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**APPLICATION NUMBER: 020844**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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Topamax<sup>TM</sup> (topiramate)  
NDA 20-844

Submission Date: July 31, 1997

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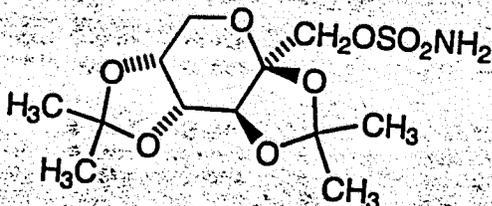
TOPAMAX (topiramate) Tablets were approved on December 24, 1996 for the adjunctive treatment for adults with partial onset seizures. The Sponsor RW Johnson plans to market topiramate sprinkle formulation (15, 25, and 50 mg strengths) for patients who have difficulty swallowing tablets. The Sponsor has submitted two oral bioavailability studies comparing sprinkle formulation with 100 mg tablet formulation. One study assess the effect of food on the bioavailability of sprinkle formulation. The sponsor has also submitted studies on acceptability and palatability for the sprinkle formulation.

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## Summary of Topiramate Pharmacokinetics (previous Tablet NDA)



Topamax<sup>TM</sup> (topiramate) is a chemical compound classified as a sulfamate-substituted monosaccharide, claimed by the Sponsor to be an antiepileptic. Chemically Topamax is designated as 2,3:4,5-bis-O-(1-methylethylidene)-b-D-fructopyranose sulfamate.

Topiramate is rapidly and well-absorbed after oral administration. Following 400 mg multiple oral dosing every 12 hours, peak plasma concentration of 27 µg/mL is reached in about two hours. There is no effect of food on the bioavailability of topiramate. The volume of distribution of topiramate following 100 to 1200 mg oral dose ranged from

Plasma protein binding of topiramate is about 17 percent.

Topiramate is not extensively metabolized. At least six minor inactive metabolites formed through hydroxylation or hydrolysis of the isopropylidene groups and glucuronidation have been identified from plasma and urine of humans. About 70% of the dose of topiramate is excreted unchanged in human urine. The mean elimination half-life of topiramate in humans is approximately 21 hrs. Oral clearance is approximately 29 ml/min in humans following oral administration. Clearance of topiramate is not affected by age, gender or race. The mean renal clearance of topiramate is 14 ml/min.

Multiple q 12h dosing of 50 and 100 mg doses of topiramate for at least 14 days results in topiramate C<sub>max</sub> and AUC values that increased in a linear and dose-proportional manner.

The pharmacokinetics of topiramate is affected by renal impairment. Oral clearance decreased by 56% in the severe group (creatinine clearance <30 ml/min/1.73m<sup>2</sup>) and by 46% in the moderate group (creatinine clearance ml/min/1.73m<sup>2</sup>) as compared to normals. Topiramate is effectively removed from the plasma by hemodialysis.

In three multicenter clinical studies designed to compare the safety and efficacy of different doses of topiramate (200-1000 mg/day) in patients with refractory partial epilepsy, the median percent reduction in seizure rate increases with increasing plasma topiramate concentrations up to 5.2 µg/mL. At plasma topiramate concentrations above 5.2 µg/mL, a decrease from the peak seizure rate reduction is observed.

## Summary of the Studies Submitted in this NDA

### Bioavailability and bioequivalence studies:

In a preliminary comparative bioavailability study 9 subjects received \_\_\_\_\_ sprinkle formulation, \_\_\_\_\_ sprinkle formulation, and a 100 mg market image tablet formulation. This was open label, randomized, three way cross-over study. Subjects in Treatment A received a single 100 mg dose of topiramate administered as one 100 mg market-image tablet following ingestion of two tablespoons (30 mL) of applesauce. In Treatment B, subjects received two tablespoons of applesauce (30 mL) which contained a 100 mg dose of topiramate as the contents of two 50 mg capsules of a \_\_\_\_\_ sprinkle formulation. In Treatment C, subjects received two tablespoons of applesauce (30 mL) which contained a 100 mg dose of topiramate as the contents of two 50 mg capsules of a \_\_\_\_\_ sprinkle formulation. Blood samples were collected till 72 hours and plasma samples were analyzed by a validated \_\_\_\_\_. The results of the study indicated that C<sub>max</sub>, T<sub>max</sub>, and AUC were comparable among three formulations. The half-life of \_\_\_\_\_ sprinkle formulation, was 4 hours shorter than \_\_\_\_\_ sprinkle formulation and 100 mg market image tablet formulation (Study #1).

