SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: TOPAMAX® (topiramate) NAME OF ACTIVE INGREDIENT(S): 2,3:4,5 Di-*O*-isopropylidene-β-D-fructopyranose sulfamate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: TOPMAT-PHI-389

Title of Study: A comparative study of the steady-state pharmacokinetics (PK) of risperidone and topiramate (TPM) on monotherapy and during combination therapy in subjects with bipolar or schizoaffective disorders.

Coordinating Investigator: Robert Litman, M.D., Center for Behavioral Health, Rockville, MD, USA

Publication (Reference): none

Studied Period (years): Clinical Conduct: 11 April 2001 to 23 August 2002 | **Phase of development:** 1

Methodology: This was an open-label, nonrandomized PK study evaluating the interaction of TPM and risperidone in patients with bipolar disorder. The study consisted of a screening phase and 3 treatment periods. In *Period I*, subjects were stabilized to a clinically appropriate dose of risperidone within the range of 1 to 6 mg/day, administered in divided doses every 12 hours (q12h) during a 2- to 3-week period (or longer as clinically necessary). Upon risperidone stabilization, serial blood and urine samples were obtained through 12 hours postdose for estimation of risperidone and 9-OH-risperidone concentrations in Period I. In *Period II*, which lasted up to 6 weeks or longer as clinically necessary, TPM was gradually escalated to 3 steady-state target doses, while risperidone therapy continued unchanged. There were up to 3 PK sampling periods: 1) when the subject achieved steady state at 100 mg/day; 2) when/if the subject achieved steady state at 250 mg/day or maximum tolerated dose (MTD); and 3) when/if the subject achieved steady state at 400 mg/day or MTD. During each PK sampling visit in Period II, serial blood and urine samples were obtained through 12 hours postdose for estimation of risperidone, 9-OH risperidone, and TPM concentrations. In *Period III*, risperidone was gradually tapered while the 400-mg/day dose (or MTD) of TPM was maintained. There were 2 PK sampling visits: 1) when subjects had attained steady state at a dose of 50% of the maximal risperidone dose reached in Period I; 2) when risperidone was discontinued for 7 days and subjects were maintained on TPM 400 mg/day or their respective MTD. During each PK sampling visit in Period III, serial blood and urine samples were obtained through 12 hours postdose for estimation of risperidone, 9-OH risperidone, and TPM concentrations.

Number of Subjects (planned and analyzed): Planned (M/F): 24 (12/12); Evaluated for safety (M/F): 57 (25/32). Evaluated for PK (M/F): (24/28).

Diagnosis and Main Criteria for Inclusion: Subjects were men or women aged 18 to 55 years, inclusive, with a documented DSM IV diagnosis of various bipolar spectrum disorders (including Bipolar I, II, and Cyclothymic Disorder) Bipolar Disorder NOS, or Schizoaffective Disorder (bipolar type).

Test Product, Dose and Mode of Administration, Batch No.: TPM for oral administration was supplied as 25-mg white film-coated tablets (FD-17021-000-AQ-22, Batch R11601; NDC-0045-0639-65, Batch R10872) and 100-mg yellow film-coated tablets (FD-17021-000-AK-22, Batch R11602; NDC-0045-0641-65, Batch R10873). Risperidone for oral administration was supplied as 0.25-mg tablets (NDC: 50458-301-04, Batch R10674; NDC: 60458-302-06, Batch R11603), 0.50-mg tablets (NDC: 50458-302-06: Batch R10875; NDC: 60458-302-06, Batch R11604), and 1.0-mg tablets (NDC: 50458-300-06: Batches R11605, R10876).

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

Duration of Treatment: Period I (risperidone stabilization): risperidone 1-6 mg/day was administered for 2 to 3 weeks. Period II (TPM dose escalation): TPM was administered for approximately 6 weeks titrated up to 3 potential target doses of 100 mg/day, 250 mg/day and 400 mg/day, and risperidone continued unchanged. Period III (risperidone dose reduction): the risperidone dose was tapered to zero over a 4-week period, while TPM was maintained at the target dose of 400 mg/day (or MTD).

