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	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: R076477-P01-1004, CR004150

Title of Study: Investigation of the Potential Effects of Trimethoprim on the Pharmacokinetics of ER OROS® Paliperidone in Healthy Male Subjects

Principal Investigator: J. Leempoels, M.D. - Clinical Pharmacology Unit, A.Z. Jan Palfijn, Antwerp; Belgium

Publication (Reference): None

Studied Period (years): Clinical Conduct: 6 October 2004 – 7 November 2004	**Phase of development:** 1

Objectives: To evaluate the effects of an organic cation transporter inhibitor, trimethoprim, on the pharmacokinetics of orally administered ER OROS paliperidone, and to assess the safety and tolerability of the treatments in healthy subjects.

Methodology: This was a single-center, open-label, randomized, 2-treatment period crossover study in healthy male subjects. The study consisted of a screening period (within 21 days before the first study drug administration) before randomization; an open-label treatment phase consisting of 2 periods during which subjects received a single oral dose of ER OROS paliperidone alone (Treatment A) or in combination with 200 mg trimethoprim b.i.d. (Treatment B); and end-of-study evaluations upon completion of all the study procedures in Period 2 or early withdrawal. The pharmacokinetic blood and urine samples were collected over a 96-hour period after ER OROS paliperidone administration. Successive ER OROS paliperidone administrations were separated by at least 14 days. A blood sample for genotyping was collected at any time on Day 1 of Period 1 after a separate informed consent for DNA sampling was signed. Participation in the pharmacogenomic part of the study was optional.

Number of Subjects (planned and analyzed): Planned: 30 subjects were planned to be enrolled in the study. Analyzed: 30 subjects for pharmacokinetics (PK); 30 subjects for safety.

Diagnosis and Main Criteria for Inclusion: Subjects were healthy men, aged 18 to 55 years, inclusive, with a body mass index (BMI) range of 18.0 to 28.0 kg/m², inclusive, who were normotensive with a supine (5 minutes) blood pressure within the range of 100 to 140 mmHg systolic, inclusive, and 60 and 90 mmHg diastolic, inclusive. Considered healthy based on a prestudy physical examination, medical history, ECG, and the laboratory results of serum chemistry, hematology and urinalysis performed within 21 days before the first dose. Creatinine clearance value ≥ 80 mL/min, and signed the Informed Consent Forms (for participation in the study, in the genetic part of the study, or both).

Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone 6 mg tablets (formulation number F047, batch number 0406837). Trimethoprim 200 mg tablets were provided as commercial bottles. Treatment A: a single dose of 6 mg ER OROS paliperidone on Day 1; Treatment B: a 200 mg trimethoprim tablet b.i.d. from Day 1 to Day 8 and a single dose of 6 mg ER OROS paliperidone on Day 5. All subjects received each of these 2 treatments (1 during each treatment period).

Reference Therapy, Dose and Mode of Administration, Batch No.: None

Duration of Treatment: Treatment A: 1 day; Treatment B: 8 days.

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Criteria for Evaluation:

Pharmacokinetics: Concentrations of the paliperidone enantiomers in plasma and urine were determined using a LC-MS/MS method. The concentration of paliperidone was calculated as the sum of the 2 enantiomers. Plasma concentrations of trimethoprim were determined using a LC method.

Based on the actual pharmacokinetic blood sampling times and actual urine collection times, the following plasma and urine pharmacokinetic parameters were determined for paliperidone and its enantiomers: C_{max}, unbound C_{max} t_{max}, t_{last}, $t_{1/2}$, λ_z, AUC_{last}, AUC_{∞}, unbound AUC_{∞}, total (apparent) plasma clearance (CL/F), unbound (apparent) plasma clearance (CL_u/F), excretion rate, renal clearance (CL_R), clearance by glomerular filtration (CL_{GFR}) and active clearance (CL_{act}).

Pharmacogenomics: Part 1a: Analysis of the *CYP2D6* genotype. Part 1b: if needed, analysis of genes involved in absorption, distribution, metabolism, excretion, and transportation, and genes related to schizophrenia..

Safety: Safety was evaluated by examining incidence, severity, and type of adverse events; physical examination results; vital sign measurements; 12-lead electrocardiograms (ECG); changes in clinical laboratory results including prolactin; and concomitant medications/therapy.