In a bioequivalence study 18 subjects (16 completed) received \_\_\_\_\_ sprinkle formulation and a 100 mg market image tablet formulation. This was open label, randomized, two way cross-over study. Subjects either received a single 100 mg dose of topiramate administered as one 100 mg market-image tablet with 120 mL water or two tablespoons of applesauce (30 mL) which contained a 100 mg dose of topiramate as the contents of two 50 mg capsules of a \_\_\_\_\_ sprinkle formulation. Blood samples were collected till 72 hours and plasma samples were analyzed by a validated \_\_\_\_\_. The

results of the study indicated that  $C_{max}$  and AUC of both formulations are within confidence interval limit of 80 -125%

#### **Effect of food on the pharmacokinetics of sprinkle formulation:**

Twenty-four healthy men and women took part in this study. After overnight fast, the subjects received either 100 mg topiramate \_\_\_\_\_ sprinkle formulation in 2 tablespoons (30 mL) of applesauce under fasted condition (Treatment A), or 100 mg topiramate \_\_\_\_\_ sprinkle formulation after receiving a standard breakfast (Treatment B), or 2x50 mg topiramate capsules under fasted condition (Treatment C). The standard breakfast contained: two slices of toast with butter, two eggs fried in butter, two strips of fried bacon, one serving of hash brown potatoes and 180 mL of whole milk. There was a 3 week wash out period between the treatments. Blood samples were collected till 72 hours and plasma samples were analyzed by a validated \_\_\_\_\_

\_\_\_\_\_ The results of the study indicated that the  $C_{max}$ , AUC and  $t_{1/2}$  were comparable among the three treatments. The  $T_{max}$  for the capsule under fasted condition was almost 50% lower than the sprinkle formulation given under fasted state (Study #3).

#### **Acceptability of topiramate sprinkle formulation:**

The objective of this study was to determine the acceptability of three coating \_\_\_\_\_ to mask the bitter taste of topiramate. Forty-eight healthy male subjects (18 to 55 years) took part in this study. The subjects were divided into 6 groups and each subject sequentially tasted each of the three coated bead formulations with 20 minute intervals between tasting the different formulations. During each taste test, subjects first tasted a bitter standard solution consisting of 0.05% caffeine and then tasted one of the three coated bead formulations. Subjects were asked to evaluate the taste

acceptability of each formulation to compare the bitterness intensity of each formulation with the bitterness intensity of the standard caffeine solution. Taste acceptability was evaluated at 30 and 60 seconds on a scale of -4 (extremely unacceptable) to 4 (extremely acceptable) with 0 being neutral. Bitterness intensity was evaluated at 30 and 60 seconds on a magnitude scale in comparison to the standard caffeine solution, with the standard having a rating of 100. Overall taste acceptability was evaluated based on the willingness to take the product as a medicine for a serious illness based on yes or no answer at the end of 60 seconds.

The taste acceptability increased with increasing coating percentage whereas bitterness intensity decreased with increasing coating percentage. Only 29% subjects found \_\_\_\_\_ coating bead acceptable as compared to 56% subjects who thought \_\_\_\_\_ coating bead was acceptable. For the bitterness intensity test, the mean score was 246 and 204 for the \_\_\_\_\_ formulation, respectively. The \_\_\_\_\_ formulation did not differ significantly in their ability to mask the taste of topiramate (Study #4).

