# SYNOPSIS

| NAME OF SPONSOR/COMPANY:<br>Johnson & Johnson Pharmaceutical Research & Development, L.L.C.<br>NAME OF FINISHED PRODUCT:<br>TOPAMAX® (topiramate)<br>NAME OF ACTIVE INGREDIENT(S):<br>2,3:4,5-bis-*O*-(1-methylethylidene)β-D-fructopyranose sulfamate | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER<br>Volume:<br>Page: | (FOR NATIONAL AUTHORITY USE ONLY) |
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**Protocol No.:** TOPMAT-PHI-374

**Title of Study:** A Comparative Study of the Steady-State Pharmacokinetics of Lithium Before and During Multiple Oral Daily Topiramate (RWJ-17021) Dosing in Subjects With Bipolar Disorder.

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**Publication (Reference):** None

| **Studied Period (years):** Clinical Conduct: 29 May 2001 to 11 November 2002<br>Sample Analysis: | **Phase of development:** 1 |
|---|---|

**Objectives:** The objectives of this study were to determine the initial (1-week maintenance dosing) and extended (3-week maintenance dosing) effect of topiramate, at doses up to 600 mg/day, on the steady-state pharmacokinetics (PK) of lithium carbonate.

**Methodology:** This was an open-label, sequential treatment, multicenter study evaluating the interaction of topiramate and lithium in 24 subjects. The study consisted of a screening phase, 2 treatment phases — topiramate titration and lithium and topiramate maintenance, and 3 PK sampling periods. After admission to the study, serial blood and urine samples were collected for estimation of lithium serum and urine concentrations (PK Period 1). Subjects were randomized to receive either low-dose topiramate of 200 mg/day (Group 1) or high-dose topiramate of 600 mg/day (Group 2), or a maximum tolerated dose (MTD) greater than 200 mg/day. During the topiramate titration phase, an initial dose of 25 mg/day of topiramate was titrated upward until the target dose of 200 mg/day was reached in Group 1, or a target dosage of 600 mg/day (or MTD) was reached in Group 2. Once the topiramate titration phase was completed, subjects were maintained on a constant dose of topiramate and lithium carbonate for the 3-week period. For Groups 1 and 2, serial blood and urine samples for estimation of lithium serum and urine concentrations and plasma topiramate concentrations were obtained during PK Sampling Period 2 and Period 3, which took place approximately 1 week and 3 weeks, respectively, after achieving the assigned maintenance doses of topiramate.

**Number of Subjects (planned and analyzed):** Thirty-two subjects were enrolled for 24 subjects to complete; 24 subjects completed. Subjects with sufficient plasma and urine concentration data to estimate PK parameters were included in the PK analysis. In addition, a subset analysis was performed that included subjects with complete PK parameter data for all 3 PK Sampling Periods only. (See Section 4.3.1 Datasets Analyzed). Any subject who received a dose of study medication was included in the safety analyses.

**Diagnosis and Main Criteria for Inclusion:** Subjects were men or women aged 18 to 60 years, inclusive, with a documented DSM-IV diagnosis of Bipolar I, Bipolar II, or Cyclothymic Disorder, or Bipolar Disorder NOS), and were on monotherapy treatment with lithium carbonate with a maintained steady-state level for a minimum of 2 weeks prior to assignment. All subjects weighed within 30% of ideal body weight according to height and frame size. Subjects with a history of significant medical disease (excluding psychiatric history), or seizures were excluded.

**Test Product, Dose and Mode of Administration, Batch No.:** Topiramate for oral administration was supplied as 25-mg white-coated tablets (FD-17021-000-AQ-22; Batches R11727, R11413, R10845), 50-mg light yellow-coated tablets (FD-17021-000-AR-22; Batches R11728, R11414, R10846), 100-mg yellow-coated tablets (FD-17021-000-AK-22; Batches R11729, R11415, R10847), and 200-mg yellow coated tablets NDC-0045-0642-65, Batches R10848, R11730, R11827, R11416). Lithium carbonate for oral administration was supplied by the subjects, not by the sponsor.

**Duration of Treatment:** Subjects were maintained on a stable dose of an immediate release lithium carbonate formulation, dosed every 12 hours, for a minimum of 2 weeks prior to the start of the study. PK Sampling Period 1 took place 3 days prior to beginning the topiramate titration phase. In the topiramate titration phase, topiramate was administered every 12 hours at a starting dose of 25 mg/day. Subjects in the low-dose group were titrated to a target dose of 200 mg/day over a period lasting up to 10 days. Subjects in the high-dose group were titrated to a target dose of 600 mg/day (or maximum tolerated dose) over a period lasting up to 30 days. The lithium and topiramate maintenance phase (which started after these target doses were reached) lasted for an additional 3 weeks.