Criteria for Evaluation: Pharmacokinetics: Following morning dose administration, blood samples (5 mL) were collected for estimation of risperidone and 9-OH risperidone plasma concentrations during Periods I, II (for each dose escalation) and III (for 50% reduction and discontinuation at the following times during each PK sampling visit: 0 hour (predose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose. Urine samples were also collected for

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Criteria for Evaluation (Cont'd): for estimation of risperidone, 9-OH risperidone, and TPM (during Periods II and III only) concentrations during the following collection intervals: 0 to 2, 2 to 4, 4 to 8, and 8 to 12 hours postdose. The following PK parameters were estimated for the total active moiety, risperidone, 9-OH risperidone, and TPM by standard model-independent (noncompartmental) methods: AUC_{12}, C_{max}, t_{max}, CL/F for risperidone and TPM only, Ae (also referred to as Au), and CL_R for TPM and risperidone only. (See abbreviations section for definitions).

Safety: Safety evaluations were based on reports of treatment-emergent adverse events, and changes from baseline in clinical laboratory analyte values, vital sign measurements, electrocardiograms (ECGs), and physical examination findings. The subject's clinical status was monitored at each PK sampling period using the Global Assessment Scale (GAS).

Statistical Methods: Pharmacokinetics: The dose-normalized PK parameters (AUC_{12} and C_{max}) of the total active moiety, risperidone, and 9-hyrdoxyrisperidone estimated during treatment with risperidone alone (Period I) and with co-administration of the 3 doses of TPM (Period II) were compared using ANOVA to determine the interaction potential of TPM on risperidone. Selected PK parameters (AUC_{12} and C_{max}) of TPM obtained from the final sampling during the TPM titration period (Period II) and during Period III (at 50% risperidone reduction and on TPM monotherapy) were compared using ANOVA to determine the interaction potential of risperidone on TPM. The estimated least square means and intra-subject variability from the mixed-effect model were used to construct 90% confidence intervals (CI) for the difference in means for each comparison.

Safety: The nature and frequency of treatment-emergent adverse events were summarized. Changes from baseline in vital sign, physical examination, and laboratory measurements were also summarized.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: Mean estimates for dose-normalized C_{max} for the total active moiety were similar for risperidone treatment alone and during combination treatment with TPM at 100 mg/day, 250 mg/day, and 400 mg/day. Dose-normalized mean estimates for AUC_{12} were 12.5% higher during treatment with TPM 100 mg/day compared to risperidone treatment alone, but were similar during treatment with higher daily doses of TPM. Renal clearance of the total active moiety decreased when risperidone and TPM were administered together, resulting in an approximately 24%, 31%, and 14% reduction in CL_R at the 100 mg/day, 250 mg/day, and 400 mg/day TPM dose, respectively. Mean SD estimates for dose-normalized C_{max} and AUC_{12} for the total active moiety are summarized in the table below.

Differences in the PK parameter estimates (AUC_{12}, C_{max} and Au) for the total active moiety between treatment with risperidone alone and combination treatment with TPM administered as 3 different daily doses were not statistically significant as p-values exceeded 0.05 for all parameters tested except for Au at the 250 mg/day dose of TPM (p=0.0072). The estimated geometric mean ratios comparing combination risperidone and TPM treatment to risperidone treatment alone approximated 100% for both AUC_{12} and C_{max} for all TPM doses tested. The 90% CI for total active moiety AUC_{12} and C_{max} were within the range of 80% to 125% indicating that all combination treatments (TPM at escalating doses + risperidone) were equivalent to risperidone treatment alone.

Risperidone was rapidly absorbed with peak concentrations occurring at approximately 1 to 1.5 hours following oral administration. Mean estimates for dose-normalized C_{max} and AUC_{12} for risperidone were similar when administered alone and during combination treatment with TPM at 100 mg/day. There was a 13% and 24% reduction in mean dose-normalized C_{max} following administration of TPM at doses of 250 mg/day and 400 mg/day, respectively.

There was a 16% and 33% reduction in dose-normalized AUC_{12} following administration of TPM at doses of 250 mg/day and 400 mg/day, respectively. Mean estimates for CL/F were 22% and 47% higher following administration of TPM at doses of 250 mg/day and 400 mg/day, respectively.

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PHARMACOKINETIC RESULTS (Cont'd): Risperidone was minimally excreted in the urine unchanged (~ 6% or less). Renal clearance of risperidone appeared to decrease during combination treatment with TPM, resulting in an approximately 33%, 49%, and 28% reduction in CL_R at the 100 mg/day, 250 mg/day, and 400 mg/day TPM doses, respectively. Mean SD estimates for dose-normalized C_{max} and AUC_{12} for risperidone are summarized below.