#### **Palatability of topiramate sprinkle formulation:**

The study was conducted in 15 pediatric subjects (3 to 14 years) with epilepsy who were taking topiramate tablets. Topiramate sprinkle formulation replaced the morning tablet dose once daily for three days. Study drug was mixed with approximately one tablespoon of soft food (applesauce). If the food was spit out or vomited the subject was to be given his or her normal dose in regular tablet form. On days 2 and 3 drug was given at home and parents or guardian recorded whether or not child spit out the sprinkle. On day 3, the subjects completed a pictogram depicting his or her reaction to the tablet and the sprinkle and parents or guardians made an overall assessment. The results of the study indicated that topiramate sprinkle formulation was an acceptable substitute in children for the tablet (Study #5).

**Dissolution:**

The Sponsor's proposed Dissolution Method and Specifications for topiramate sprinkle  
are as follows:

Dosage Form: Sprinkle  
Strengths: 15, 25, and 50 mg  
Apparatus: USP Apparatus II (Paddle)  
Medium: \_\_\_\_\_ mL  
Speed: \_\_\_\_\_ rpm.  
Sampling Times: \_\_\_\_\_ minutes

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Sponsor's proposed Specifications: Q \_\_\_\_\_ at \_\_\_\_\_ minutes  
FDA's proposed Specifications: Q \_\_\_\_\_ at \_\_\_\_\_ minutes

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### Labelling Comments

The Sponsor is requested to make following changes in their labelling:

1. Under **Pediatric Pharmacokinetics** please add:

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2. Under **Oral Contraceptive Pharmacokinetics** please add:

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### Comments

The Sponsor has provided evidence that 50 mg sprinkle formulation is bioequivalent to 100 mg market image tablet. The Sponsor also intends to market 15 and 25 mg sprinkle capsules.

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Therefore, a biowaiver can be granted for 15 and 25 mg sprinkle capsules.

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**Recommendation:**

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The Sponsor is requested to incorporate all the 'Labelling' changes.

Please convey the Labelling Comments and FDA's proposed dissolution specifications to the Sponsor.

Iftexhar Mahmood, Ph.D.

/S/

6/3/98

RD/FT initialed by Chandra Sahajwalla, Ph.D.

/S/

6/3/98

Division of Pharmaceutical Evaluation I  
Office of Clinical Pharmacology and Biopharmaceutics

CPB Briefing: June 2, 1998

CC: NDA 20-844, HFD-120, HFD-860 (Mahmood, Sahajwalla, Malinowski), HFD-340 (Viswanathan), CDR (Barbara Murphy) and FOI (HFD-19) files.

