SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: 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.: TOPMATPEP1001 CR002239

Title of Study: An Open-Label, Randomized, 2-Way Crossover Study of the Bioavailability of an Oral Liquid Formulation Relative to the Marketed Sprinkle Capsule Formulation of Topiramate RWJ-17021-000 in Healthy Subjects

Principal Investigator: Dennis Morrison, D.O. - Bio-Kinetic Clinical Applications, Inc., Springfield, Missouri; USA

Publication (Reference):

Studied Period (years): Clinical Conduct: 9 November 2004 – 21 December 2004 Sample Analysis: 30 December 2004 to 03 February 2005	**Phase of development:** 1

Objectives: The primary objective of this study was to estimate the bioavailability of the oral liquid formulation of topiramate relative to the commercially available oral sprinkle capsule formulation in healthy subjects. Bioequivalence between the oral liquid formulation and the sprinkle capsule formulation was assessed. Safety and tolerability was assessed throughout the study.

Methodology: This was a single center, randomized, open-label, 2-way crossover, Phase 1 bioavailability study, which was conducted in 3 phases: a pretreatment phase (Days -14 to -1), a 25-day open-label treatment phase, and a 7-day follow-up phase. Following an overnight fast, subjects received topiramate as a single 100-mg dose of the oral liquid formulation or the oral sprinkle capsule formulation in the morning of Days 1 and 21 in the sequence specified by the randomization schedule. Serial blood samples were collected for estimation of plasma topiramate concentrations at scheduled times through 96 hours after each dose administration. Subjects were sequestered from the evenings of Days –1 and 20 through completion of the 48-hour postdose blood sample collection (Days 3 and 23, respectively) and had to return to the study site for collection of the 60-hour, 76-hour, and 96-hour postdose samples on Days 3 to 5 and 23 to 25, respectively. There was a 21-day washout period between the treatments. Safety and tolerability were monitored throughout the study.

Number of Subjects (planned and analyzed): Planned: 40, analyzed: for safety 40, for pharmacokinetics (PK) 40.

Diagnosis and Main Criteria for Inclusion: Male and female subjects between 18 and 45 years of age, extremes included, and healthy based on medical history, physical examination, electrocardiograms (ECG), vital signs, and laboratory evaluations with a body mass index between 19 and 32 kg/m^2, extremes included.

Test Product, Dose and Mode of Administration, Batch No.: topiramate oral liquid formulation (30 mg/mL), Batch No. D04LK1389; topiramate oral sprinkle capsules (25 mg), Batch No. D04LH1330.

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

Duration of Treatment: Each subject received 1 single topiramate dose of 100 mg as 4 X 25-mg sprinkle capsule formulation and 1 single topiramate dose of 100 mg as 20 mL of a 5 mg/mL oral liquid formulation with a 21-day washout period between the 2 doses.

SYNOPSIS (CONTINUED)

Criteria for Evaluation:

Pharmacokinetics: The following pharmacokinetic parameters of topiramate were estimated for each subject for each treatment: C_{max}, t_{max}, $t_{1/2}$, λ_z, AUC_{last}, AUC_∞, $\%AUC_{\infty,ex}$, CL/F, and F_{rel} (%).

Safety: Safety was evaluated by the incidence and severity of adverse events, evaluation of laboratory safety (hematology, serum chemistry and urinalysis), 12-lead ECG, vital signs, physical examination, measurements of body weight, pregnancy tests, urine toxicology tests and urine, breath or saliva alcohol test.

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Statistical Methods:

Pharmacokinetics: The analyses of AUC_{last}, AUC_∞, and C_{max} were performed on log-transformed estimations using only the data from subjects who completed the study. Analysis of variance (ANOVA) models were fitted to the data with 1 of the estimated PK parameters of interest as the dependent variable, and the effects due to sequence group, subjects nested within the sequence groups, treatment and period as fixed effect. Testing for the treatment sequence group effect was carried out at 10% level of significance, by using the mean square due to the subjects nested within sequence groups as the error term. Testing for the period effect was carried out at 5% level using the residual error term. The estimated least square means and intrasubject variability from the ANOVA model were used to construct 90% confidence intervals for the difference in means on the log scale between the 2 treatments. The limits of the confidence intervals were retransformed using antilogarithms to obtain 90% confidence intervals for the ratio of the mean PK parameters before and after normalizing for treatment formulation potency of the oral liquid formulation to the sprinkle capsule formulation. This normalization was made by multiplying by the ratio of the potency of the reference formulation (sprinkle) to that of the test formulation (liquid). The 2 treatments were considered bioequivalent if the 90% confidence intervals for the ratio of the means fell within 80% to 125%.