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

**Criteria for Evaluation:**

Pharmacokinetics: Serial blood and urine samples were collected during 3 separate PK sampling periods (3 days prior to starting the topiramate titration, and Days 7 to 9 and 21 to 23 after reaching lithium and topiramate maintenance dosing). Blood samples were collected for estimation of lithium concentrations and electrolytes (sodium, potassium, chloride, and bicarbonate) in serum, and topiramate concentrations in plasma at the following times during each sampling period: at 0.0 (predose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-morning dose. Urine samples were also collected for determination of lithium concentrations during the following intervals: 0-2, 2-4, 4-8, and 8-12 hours postdose. The following pharmacokinetic parameters for lithium and topiramate were determined by standard noncompartmental methods: $AUC_{12}$, $C_{max}$, $t_{max}$, $CL/F_{ss}$ (topiramate only), and Au (lithium only).

Safety: The safety assessment included the incidence, type, and severity of treatment-emergent adverse events, evaluation of clinical laboratory analyte values, including serum electrolytes, measurements of vital signs, ECG, and physical examination findings. A Global Assessment Scale rating was also obtained at each PK Sampling Period to monitor subject stability.

**Statistical Methods:**

Pharmacokinetics The analysis was done separately for each dose group of topiramate. Analysis of variance models appropriate for a repeated measures design were fit to log-transformed lithium pharmacokinetic parameters of interest ($AUC_{12}$, $C_{max}$, $t_{max}$, Au). The initial effect (Period 2 vs. Period 1) and extended effect (Period 3 vs. Period 1) of topiramate the steady-state pharmacokinetics of lithium was tested at a 5% level of significance using appropriate linear contrasts. Using the estimated least square means and intra-subject variability, 90% confidence intervals were constructed for the ratio of mean $AUC_{12}$ and $C_{max}$ from: Period 2 to Period 1 (initial effect) and Period 3 to Period 1 (extended effect). The statistical analysis was conducted using 2 approaches. The initial approach used all available PK parameter data for each sampling Period. In addition, a subset analysis was performed that included PK parameter data from subjects who completed all 3 PK Sampling Periods only. Pharmacokinetic results are summarized and descriptive statistics were generated for each group. The topiramate pharmacokinetic parameters are compared to historical data.

Safety: The type and incidence of treatment-emergent adverse events were summarized, as were changes from baseline in clinical laboratory analyte values, physical exams, ECGs, vital signs.

**SUMMARY – CONCLUSIONS**

PHARMACOKINETIC RESULTS:

For subjects in Group 1, lithium was rapidly absorbed following oral administration with a $t_{max}$ occurring at approximately 1.5 to 2 hours during all PK Periods. Mean estimates for lithium $C_{max}$ and $AUC_{12}$ were similar before and during topiramate treatment. Urinary excretion appeared to be affected during topiramate treatment in Period 2, where Au decreased by 13%, which subsequently normalized during Period 3. Lithium pharmacokinetic parameter estimates for Group 1 are summarized in the table below.

| Parameter | Before Topiramate (PK Period 1) | | During Topiramate (PK Period 2) | | During Topiramate (PK Period 3) | |
|---|---|---|---|---|---|---|
| $C_{max}$ (mEq/L) | 1.32 (0.385) | n=20 | 1.40 (0.421) | n=16 | 1.28 (0.426) | n=15 |
| $t_{max}$[a](h) | 1.42 (0.00, 4.00) | n=20 | 1.50 (0.00, 12.00) | n=16 | 2.00 (1.00, 12.00) | n=15 |
| $AUC_{12}$ (mEq•h/L) | 12.0 (3.31) | n=19 | 11.6 (3.56) | n=15 | 11.0 (3.42) | n=15 |
| Au (mEq) | 7.607 (3.502) | n=19 | 6.597 (2.071) | n=14 | 7.843 (2.798) | n=12 |

[a] All parameters are presented as mean (SD) except for $t_{max}$, which is presented as median (range).

Results of the ANOVA analysis indicated that the differences in the lithium pharmacokinetic parameters between lithium treatment alone and combined treatment of lithium and topiramate for 1 week (Period 2) and 3 weeks (Period 3) were not statistically significant, as p-values exceeded 0.05 for all parameters tested. The estimated geometric mean ratios approximated 100% for all parameters tested for the Period 2 and 3 versus Period 1 comparisons. In addition, the 90% confidence intervals for $AUC_{12}$ and $C_{max}$, were within the range of 80% to 125% indicating that the two treatments were equivalent at both treatment periods. Results of the subset analysis, which excluded subjects who did not complete all 3 PK Periods, were generally agreement with the results that were generated using all available PK data.