At the 100 mg/day dose of TPM, differences in the PK parameter estimates were not statistically significant for AUC_{12} and C_{max} as p-values exceeded 0.05, however, differences in Au estimates were statistically significant (p=0.0471). For the 250 and 400 mg/day doses of TPM, differences in all of the PK parameter estimates tested (AUC_{12}, C_{max}, and Au) were statistically significant as all p-values were less than 0.05. Point estimates for risperidone AUC_{12} and C_{max} were approximately 8% and 13% lower during treatment with TPM 100 mg/day. Their associated 90% CI were within the 80% and 125% limits for AUC_{12}, but not for C_{max}. In contrast, point estimates for risperidone AUC_{12} and C_{max} were approximately 21% lower during treatment with TPM 250 mg/day and their associated 90% CI were outside the 80% to 125% limits, indicating that the 2 treatments were not equivalent. Similarly, point estimates for risperidone AUC_{12} and C_{max} were approximately 25% and 30% lower, respectively, during treatment with TPM 400 mg/day and their associated 90% CI were outside the 80% to 125% limits, indicating that the 2 treatments were not equivalent.

Mean estimates for dose-normalized C_{max} for 9-OH risperidone were 11%, 5%, and 11% higher during combination treatment with TPM at doses of 100 mg/day, 250 mg/day, and 400 mg/day, respectively. Similarly, mean estimates for dose-normalized AUC_{12} for 9-OH risperidone were 14%, 9%, and 12% higher during combination treatment with TPM at doses of 100 mg/day, 250 mg/day, and 400 mg/day, respectively. Approximately 35% of the risperidone dose was excreted in the urine as 9-OH risperidone. Renal clearance of 9-OH risperidone appeared to decrease when risperidone and TPM were administered together, resulting in an approximately 24%, 30%, and 17% reduction in CL_R at the 100 mg/day, 250 mg/day, and 400 mg/day TPM doses, respectively. Mean SD estimates for dose-normalized C_{max} and AUC_{12} for 9-OH risperidone are summarized in the table below.

Parameter		**Risperidone Stabilization (Period I)**	**TPM Dose-Escalation (Period II)**		
			100 mg/day	250 mg/day	400 mg/day
Total Active Moiety	C_{max} (ng/mL)	23.0 (10.87)	25.2 (11.0)	22.8 (6.92)	23.0 (11.5)
	AUC_{12} (ng•h/mL)	200 (108)	225 (107)	203 (64.8)	203 (90)
Risperidone	C_{max} (ng/mL)	8.62 (7.25)	8.81 (7.87)	7.50 (6.36)	6.59 (5.38)
	AUC_{12} (ng•h/mL)	52.1 (65.7)	54.1 (73.2)	43.9 (54.6)	35.0 (38.5)
9-OH Risperidone	C_{max} (ng/mL)	15.4 (7.51)	17.1 (8.08)	16.2 (6.38)	17.1 (8.7)
	AUC_{12} (ng•h/mL)	149 (77.8)	170 (84.8)	162 (63.1)	167 (85)

Results of ANOVA analysis demonstrate that the differences in the PK parameter estimates for 9-OH risperidone between treatment with risperidone alone and combination treatment with TPM administered as 3 different daily doses were not statistically significant as p-values exceeded 0.05 for all parameters tested except for Au (p=0.0245), corresponding to the 250 mg/day dose of TPM. Point estimates for 9-OH risperidone AUC_{12} and C_{max} approximated 100% during treatment with TPM at 100 mg/day, 250 mg/day, and 400 mg/day. Their associated 90% CI were within the 80% to 125% limits indicating that treatment with risperidone alone and risperidone combined with TPM administered as escalating daily doses were equivalent for 9-OH risperidone. These were slight deviations (1% to 3%) from 80% lower limit and were not considered clinically significant.

