Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Clinical Study Report Synopsis

A Drug Interaction Study of the Pharmacokinetics of Flunarizine and Topiramate (RWJ-17021-000) During Mono- and Concomitant Therapy

Protocol PRI/TOP-INT-58 (TOPMAT-PHI-382); Phase 1

RWJ-17021-000 (topiramate)

COORDINATING INVESTIGATOR:
C. Avendaño, M.D. – Hospital Puerta de Hierro, Madrid; Spain

DATE STUDY INITIATED:
31 March 2003

DATE STUDY COMPLETED:
03 March 2004

Issue/Report Date: 09 AUGUST 2005
Department: Drug Development
Document No.: EDMS-USRA-7287331:2.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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-ß-D-fructopyranose sulfamate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

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Title of Study: A Drug Interaction Study of the Pharmacokinetics of Flunarizine and Topiramate (RWJ-17021-000) During Mono- and Concomitant Therapy

Coordinating Investigator: C. Avendaño, M.D. - Hospital Puerta de Hierro, Madrid; Spain

Publication (Reference): Not applicable.

Studied Period (years): Clinical Conduct: 31 March 2003 to 03 March 2004.
Sample Analysis: topiramate in plasma: 26 June 2003 - 2 April 2004
topiramate in urine: 7 July 2003 - 10 July 2003
flunarizine in plasma: 26 June 2003 - 26 April 2004

Phase of development: 1

Objectives: The primary objective of this open-label study was to determine if concomitant therapy with topiramate and flunarizine affects the pharmacokinetics of either drug. Safety was assessed for all subjects throughout the study.

Methodology: This was a multicenter, randomized, open-label, Phase 1 study to investigate the possible interaction of topiramate and flunarizine given orally. The study was conducted in 2 groups:

Group 1 comprised 47 men and women with a history of migraine who had been taking flunarizine for at least 4 weeks before study start. These subjects, who were enrolled at multiple sites, entered a 6-week run-in phase to receive 5 mg flunarizine every 24 hours (q24h). After the run-in phase, the subjects were randomized to 1 of 2 treatment subgroups:

Subgroup 1a received flunarizine (5 mg q24h) with topiramate titrated to 50 mg/day and then to 100 mg/day and Subgroup 1b received flunarizine 5 mg q24h alone. Sparse blood samples were obtained through 12 hours after the evening study drug administration on Days 18 and 81 for estimation of topiramate concentrations for Subgroup 1a. For Subgroups 1a and 1b, serial blood samples were obtained through 24 hours after the evening study drug administration on Days 3, 18, and 81 for estimation of flunarizine concentrations.

Group 2 comprised 28 healthy men and women at a single site. Subjects were titrated upwards to a topiramate dose of 50 mg q12h on Day 5 and continued this regimen through the morning dose of Day 18. Beginning on Day 12, they received 5 mg flunarizine q24h for 6 days. Serial blood and urine samples were obtained through 12 hours after the morning study drug administration on Days 12 and 18 for estimation of topiramate concentrations. Sparse blood samples were collected through 12 hours after the morning study drug administration on Day 18 for estimation of flunarizine concentrations.

Number of Subjects (planned and analyzed): Subgroup 1a: Planned, 18 (at least 4 men and 4 women); analyzed, 21 (6 men, 15 women). Subgroup 1b: Planned, 18 (at least 4 men and 4 women); analyzed, 21 (6 men, 15 women). Group 2: Planned, 28 (at least 6 men and 6 women); analyzed, 26 (13 men and 13 women).

Diagnosis and Main Criteria for Inclusion: Group 1 subjects were men and women, 18 to 55 years of age, diagnosed with migraine according to International Headache Society (IHS) criteria for at least 1 year, who took flunarizine for migraine prophylaxis for at least 4 weeks before run-in. They were otherwise healthy. Group 2 subjects were healthy men and women, 18 to 55 years of age. Health was determined by physical examination, medical history, clinical laboratory tests (including hematology, chemistry, urinalysis), and a 12-lead ECG. Subjects were prohibited from using other medications, grapefruit-, Seville orange- and methylxanthine-containing products, and herbal medications. All subjects had to consent to pharmacogenomic analysis of a blood sample.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate oral 25-mg tablet: (V02PE8028, V03PD8432); topiramate oral 50-mg tablet (V02PL8274, V03PA8333, V03PD8433). Flunarizine oral 5-mg capsule (V03PB8386).