Statistical Methods:

Pharmacokinetics: Descriptive statistics and graphical presentation for the plasma and urine concentrations at each sampling time, and for all derived plasma and urine PK parameters of paliperidone and its enantiomers for both treatments. Statistical analysis of ln-transformed C_{max}, $C_{max,u}$, AUC_{last}, AUC_{∞}, $AUC_{\infty,u}$, and CL_R of paliperidone and its enantiomers, using a mixed-effect ANOVA model including sequence, period, and treatment as fixed effects, and subject (nested within sequence) as random effect. Subsequent calculation of the classical 90% confidence intervals for the ratio of the mean pharmacokinetic parameters of paliperidone and its enantiomers with and without co-administration of trimethoprim. Descriptive statistics and graphical presentation for the plasma concentrations of trimethoprim (Treatment B only).

Pharmacogenomics A Composite Genotype and Predicted Phenotype (where possible) were derived from the raw genotyping data. After stratifying by treatment group, allele and genotype frequencies were tabulated, and relationships between Genotype or Predicted Phenotype (as applicable) and C_{max}, AUC_{last}, and AUC_{∞} of paliperidone and its enantiomers were explored graphically.

Safety: Safety data were summarized using descriptive statistics and incidence tables.

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Demographic and Baseline Characteristics: Thirty men were enrolled in this study (age 19 to 51 years, BMI 19-28 kg/m^2). No clinically relevant medical history or physical examination findings were noted at entry.

Pharmacokinetic Results: Plasma and urine pharmacokinetic parameters were available for all 30 subjects after administration of 6 mg ER OROS paliperidone with and without co-administration of trimethoprim.

Trimethoprim intake caused a slight increase in the fraction of unbound paliperidone in plasma. Trimethoprim did not result in any relevant increase in peak plasma concentration or exposure of paliperidone. On average, intake of trimethoprim slightly increased peak concentration (by 9%) and renal clearance (by 12%), and slightly decreased AUC (by 5 to 9%) and terminal half-life (by 19%). Mean time to peak and urinary excretion as unchanged paliperidone were not modified.

Table A: Paliperidone Plasma and Urine Pharmacokinetic Parameters (Mean ± SD)

Parameter; N=30	Paliperidone Alone	Paliperidone + Trimethoprim
f_u, %	25.7 ± 3.81	29.7 ± 3.77
C_{max}, ng/mL	9.78 ± 3.45	10.7 ± 3.67
$C_{max,u}$, ng/mL	2.48 ± 0.840	3.16 ± 1.09
AUC_{last}, ng.h/mL	348 ± 119	330 ± 130
AUC_{∞}, ng.h/mL	391 ± 138	356 ± 148
$AUC_{\infty,u}$, ng.h/mL	99.0 ± 33.2	106 ± 44.0
t_{max}, h	24.00 (16.00-28.00)	23.78 ± 2.63
$t_{½}$, h	26.8 ± 5.09	21.8 ± 3.57
Ae_{0-96h}, mg	1.15 ± 0.349	1.18 ± 0.351
CL/F, mL/min	290 ± 108	327 ± 135
CL_R, mL/min	52.4 ± 16.1	59.2 ± 17.9
CL_{GFR}, mL/min	30.7 ± 7.88	30.4 ± 7.61
CL_{act}, mL/min	21.7 ± 11.8	28.7 ± 13.8

t_{max}: median (min-max)

The mean cumulative amount of paliperidone excreted unchanged in urine was not affected by trimethoprim (about 1.15 mg). The mean renal clearance was increased by 12% when trimethoprim was coadministered. The clearance caused by glomerular filtration rate and active secretion was similar in both treatments.

The statistical analysis (ANOVA; N=30 subjects) did not reveal any significant effect of trimethoprim intake on the pharmacokinetic parameters (C_{max} and AUC) of paliperidone or its enantiomers. All 90% confidence intervals for the paliperidone with trimethoprim treatment versus paliperidone alone treatment ratios were included within 80 to 125%, except for AUC_{∞}, which had a 90% CI with a lower bound just outside the acceptance range (79.37-101.51). Although, there was a slight increase on the renal clearance of paliperidone by trimethoprim coadministration, this effect was of minor amplitude as the 90% CI of the ratio was included within 80 to 125%.

While the mean unbound paliperidone peak plasma concentration was significantly increased after trimethoprim administration, the mean total systemic exposure of unbound paliperidone was only slightly higher. Similar results were observed for the 2 paliperidone enantiomers, R078543 and R078544.

Steady-state of trimethoprim was reached by Day 4. The mean±SD trough trimethoprim concentrations on Day 4 (=before paliperidone administration) were 2480 ± 718 ng/mL (morning) and 2320 ± 697 ng/mL (evening). Following single ER OROS paliperidone administration on Day 5, mean evening trough trimethoprim concentration was 2160 ng/mL, indicating no effect of paliperidone on the pharmacokinetics of trimethoprim.