Safety: Standard safety parameters were summarized using descriptive statistics.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: Following oral administration, topiramate was rapidly absorbed with peak concentrations occurring at approximately 1 hour for the oral liquid formulation and 2 hours for the sprinkle capsule formulation. Mean topiramate C_{max} and AUC_∞ were similar between liquid and sprinkle capsule formulations. Mean estimates for topiramate CL/F were similar for both formulations and consistent with that observed in historical studies for the tablet formulation. The relative bioavailability (F_{rel} [%]) for the oral liquid to the sprinkle capsule formulation was 101%. Mean (SD) Topiramate PK parameters are summarized below:

Parameters	Topiramate 100 mg Liquid (N=40)	Topiramate 100 mg Sprinkle Capsule (N=40)
C_{max} (µg/mL)	1.70 (0.313)	1.79 (0.363)
t_{max}[a] (h)	1.00 (0.50-4.00)	2.00 (0.50-8.00)
AUC_{last} (µg.h/mL)	61.7 (10.9)	62.2 (11.0)
AUC_∞ (µg.h/mL)	74.0 (13.1)	73.8 (13.0)
$\%AUC_{\infty,ex}$	16.5 (4.27)	15.7 (3.41)
$t_{1/2}$ (h)	38.2 (6.08)	36.8 (4.24)
CL/F (mL/min)	23.2 (4.29)	23.2 (3.96)

[a] t_{max} represented as median (range)

The ratios of the geometric means for C_{max}, AUC_{last} and AUC_∞ were between 96% and 100%. The 90% confidence intervals of the geometric mean ratios for topiramate PK parameters C_{max}, AUC_{last} and AUC_∞ of the oral liquid formulation relative to the sprinkle capsule formulation were all contained within the 80% to 125% limits, indicating that the 2 treatments were bioequivalent. The ratios of the geometric means and their corresponding 90% confidence intervals for topiramate PK parameters are listed below.

SYNOPSIS (CONTINUED)

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Parameter	Geometric Mean			90% confidence limits	
	Topiramate Liquid (test) n=40	Topiramate Sprinkle Capsule (Reference), n=40	Ratio (%)	Lower limit (%)	Upper limit (%)
C_{max} (µg/mL)	1.67	1.75	95.62	91.78	99.63
AUC_{last} (µg.h/mL)	60.78	61.27	99.20	96.47	102.01
AUC_{∞} (µg.h/mL)	72.85	72.75	100.14	97.27	103.09

SAFETY RESULTS: Adverse events were reported by about one-third of the subjects following administration of either formulation. The most frequently reported adverse events were dizziness (28%), paresthesia (23%), headache (13%), difficulty with concentration/attention (13%), and hypoesthesia (10%). There was no difference in the adverse event profile between the 2 formulations. All adverse events were mild and most were considered possibly related to the study medication. There were no deaths or serious adverse events, and no subjects withdrew from the study. One subject had an AST value of more than 3 times the upper normal limit at the end of the study, but this was not considered clinically significant by the investigator. Although for several subjects, hematology and chemistry parameters changed from within to out of the normal range during the study, and several subjects had abnormal QTc or PR values, or heart rates, none of the values were considered clinically significant.

CONCLUSIONS:

The oral liquid formulation and sprinkle capsule formulations of topiramate are bioequivalent.

Single topiramate doses of 100 mg of the oral liquid formulation and the oral sprinkle capsule formulation were considered to be safe and well tolerated in healthy adults.

There was no evidence of clinically significant differences between the formulations with respect to adverse events, clinical laboratory test results, vital signs, and ECG parameters. No unexpected safety findings were observed in this study.

Date of the report: 1 August 2005

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