of formulation.

The safety profile of all 4 oral paliperidone treatments was similar. The overall incidence of adverse events was noticed to be higher with i.v. paliperidone treatment, compared to the 4 oral treatments. There were no unexpected or unusual clinically relevant findings with respect to laboratory test results, vital signs and ECG parameters.

Date of the report: 27 October 2005

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