NAME OF COMPANY: R.W. Johnson Pharmaceutical Research Institute and Cilag NAME OF FINISHED PRODUCT: Topamax® (topiramate) NAME OF ACTIVE INGREDIENT(S): 2,3:4,5-bis-*O*-(1-methylethylidene) β-D-fructopyranose sulfamate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: 42 Page: 14766	(FOR NATIONAL AUTHORITY USE ONLY)

Title of the Study:
Double-Blind Parallel Comparison of Three Doses of Topiramate (RWJ-17021-000) (Mid to High Range) and Placebo in Refractory Partial Epilepsy (Protocol CR005452)

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Publication (Reference): None

Studied Period: 22 March 1988 to 13 January 1991. **Clinical Phase II/III**

Objectives: The primary objective of this placebo-controlled trial was to evaluate the safety and efficacy of topiramate 600, 800, and 1,000 mg/day as adjunctive therapy in subjects with refractory partial onset seizures with or without secondarily generalised seizures. Secondary objectives included the evaluation of the relationship between steady-state plasma concentration and clinical safety and efficacy, and the investigation of potential antiepileptic drug (AED) interactions.

Methodology: This randomized, double-blind, placebo-controlled, parallel-group, multicentre trial included a baseline phase during which subjects received one or two standard AEDs (phenytoin, carbamazepine, phenobarbital, primidone, valproic acid) and a double-blind phase during which subjects received one of three oral dosages of topiramate or placebo while continuing on their background AED regimen. The double-blind phase of the trial began with a titration period in which the dosage of topiramate was increased incrementally until the assigned or maximum tolerated dosage, if less, was attained followed by a stabilisation period during which subjects were maintained on this regimen.

Number of Subjects: One hundred ninety subjects qualified for the double-blind phase of the trial and were randomized to receive placebo (47 subjects), 600 mg/day topiramate (48 subjects), 800 mg/day topiramate (48 subjects), or 1,000 mg/day topiramate (47 subjects).

Diagnosis and Criteria for Inclusion: For entry into the double-blind phase, subjects were required to have at least 12 partial seizures in the 12-week baseline phase while maintained at therapeutic AED plasma concentrations; no seizure-free interval of more than three weeks duration and no more than one such interval during the 12-week baseline phase was permitted.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate; 300, 400, or 500 mg twice daily as 100-mg oral tablets; batch number R4330.

Duration of Treatment: Total duration was 18 weeks including the six-week titration period and 12-week stabilisation period. The duration of these periods could vary for individual subjects depending on their ability to tolerate the titration schedule.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo administered twice daily as oral tablets; batch number R4336.

Criteria for Evaluation: The primary efficacy variable was percent reduction in the average monthly seizure rate. Secondary efficacy results included percent treatment responders (subjects with a 50% or greater reduction in seizure rate), investigator's and subject's global assessments, and percent reduction in the generalised seizure rate. Safety evaluations included: adverse events; clinical laboratory tests (haematology, serum chemistry, and urinalysis); physical, neurologic, ophthalmologic, and audiometric examinations; vital sign measurements; and ECGs. In addition, plasma AED concentrations were measured to assess comparability between topiramate- and placebo-treated groups.

Statistical Methods: The intent-to-treat efficacy analysis included data from all subjects who entered the double-blind phase. All statistical tests were two-sided. The primary efficacy variable, percent reduction in the average monthly seizure rate, was assessed by pairwise comparisons of each of the three topiramate dosages to placebo using analyses of variance on ranks. For the analysis of percent reduction in secondarily generalised seizures, since there were few subjects with generalised seizures all topiramate groups were combined and compared with the placebo group. Plasma concentrations of concomitant AEDs were analyzed and a one-way analysis of variance based on the mean changes in plasma AED concentrations was used to assess comparability between topiramate and placebo-treated groups.

SUMMARY-CONCLUSIONS

Demographics: One hundred ninety subjects, 152 men and 38 women, entered the double-blind phase of the trial and were included in the analyses of efficacy and safety. Baseline demographic characteristics including sex, age, race, body weight, and seizure type were comparable among the treatment groups. The mean age of subjects enrolled was 35.3 years.

Efficacy Results: The results of the efficacy analysis are summarised in following table and discussed below.