Pharmacogenomics: The CYP2D6 phenotypes of the 29 subjects who participated in the pharmacogenomic part of the study were as follows: 3 ultrarapid, 20 extensive, 2 intermediate, and 4 poor metabolizers. There was no relationship between the CYP2D6 phenotype and the pharmacokinetic parameters (C_{max} and AUC) of paliperidone and its enantiomers.

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Safety Results: There were no deaths or other serious adverse events during the study, and no subjects had adverse events leading to discontinuation of treatment. Most adverse events resolved without treatment intervention. After a single dose of paliperidone (Treatment A), the most common adverse events (>5% incidence) were: fatigue (17%), flatulence (13%), postural hypotension (10%), headache (10%) and somnolence (10%). During treatment with trimethoprim for 4 days, the adverse events included flatulence, diarrhea, headache and somnolence, each reported in 1 (3%) subject. After a single dose of paliperidone in subjects who had already received trimethoprim for 4 days and continued to receive trimethoprim for a further 4 days, the incidence of adverse events was higher. Adverse events included flatulence (33%), postural hypotension (27%), somnolence (17%), headache (13%) and dry mouth (10%). Most of the adverse events were either of mild or moderate intensity. The most common severe adverse event was flatulence (10%). One subject receiving trimethoprim+paliperidone had severe postural hypotension. Most adverse events were considered as not related or doubtfully related to study drug. Postural hypotension, flatulence, headache, somnolence, fatigue, dizziness, and nausea were mostly considered as possibly, probably, or very likely related to the study drug.

Overall, there was no consistent relationship between increased ALT, AST, or GGT levels and treatment given. None of the increased ALT, AST or GGT levels was greater than 3 times the upper laboratory reference point, suggesting that the treatment-emergent increased enzyme levels were probably of limited clinical importance. There were no laboratory abnormalities reported as adverse events. One subject (paliperidone+trimethoprim treatment arm) had a treatment-emergent markedly abnormal eosinophils value of 11.6% (markedly abnormal upper limit: 10 %; upper laboratory limit 2%). Nine subjects had treatment-emergent markedly abnormal LDH levels by the criteria set by the sponsor (>500 U/L). However, only 3 out of these 9 LDH values were above the upper laboratory limit (618 U/L) for LDH. Two subjects (paliperidone alone treatment arm) had treatment-emergent markedly abnormal LDH values of 661 U/L and 746 U/L, respectively, at the end of treatment. The subject with 746 U/L LDH had a concomitant markedly abnormal laboratory ALT value of 201 U/L (markedly abnormal upper limit: 200 U/L) at the end of treatment (paliperidone alone). One subject (paliperidone+trimethoprim treatment arm) had a markedly abnormal LDH value of 661 U/L at the end of treatment.

Seven subjects experienced increased heart rate upon standing (PAL alone: 1 subject; PAL+trimethoprim: 2 subjects; both after PAL alone and PAL+trimethoprim: 4 subjects). There did not appear to be a relationship between study drug treatment and incidence of increased heart rate. Postural hypotension was reported as an adverse event for 9 subjects. There were no associated symptoms with any of these cases of orthostatism.

None of the subjects had a QTc interval increase >60 ms from baseline, and no subjects had a QTc interval >500 ms. One subject with normal QTcF, QTlc and QTcB at baseline had increases of 47, 45 and 96 ms, respectively at the end of the study. His end-of-study QTcB (466 ms) was prolonged according to the criteria used in the study (>450 ms). His end-of-study QTcF and QTlc were 425 ms and 419 ms, respectively. This subject also had an above-normal heart rate (HR) at the end of the study (HR=104 bpm). One subject with normal QTcF, QTlc and QTcB at baseline had increases of 32, 39 and 41 ms respectively, at the end of the study. However, none of these end-of-study QTc values was borderline or prolonged, according to the criteria used in the study (430-450 ms and >450 ms, respectively). One subject with a normal QTcB at baseline had an increase of 3 ms at the end of the study. The end-of-study QTcB (431 ms) was borderline according to the criteria used in the study (430-450 ms). One subject had borderline QTcF, QTlc and QTcB at all time points, except for a normal QTcB at predose in period 2.

Conclusion: Co-administration of 200 mg trimethoprim b.i.d. with a single oral dose of 6 mg ER OROS paliperidone did not cause a relevant change in the plasma and urine pharmacokinetic parameters of paliperidone and its two enantiomers. Co-administration of ER OROS paliperidone and trimethoprim was well tolerated in healthy subjects in this study.

Date of the report: 16 August 2005

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