

<p><u>NAME OF COMPANY:</u> R.W. Johnson Pharmaceutical Research Institute and Cilag</p> <p><u>NAME OF FINISHED PRODUCT:</u> Topamax® (topiramate)</p> <p><u>NAME OF ACTIVE INGREDIENT(S):</u> 2,3:4,5-bis-O-(1-methylethylidene) β-D-fructopyranose sulfamate</p>	<p><u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u></p> <p>Volume: 32</p> <p>Page: 9996</p>	<p><u>(FOR NATIONAL AUTHORITY USE ONLY)</u></p>
<p><b>Title of the Study:</b> Double-Blind Parallel Comparison of Three Doses of Topiramate (RWJ-17021-000) (Low to Mid Range) and Placebo in Refractory Partial Epilepsy (Protocol CR005458)</p>		
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<p><b>Publication (Reference):</b> None</p>		
<p><b>Studied Period:</b> 29 February 1988 to 20 December 1990.</p>	<p><b>Clinical Phase II/III</b></p>	
<p><b>Objectives:</b> The primary objective of this trial was to evaluate the safety and efficacy of topiramate 200, 400, and 600 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 topiramate concentrations and clinical safety and efficacy, and the investigation of potential antiepileptic drug interactions.</p>		
<p><b>Methodology:</b> 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.</p>		
<p><b>Number of Subjects:</b> One hundred eighty-one subjects qualified for the double-blind phase of the trial and were randomized to receive placebo (45 subjects), 200 mg/day topiramate (45 subjects), 400 mg/day topiramate (45 subjects), or 600 mg/day topiramate (46 subjects).</p>		
<p><b>Diagnosis and Criteria for Inclusion:</b> 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.</p>		
<p><b>Test Product, Dose and Mode of Administration, Batch No.:</b> Topiramate; 100, 200, or 300 mg twice daily as 100-mg oral tablets; batch numbers R4328, R4330, and R4371.</p>		
<p><b>Duration of Treatment:</b> Total duration was 16 weeks including the 4-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.</p>		
<p><b>Reference Therapy, Dose and Mode of Administration, Batch No.:</b> Placebo administered twice daily as oral tablets; batch number R4336.</p>		
<p><b>Criteria for Evaluation:</b> 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.</p>		
<p><b>Statistical Methods:</b> 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.</p>		

**SUMMARY - CONCLUSIONS**

**Demographics:** One hundred eighty-one subjects, 143 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 36.9 years.

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

Efficacy Variable	Placebo	Topiramate Dosage		
		200 mg/day	400 mg/day	600 mg/day
<b>Primary Efficacy Variable</b>				
Percent reduction in average monthly seizure rate				
Median	13.1	29.6**	47.8*	44.7*
p-value <sup>a</sup>	-	0.051 <sup>b</sup>	0.007 <sup>b</sup>	<0.001
<b>Secondary Efficacy Variables</b>				
Percent treatment responders <sup>c</sup>	18	27	47*	46*
Investigator's global assessment <sup>d</sup>	24	44*	70*	61*
Subject's global assessment <sup>e</sup>	38	64*	65*	54**
Median percent reduction in generalised seizure rate <sup>f</sup>	1.3	61.7*	100.0*	88.8*

<sup>a</sup> Topiramate vs. placebo; two-factor ANOVA on ranks with type III sums of squares.

<sup>b</sup> Statistically significant treatment-by-centre interaction ( $p \leq 0.10$ ).

<sup>c</sup> Percent of subjects with  $\geq 50\%$  monthly seizure rate reduction from baseline.

<sup>d</sup> Percent of subjects with marked or moderate improvement.

<sup>e</sup> Percent of subjects who rated the study medication as good or excellent.

<sup>f</sup> A statistically significant difference was observed between the placebo and the three topiramate groups combined;  $p = 0.003$ .

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

\*\* denotes a statistical trend,  $0.05 \leq p \leq 0.10$ .

Topiramate 400 mg/day and 600 mg/day were superior to placebo as indicated by a statistically greater percent reduction from baseline in the average monthly seizure rate,  $p = 0.007$  and  $p < 0.001$ , respectively. Topiramate 200 mg/day tended to be superior to placebo, approaching significance,  $p = 0.051$ . The results of dose-response analyses performed by the Jonckheere-Terpstra test, both with and without data from the placebo group, showed a significant increase in percent reduction in the average monthly seizure rate with increasing dose of topiramate ( $p < 0.001$  and  $p = 0.023$ ). A statistically greater number of subjects in the topiramate 400 mg/day and 600 mg/day groups were treatment responders compared with the placebo group,  $p \leq 0.027$ . The results of dose-response analyses performed by the Cochran-Armitage test, both with and without data from the placebo group, showed a significant increase in treatment responders with increasing dose of topiramate ( $p = 0.001$  and  $p = 0.042$ ). The results of investigator and subject global assessments were statistically better for topiramate-treated than placebo-treated subjects. 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. The results of this trial show that when topiramate is administered as adjunctive therapy in subjects with partial onset epilepsy, improvement in seizure control can be seen at dosages of 400 mg/day or higher.

**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 central nervous system-related and included ataxia, cognitive dysfunction, dizziness, headache, nystagmus, somnolence, and visual disturbance. Except for cognitive dysfunction, the incidence of these adverse events did not appear to be dose-related across the topiramate groups, and in the case of headache and nystagmus, was no greater than that observed with placebo. Moreover, most treatment-emergent adverse events were classified as mild or moderate in severity and many were considered by the investigator to be either remotely related or unrelated to study medication. Fifteen subjects discontinued therapy because of an adverse event, and most of these premature discontinuations occurred during the titration period. There were no apparent differences in the rates of withdrawal for topiramate-treated subjects compared with placebo-treated subjects. Two subjects on topiramate 400 mg/day experienced serious or potentially serious adverse events (a presumptive cerebrovascular accident and an adverse behavior effect), neither of which was considered by the investigator to be drug-related. 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, haematologic or other laboratory 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 400 mg/day, and 600 mg/day is effective in the treatment of refractory partial epilepsy with or without secondarily generalised seizures. All three dosages of topiramate were better than placebo in a number of variables; however, greater efficacy was obtained with topiramate 400 mg/day and 600 mg/day. All 3 dosages of topiramate were well-tolerated.

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