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: 57 Page: 20423	(FOR NATIONAL AUTHORITY USE ONLY)

Title of the Study:
Double-Blind Parallel Comparison of Topiramate (RWJ-17021-000) 200 mg twice daily to Placebo in Patients With Refractory Partial Epilepsy (Protocol CR005563)

Investigators:
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Publication (Reference): None

Studied Period: 10 October 1989 to 18 May 1993.	**Clinical Phase II/III**

Objectives: The objective of this placebo-controlled trial was to evaluate the safety and efficacy of topiramate 400 mg/day as adjunctive therapy in subjects with refractory partial onset seizures with or without secondarily generalised seizures.

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 topiramate 400 mg/day or placebo while continuing on their background AED regimen. Clobazam or clonazepam was also permitted, but only in combination with one of the above AEDs. 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: Forty-seven subjects qualified for the double-blind phase of the trial and were randomized to receive placebo (24 subjects) or topiramate 400 mg/day (23 subjects).

Diagnosis and Criteria for Inclusion: For entry into the double-blind phase, subjects were required to have at least eight partial seizures in the eight-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 eight-week baseline phase was permitted.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate; 200 mg twice daily as 100-mg oral tablets; batch number R4328.

Duration of Treatment: Total duration was 11 weeks including the three-week titration period and eight-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 R4359.

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 and neurologic 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. Percent reduction in the average monthly seizure rate was assessed by comparison of topiramate 400 mg/day to placebo using two-factor (treatment, centre, and treatment-by-centre interaction) analysis of variance on ranks. An additional efficacy assessment compared treatment groups with respect to percent of responders, stratified by centre, using the Cochran-Mantel-Haenszel method. Investigator's global evaluation of improvement and subject's overall assessment of medication were analyzed by Wilcoxon rank-sum tests stratified by centre. All statistical tests were two-sided. To analyze secondarily generalised seizures for subjects who had generalised seizures at baseline, percent reduction was computed for generalised seizures only. The topiramate 400 mg/day group was compared against the placebo group, using analysis of variance on rank of percent generalised seizure reduction.

SUMMARY-CONCLUSIONS

Demographics: Forty-seven subjects, 40 men and 7 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 between the treatment groups. The mean age of subjects enrolled was 34.0 years.

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

Efficacy Variable	Placebo	Topiramate 400 mg/day
Primary Efficacy Variable		
Percent reduction in average monthly seizure rate		
Median	1.1	40.7
p-value[a]	-	0.065
Secondary Efficacy Variables		
Percent treatment responders[b]	8	35*
Investigator's global assessment[c]	8	57*
Subject's global assessment[d]	8	43*
Median percent reduction in generalised seizure rate	8.7	83.9*

[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.

* denotes a statistically significant difference for topiramate vs. placebo comparisons, $p \leq 0.05$.

Topiramate 400 mg/day tended to be superior to placebo as indicated by a greater percent reduction in the average monthly seizure rate ($p = 0.065$). A statistically greater number of subjects in the topiramate group were treatment responders compared with the placebo group, $p=0.033$. The results of the investigator and subject global assessments were significantly better in the topiramate than in the placebo group. Topiramate therapy also resulted in a significantly greater reduction in generalised seizures compared to placebo. In general, the results of efficacy analyses for the stabilisation period were similar to those for the double-blind phase. Taken together, the results of the various efficacy evaluations indicate that a dosage of 400 mg/day 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 somnolence, fatigue, headache, weight decrease, confusion, abnormal vision, anxiety, and upper respiratory tract infection. Somnolence, fatigue, weight decrease, abnormal vision, anxiety, and upper respiratory tract infection were more common in topiramate- than in placebo-treated subjects. Headache and confusion occurred more frequently in placebo- than in topiramate-treated subjects. Moreover, most treatment-emergent adverse events were classified as mild or moderate in severity. Six subjects in the topiramate 400 mg/day group and one subject in the placebo group discontinued therapy because of one or more adverse events, and most of the adverse events leading to premature discontinuations first occurred during the titration period. No subjects had serious adverse events, and there were no deaths. There were no noteworthy abnormal clinical laboratory findings among topiramate-treated subjects, including results of liver or renal function, haematologic, or other laboratory tests. There were no clinically noteworthy treatment-emergent changes in vital signs, ECGs, neurologic examinations, and physical examinations. Body weight tended to decrease in the topiramate 400 mg/day group, with mean decreases of up to 3.2 kg observed during the double-blind phase of the trial. In contrast, no consistent changes in body weight were observed among placebo-treated subjects.

Conclusions: Topiramate 400 mg/day was superior to placebo for every efficacy assessment. With the exception of the primary efficacy variable, all differences between the efficacy variables were statistically significant. Topiramate was well tolerated in this study.

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