

<p>NAME OF COMPANY: R.W. Johnson Pharmaceutical Research Institute and Cilag</p> <p>NAME OF FINISHED PRODUCT: Topamax® (topiramate)</p> <p>NAME OF ACTIVE INGREDIENT(S): 2,3:4,5-bis-O-(1-methylethylidene) β-D-fructopyranose sulfamate</p>	<p>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</p> <p>Volume: 66</p> <p>Page: 24713</p>	<p>(FOR NATIONAL AUTHORITY USE ONLY)</p>
<p>Title of the Study: Double-Blind Parallel Comparison of Topiramate (RWJ-17021-000) 400 mg twice daily to Placebo in Patients With Refractory Partial Epilepsy (Protocol CR005569)</p>		
<p>Investigators: E. Ben-Menachem, M.D. (Goteborg; Sweden); M. Dam, M.D., Ph.D. (Hvidovre; Denmark); O. Henriksen, M.D. (Sandvika; Norway); D. Schmidt, M.D. (Berlin; Germany).</p>		
<p>Publication (Reference): None</p>		
<p>Studied Period: 12 May 1989 to 12 February 1992.</p>	<p>Clinical Phase II/III</p>	
<p>Objectives: The objective of this placebo-controlled trial was to evaluate the safety and efficacy of topiramate 800 mg/day as adjunctive therapy in subjects with refractory partial onset seizures with or without secondarily generalised seizures.</p>		
<p>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 800 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.</p>		
<p>Number of Subjects: Fifty-six subjects qualified for the double-blind phase of the trial and were randomized to receive placebo (28 subjects) or topiramate 800 mg/day (28 subjects).</p>		
<p>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.</p>		
<p>Test Product, Dose and Mode of Administration, Batch No.: Topiramate; 400 mg twice daily as 100-mg oral tablets; batch number R4328.</p>		
<p>Duration of Treatment: Total duration was 13 weeks including the five-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.</p>		
<p>Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo administered twice daily as oral tablets; batch number R4356.</p>		
<p>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.</p>		
<p>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 800 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 800 mg/day group was compared against the placebo group, using analysis of variance on rank of percent generalised seizure reduction.</p>		

Summary of Topiramate Clinical Trial: Protocol Y3 (continued)

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