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For subjects in Group 2, lithium was rapidly absorbed following oral administration with a $t_{max}$ occurring at approximately 1.5 hours. Both $C_{max}$ and $AUC_{12}$ estimates were greater during Period 2 (13.2% and 10.4%, respectively) and Period 3 (26.9% and 26.4%, respectively) compared to Period 1. Lithium pharmacokinetic parameter estimates for Group 2 are summarized in the table below.

| Parameter | Before Topiramate (PK Period 1) | | During Topiramate (PK Period 2) | | During Topiramate (PK Period 3) | |
|---|---|---|---|---|---|---|
| $C_{max}$ (mEq/L) | 1.21 (0.205) | n=11 | 1.370 (0.255) | n=8 | 1.536 (0.414) | n=7 |
| $t_{max}$[a] (h) | 1.50 (0.50, 4.00) | n=11 | 1.50 (0.50, 2.00) | n=8 | 1.50 (1.00, 4.00) | n=7 |
| $AUC_{12}$ (mEq•h/L) | 10.6 (2.22) | n=11 | 11.7 (2.08) | n=8 | 13.4 (4.36) | n=7 |
| Au (mEq) | 9.505 (5.506) | n=11 | 9.599 (6.895) | n=9 | 8.513 (5.360) | n=8 |

[a] All parameters are presented as mean (SD) except for $t_{max}$, which is presented as median (range).

For the Period 2 versus 1 comparison, the results of the ANOVA analysis indicated that the differences in the pharmacokinetic parameters for lithium were not statistically significant for all parameters tested except $C_{max}$ ($p=0.046$). The estimated geometric mean ratios for $AUC_{12}$ and $C_{max}$ were approximately 108% and 112%, respectively, and their respective 90% confidence intervals were within the range of 80% to 125% indicating that the two treatments were equivalent. For the Period 3 versus 1 comparison, the differences in lithium $AUC_{12}$ and $C_{max}$ between the 2 treatments were statistically significant ($p< 0.05$). Overall, systemic exposure of lithium appeared to be greater during treatment with topiramate for 3 weeks compared to lithium treatment alone. Point estimates for $C_{max}$ and $AUC_{12}$ were approximately 20% greater during topiramate treatment. The 90% confidence intervals for all parameters tested were outside the range of 80% to 125% indicating that the 2 treatments were not equivalent. Results of the subset analysis, which excluded subjects who did not complete all 3 PK Periods, were generally in agreement with the results that were generated using all available PK data, except that no statistical significant comparison between Period 1 and Period 2 for $C_{max}$ ($p=0.073$) was found.

Mean plasma topiramate concentrations were similar during Periods 2 and 3 for both Groups 1 and 2. For both groups, topiramate was rapidly absorbed following oral administration with a $t_{max}$ occurring at approximately 0.75 to 1.50 hours. In addition, topiramate $C_{max}$, $AUC_{12}$, and $CL/F_{ss}$ were similar during Periods 2 and 3. Estimates of $CL/F_{ss}$ reported presently are similar to what has been observed historically.

SAFETY RESULTS:

Treatment-emergent adverse events that occurred in 15% or more subjects in the two treatment groups were associated with the central or peripheral nervous systems (dizziness, paresthesia) or were psychiatric in nature (anorexia, nervousness). One subject who was assigned to the topiramate 200 mg/day group discontinued from the study on Day 8 because of lithium toxicity, which was considered a serious adverse event. Four additional subjects discontinued because of adverse events, but none was considered serious. No deaths were reported in the study.

Individual subject changes from baseline in hematology values were not considered clinically significant. Among the subjects who developed serum chemistry values at the final visit that were outside the normal ranges, several may have been associated with adverse events. Subject 1004, who had elevated liver enzyme values, developed mild abdominal pain which was reported as a sensitive, palpable liver. Subject 1003 who had elevated serum glucose, reported lightheadedness, tremor, and paresthesia. Subject 1005 had decreased levels of total bilirubin and LDH, reported paresthesia. Subject 1010 had elevated serum glucose and discontinued because of abdominal cramping. Subject 20001 had elevated creatinine and serum glucose, and reported nausea, anorexia, taste perversion, and frequent micturition. Subject 20002 who discontinued because of lithium toxicity (see above) had elevated creatinine and total protein levels. Five subjects developed decreased serum bicarbonate levels at the final visit, but none was associated with adverse events. There were no noteworthy changes in vital signs for any subject. Three subjects (1003, 1005, 1006) had abnormal ECG changes, but none was considered serious and all 3 subjects completed the study.

CONCLUSION: The steady-state pharmacokinetics of lithium were unaffected by concomitant administration of low doses (200 mg) of topiramate when administered over a short-term (1-week) and long-term (3-week) period to patients with bipolar disorder. The systemic exposure of lithium was 10 to 25% greater following chronic administration of higher doses of topiramate (~600 mg/day). The clinical significance of the observed modest changes in PK parameters of lithium is unknown, therefore dose adjustments for lithium should be based on serum lithium trough concentrations and the clinical status of the patient when co-administering topiramate. The most common treatment-emergent adverse events were associated with the central or peripheral nervous systems or were psychiatric in nature.

Date of the report: 29 APRIL 2004

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