		Topiramate Dosage		
Efficacy Variable	Placebo	600 mg/day	800 mg/day	1,000 mg/day
Primary Efficacy Variable				
Percent reduction in average monthly seizure rate				
Median	1.2	40.7*	41.0*	37.5*
p-value[a]	-	<0.001	<0.001	<0.001
Secondary Efficacy Variables				
Percent treatment responders[b]	9	44*	40*	38*
Investigator's global assessment[c]	11	55*	54*	53*
Subject's global assessment[d]	26	62*	57*	47*
Median percent reduction in generalised seizure rate[e]	40.3	65.5	44.4	78.0

[a] Topiramate vs. placebo; two-factor ANOVA on ranks with type III sums of squares.
[b] Percent of subjects with ≥50% monthly seizure rate reduction from baseline.
[c] Percent of subjects with marked or moderate improvement.
[d] Percent of subjects who rated the study medication as good or excellent.
[e] A reduction in generalised seizures favored topiramate over placebo, but was not statistically significant, p=0.165.

* denotes a statistically significant difference for topiramate vs. placebo comparisons, p≤0.05.

Topiramate 600 mg/day, 800 mg/day, and 1,000 mg/day were superior to placebo as indicated by a statistically greater percent reduction from baseline in the average monthly seizure rate, p<0.001. A statistically greater number of subjects in each of the topiramate groups were treatment responders compared with the placebo group, p≤0.001. Topiramate therapy also resulted in a greater reduction in generalised seizures compared to placebo, although the difference was not statistically significant. In general, the results of efficacy analyses for the for the stabilization period were similar to those for the double-blind phase. Taken together, the results of the various efficacy evaluations indicate that each of the three doses of topiramate is effective in the treatment of refractory partial epilepsy.

Pharmacokinetic Results: Mean changes in plasma concentrations of each concomitant AED (carbamazepine, phenytoin, valproic acid, phenobarbital, and primidone) were comparable from the beginning to the end of the double-blind phase and between topiramate- and placebo-treated subjects, indicating that topiramate effects were not mediated through changes in plasma levels of concomitant AEDs.

Safety Results: The most commonly reported treatment-emergent adverse events were asthenia, cognitive dysfunction, confusion, dizziness, headache, nervousness, nystagmus, somnolence, and visual disturbance. Of these, nystagmus, somnolence, and visual disturbance appeared to be dose-related, occurring at a greater incidence in subjects treated with topiramate 800 mg/day or 1,000 mg/day than in subjects treated with placebo. The incidences of somnolence and nystagmus in the placebo group (13% for both) were similar to that of the topiramate 600 mg/day group. The incidence of asthenia, cognitive dysfunction, confusion, dizziness, and nervousness was higher in each of the three topiramate treatment groups compared with that of the placebo group, but there was no apparent dose-response relationship within the topiramate treatment groups. The incidence of headache was similar among the three topiramate treatment groups and the placebo group. Most treatment-emergent adverse events were considered to be mild or moderate in severity and considered by the investigator to be either possibly or probably related to study medication. Twenty-four (13%) subjects discontinued because of one or more adverse events, 10 in the topiramate 600 mg/day group, five in the topiramate 800 mg/day group, eight in the topiramate 1,000 mg/day group, and one in the placebo group. Fourteen (58%) of the 24 subjects who discontinued due to adverse events did so during the titration period. A greater number of subjects in the topiramate treatment groups discontinued the study because of adverse events than in the placebo group. Many of the adverse events that resulted in premature discontinuation were central nervous system-related and included anxiety, cognitive dysfunction, depression, and emotional lability. Four subjects experienced adverse events that were considered to be serious or potentially serious. Two subjects on topiramate 1,000 mg/day experienced serious or potentially serious adverse events (abdominal pain and shortness of breath) which were considered by the investigator to be possibly drug-related. One subject each in the topiramate 600 mg/day and placebo group suffered an accidental injury that the investigator considered to be unrelated to the study medication. There were no deaths during the trial. There were no noteworthy abnormal clinical laboratory findings among topiramate-treated subjects, including results of liver function, renal function, and haematologic tests. Similarly, there were no clinically noteworthy treatment-emergent changes in vital signs, ECGs, neurologic examinations, physical examinations, audiometric examinations, and ophthalmologic evaluations.

Conclusions: The results of this trial indicate that topiramate at dosages of 600 mg/day, 800 mg/day, and 1,000 mg/day is effective in the treatment of refractory partial epilepsy with or without secondarily generalised seizures. All three dosages of topiramate were statistically superior to placebo for median percent reduction from baseline in average monthly seizure rate, percent treatment responders, investigator's global evaluation of improvement, and subject's overall assessment of medication. The median percent reduction in generalised seizure rate favored all three topiramate groups combined over placebo, but was not statistically significant. Adverse events were not so common as to preclude the utility of topiramate at these higher dosages.

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