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

SYNOPSIS (CONTINUED)

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Duration of Treatment:
Group 1a: 124 days with 123 days of flunarizine and 79 days of topiramate; Group 1b: 123 days of flunarizine; Group 2: 17 days with 6 days of flunarizine and 17 days of topiramate.

Criteria for Evaluation:
Pharmacokinetics:
The pharmacokinetic parameters of interest included: AUC_{0-12}, AUC_{0-24}, C_{max}, C_{trough}, t_{max}, CL/F, Ae_{0-12}, %Ae, f_u and CL_R.
Safety: Subject safety was assessed using adverse event monitoring, vital signs measurements, physical examinations, clinical laboratory testing (hematology, chemistry and urinalysis), and ECGs. Neurologic and MMSE testing was used to monitor the safety of Group 1 subjects.

Statistical Methods:
Pharmacokinetics:
No formal statistical analysis was performed. Topiramate and flunarizine concentrations and pharmacokinetic parameter estimates were summarized descriptively.
Safety: Safety was evaluated based on the incidence and severity of treatment-emergent adverse events and abnormal findings of other safety evaluations (i.e., 12-lead ECG, standard clinical laboratory tests, physical examination, neurologic examinations [Group 1], and vital signs). Changes in clinical laboratory test results and vital sign results from baseline to end of study or early termination were evaluated. Summaries of the results of all safety procedures were provided for each treatment group.

SUMMARY – CONCLUSIONS
PHARMACOKINETIC RESULTS:
For subjects in Subgroup 1a, flunarizine concentrations peaked at approximately 4 hours, following oral administration. There was an approximate 22% reduction in mean estimates for flunarizine C_{max} following treatment with topiramate 50 mg/day compared to treatment with flunarizine alone. Mean C_{max} estimates were similar during treatment with topiramate 100 mg/day. Mean estimates for flunarizine AUC_{0-24} were similar during treatment with topiramate 50 mg/day and were 16% higher following treatment with topiramate 100 mg/day. Mean estimates for oral clearance (CL/F) were not affected by treatment with topiramate. For subjects in Subgroup 1b, flunarizine concentrations peaked at approximately 4 hours, following oral administration. Mean estimates for C_{max} were similar for all pharmacokinetic assessment Days. Mean estimates for AUC_{0-24} were similar on Days 3 and 18. However, there was a 14% increase from Day 18 to 81. Oral clearance estimates were consistent for all pharmacokinetic assessment days. Flunarizine was extensively protein bound with a free fraction ranging from 0.01% to 0.09%. Mean (SD) plasma pharmacokinetic parameters of flunarizine are presented in the table below.

Parameter	Subgroup 1a Flunarizine alone (Day 3) (N=24)	Subgroup 1b Flunarizine alone (Day 3) (N=21)	Subgroup 1a Flunarizine With Topiramate 50 mg/Day (Day 18) (N=22)	Subgroup 1b Flunarizine alone (Day 18) (N=22)	Subgroup 1a Flunarizine with Topiramate 100 mg/Day (Day 81) (N=21)	Subgroup1b Flunarizine alone (Day 81) (N=21)
C_{max} (ng/mL)	29.3 (36.4)	25.8 (10.1)	22.9 (12.4)	26.4 (11.1)	27.1 (16.2)	27.8 (12.7)
AUC_{0-24} (ng.h/mL)	401 (216)	421 (197)	408 (251)	424 (216)	464 (327)	485 (275)
CL/F (L/h)	16.2 (8.43)	14.1 (5.39)	16.9 (9.63)	14.0 (5.00)	15.0 (8.11)	13.4 (6.72)

For subjects in Group 2, flunarizine mean concentrations were consistent with multiple dose adminsitration.

For subjects in Subgroup 1a, topiramate was rapidly absorbed with peak concentrations occurring 2 hours following oral administration. Topiramate demonstrated an approximate doubling in systemic exposure (C_{max} and AUC_{0-12}) as the dose of topiramate increased from 50 mg/day to 100 mg/day. Mean estimates for CL/F were similar during both treatment periods and were also consistent with historical data. Mean (SD) plasma pharmacokinetic parameters of topiramate are presented in the table below.