TPM was rapidly absorbed with peak concentrations occurring at approximately 1 to 1.5 hours following oral administration. Approximately 73% of the dose was excreted unchanged in the urine. Mean estimates of CL_R were similar for all doses of TPM during treatment with risperidone as well as during the risperidone reduction phase. TPM exhibited dose-proportional PK during combination treatment with risperidone. For the TPM 400 mg/day treatments, mean estimates for TPM, Mean estimates of CL_R were similar for all doses of during treatment with risperidone as well as during the risperidone reduction phase. TPM exhibited dose-proportional PK during

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PHARMACOKINETIC RESULTS (Cont'd): combination treatment with risperidone. For the TPM 400 mg/day treatments, mean estimates for TPM C_{max}, AUC_{12}, and CL/F were similar when combined with risperidone administered at 100% of the baseline dose and during the 50% reduction. However, the systemic exposure of TPM was slightly higher following discontinuation of risperidone where mean estimates for C_{max} and AUC_{12} were 14% and 12% higher, respectively, and mean estimates for CL/F were 13% lower compared to combination treatment with risperidone administered at 100% of the baseline dose. Mean estimates for dose-normalized SD C_{max} and AUC for TPM are summarized below.

Parameter		**TPM Dose-Escalation (Period II)**			**% Reduction in Risperidone Dose During Risperidone Reduction (Period III)**	
		100 mg/day	250 mg/day	400 mg/day	50%	100%
TPM	C_{max} (ng/mL)	4.3 (0.83)	10 (2.0)	14 (3.4)	15 (4.5)	16 (3.2)
	AUC_{12} (ng•h/mL)	41.9 (8.28)	97.2 (19.7)	141 (31.4)	141 (41.6)	158 (30.3)

Results of ANOVA analysis demonstrate that the differences in the PK parameter estimates for TPM between treatment with TPM 400 mg/day alone and combination treatment with risperidone administered as 100% and 50% of the baseline dose were not statistically significant as p-values exceeded 0.05 for all parameters tested. Point estimates for TPM AUC_{12} and C_{max} were approximately 10% lower during treatment with risperidone when administered at 100% of the baseline dose and 12% lower when administered as 50% of the baseline dose. Their associated 90% CI were outside the 80% to 125% limits indicating that the 2 treatments were not equivalent.

SAFETY RESULTS: Overall, 52 subjects (91%) experienced an adverse event during the study. During Period I with risperidone stabilization, 54% (31 of 57) of subjects experienced treatment-emergent adverse events with headache (9 subjects, 16%) as the most commonly experienced adverse event. Sixteen percent (8 of 51) of the subjects during Period II and 3% (1 of 31) of the subjects during Period III experienced headache. Ninety percent of the subjects (46 of 51) experienced adverse events when TPM was added to risperidone treatment during Period II and 52% of the subjects (16 of 31) experienced adverse events during Period III where the dose of TPM was maintained and the risperidone dose was reduced. Somnolence (14 subjects, 27%) was the most commonly experienced adverse event during Period II and was experienced by 7 subjects (12%) in Period I. The incidence of paresthesia was also greater during Period II (11 subjects, 22%) than in Period I (2 subjects, 6%). Subjects also experienced nausea throughout the study (5 subjects, 9%; 9 subjects, 18%; and 2 subjects, 6% in Periods I, II, and III, respectively). A total of 18 subjects discontinued the study due to adverse events. None of the adverse events that led to discontinuation met the criteria for a serious adverse event and most were considered mild to moderate in severity. Three serious adverse events were reported during the study, two events which occurred after study drug discontinuation. No clinically significant changes were seen in laboratory values and no noteworthy events were reported for vital signs, physical examination, or ECG measurements.

CONCLUSION: Overall, the steady-state PK of the total active moiety and 9-OH risperidone were unaffected by concomitant administration of escalating doses of TPM under chronic dosing conditions in patients with bipolar disorder. Systemic exposure of risperidone was reduced during treatment with TPM at doses of 250 and 400 mg/day. The mechanism by which TPM increases clearance (reduces concentrations) of risperidone appears to be related to an increase in metabolic clearance that does not affect the extent of biotransformation to the 9-OH risperidone metabolite. As there was no clinically significant change in the systemic exposure of the total active moiety when risperidone and TPM were administered together, this interaction is not likely to be of clinical significance. The steady state PK of TPM were unaffected by co-administration with risperidone in patients with bipolar disorder. In general, the treatment with TPM alone and concomitantly with risperidone appeared to be safe and well tolerated in subjects who had either bipolar or schizoaffective disorders.

Date of the report: 31 August 2004

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