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Parameter	Subgroup 1a Topiramate 50 mg/Day With Flunarizine (Day 18) (N=22)	Subgroup 1a Topiramate 100 mg/Day with Flunarizine (Day 81) (N=21)	Group 2 Topiramate 100 mg/Day alone (Day 12) (N=26)	Group 2 Topiramate 100 mg/Day With Flunarizine (Day 18) (N=26)
C_{max} (µg/mL)	1.96 (0.439)	3.91 (0.749)	4.71 (0.960)	4.77 (1.00)
AUC_{0-12} (µg.h/mL)	20.9 (4.78)	42.1 (8.29)	45.8 (10.2)	46.7 (10.2)
CL/F (mL/min)	21.0 (5.17)	20.5 (3.94)	19.0 (4.06)	18.7 (4.04)
Ae_{0-12} (µg)	--	--	36580 (5157)	35480 (6611)
%Ae	--	--	73.2 (10.3)	71.0 (13.2)
CL_R (mL/min)	--	--	14.0 (3.92)	13.3 (4.25)

For subjects in Group 2, topiramate was rapidly absorbed with peak concentrations occurring approximately 1 hour after oral administration. Systemic exposure of topiramate remained unaffected during treatment with flunarizine as shown by similar mean estimates for C_{max} and AUC_{0-12} for both treatments. Mean estimates of CL/F were also similar during both treatments and are comparable to estimates reported in previous studies. Approximately 73% of topiramate was excreted unchanged in the urine. Renal clearance was unaffected by treatment with flunarizine as mean estimates were similar for both treatments.

SAFETY RESULTS: Overall, 88% of the subjects in Subgroup 1a, 70% in Subgroup 1b, and 79% in Group 2 experienced adverse events. Central and peripheral nervous system disorders (except migraine and aggravated migraine), and psychiatric disorders were more frequently reported during topiramate treatment (Subgroup 1a and Group 2), which is consistent with the adverse event profile of topiramate. Somnolence (32%), headache (32%), and dizziness (25%) were more commonly reported in Group 2 (healthy volunteers, topiramate with flunarizine), whereas paresthesia (46%), difficulty with concentration/attention (21%), depression (17%) and fatigue (17%) were more frequently experienced in Subgroup 1a (migraine subjects, topiramate with flunarizine). Migraine (9%) and aggravated migraine (26%) were more commonly reported by subjects receiving flunarizine alone (Subgroup 1b). Most adverse events occurring during the open-label treatment phase were mild or moderate in intensity. The majority of Group 1 subjects had adverse events that were considered not related to the study medication, while the majority of Group 2 subjects had adverse events that were assessed possibly related to the study medication. No deaths or other serious adverse events occurred. Five subjects discontinued treatment because of adverse events. Two subjects in Subgroup 1b had adverse events reported for serum chemistry analytes. One subject discontinued treatment due to increased liver transaminases and another subject had moderately increased total bilirubin reported as an adverse event. In addition, 1 subject in Subgroup 1a experienced a persisting mild anemia. Two subjects reported visual adverse events: 1 subject (Group 2) discontinued treatment due to double vision, dizziness and faintness, and another subject in Group 2 reported mild eye pain. Neurological examinations and MMSE did not reveal any additive effects of the combined treatment compared to flunarizine monotherapy. One subject in Subgroup 1a had clinically relevant abnormal responses to pain/temperature testing of the left and right index fingers on all measurements, which was reported as adverse event. In addition, 2 subjects, 1 in each subgroup, experienced mild orthostatic hypotension.

CONCLUSION: The steady-state pharmacokinetics of flunarizine were minimally affected by coadministration with topiramate. The steady-state pharmacokinetics of topiramate were unaffected by coadministration of flunarizine. Therefore, this is unlikely to be of clinical significance and dose adjustments do not appear to be necessary when both agents are administered concomitantly.

The study demonstrated that oral administration of topiramate (50 mg q12h), alone and concomitantly with flunarizine (5 mg q24h), and of flunarizine alone appeared safe and well-tolerated.

Date of the report: 09 August 2005

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