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Study # 1

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SYNOPSIS

<b>NAME OF SPONSOR/COMPANY:</b> The R.W. Johnson Pharmaceutical Research Institute			
<b>NAME OF FINISHED PRODUCT:</b> TOPAMAX® (topiramate)			
<b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3:4,5-bis-O-(1-methylethylidene) β-D-fructopyranose sulfamate			
<b>Protocol No.:</b> TOPMAT-PHI-357 <b>Title of Study:</b> Comparative Bioavailability of Topiramate (RWJ-17021-000) From Two Prototype Sprinkle Formulations Relative to a 100 mg Market-Image Tablet Formulation Administered as a 100 mg Single Oral Dose to Healthy Male Subjects			
<b>Investigators:</b>			
<b>Study Centre:</b>			
<b>Publication (Reference):</b> None			
<b>Studied Period (years):</b> 0.25 (date of first enrollment) July 27, 1995 (date of last completed) September 11, 1995		<b>Phase of development:</b> 1	
<b>Objectives:</b> The objective of this study was to make a preliminary assessment of the comparative bioavailability of topiramate from a _____ sprinkle formulation and a _____ sprinkle formulation relative to a 100 mg market-image tablet formulation administered as a 100 mg single oral dose to healthy male subjects.			
<b>Methodology:</b> This was an open-label, randomized, complete three-way cross-over study conducted at one ex-U.S. center. During Period 1, subjects assigned to receive Treatment A received a single 100 mg dose of topiramate administered as one 100 mg market-image tablet following ingestion of 2 tablespoons (30 mL) of applesauce. Subjects assigned to receive Treatment B received a single 100 mg dose of topiramate administered as the contents of two 50 mg capsules of a _____ sprinkle formulation mixed with 2 tablespoons (30 mL) of applesauce and subjects assigned to receive Treatment C received a single 100 mg dose of topiramate administered as the contents of two 50 mg capsules of a _____ sprinkle formulation mixed with 2 tablespoons (30 mL) of applesauce. Blood samples were collected for 72 hours following administration of the topiramate dose and the plasma analyzed for topiramate concentration by a validated and specific _____ Following a washout period of at least 3 weeks, the subjects were crossed-over to receive the alternative treatments in Periods 2 and 3.			
<b>Number of Subjects (planned and analyzed):</b> Nine healthy male subjects were divided evenly into three treatment sequence groups according to a computer-generated randomization schedule. All subjects enrolled in the study completed the study as outlined in the protocol. All nine subjects were included in the safety data analysis. Eight subjects were included in the pharmacokinetic data analysis. The pharmacokinetic data from Subject 109 were excluded because the subject had no plasma concentrations for the third dosing period, suggesting a lack of dosing compliance.			
<b>Diagnosis and Main Criteria for Inclusion:</b> Only healthy male subjects between the ages of _____ were enrolled. Subjects were determined to be healthy based on results of clinical laboratory tests, vital signs, a medical history, and a physical exam. Subjects were required to test negative for hepatitis B, hepatitis C, HIV and drugs of abuse. Subjects with a known sensitivity to carbonic anhydrase inhibitors were excluded from the study.			
<b>Test Product, Dose and Mode of Administration, Batch No.:</b> Topiramate _____ sprinkle formulation (Formula FD17021-000-BB-34, Batch R6112) administered as a single oral 100 mg topiramate dose as the contents of two 50 mg capsules of the _____ mixed with 2 tablespoons of applesauce. Topiramate _____ sprinkle formulation (Formula FD17021-000-BF-34, Batch R6116) administered as a single oral 100 mg topiramate dose as the contents of two 50 mg capsules of the _____ coated formulation mixed with 2 tablespoons of applesauce.			
<b>Duration of Treatment:</b> A single dose was administered during each of three study dosing periods. Each study period was separated by a washout period of three weeks.			
<b>Reference Therapy, Dose and Mode of Administration, Batch No.:</b> Topiramate 100 mg market-image tablet (Formula 37, Batch R5572) administered orally as a single tablet immediately following the administration of 2 tablespoons of applesauce.			

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SYNOPSIS (Continued)

<p><b>NAME OF SPONSOR/COMPANY:</b> The R.W. Johnson Pharmaceutical Research Institute</p>			
<p><b>NAME OF FINISHED PRODUCT:</b> TOPAMAX® (topiramate)</p>			
<p><b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3:4,5-bis-O-(1-methylethylidene) β-D-fructopyranose sulfamate</p>			
<p><b>Criteria for Evaluation:</b></p> <p><b>Pharmacokinetics:</b> The topiramate pharmacokinetic parameters, peak concentration (<math>C_{max}</math>), time to peak concentration (<math>t_{max}</math>), and area under the concentration versus time curve to the time of the last concentration above the assay quantification limit [AUC (0-*)] and to infinity [AUC (0-∞)] were estimated from plasma data and were tabulated to assess the bioavailability of each sprinkle formulation relative to the tablet. Oral clearance (CL/F), terminal elimination rate constant (<math>k_e</math>) and plasma elimination half-life (<math>t_{1/2}</math>) were estimated and summarized.</p> <p><b>Safety:</b> Safety evaluations were based on changes in physical examination findings, vital signs, clinical laboratory tests (hematology, blood chemistry, and urinalysis) from predosing to postdosing in each study period, and adverse events reported throughout the study. Subjects were observed for 72 hours after dosing for each study period.</p>			
<p><b>Statistical Methods:</b> The ratio of the <math>C_{max}</math> and AUC's from each sprinkle formulation to the <math>C_{max}</math> and AUC from the tablet are taken as the estimate of the relative bioavailability. The standard deviation of the ratios will also be estimated. No comparative statistical analyses were conducted.</p>			
<p><b>SUMMARY - CONCLUSIONS</b></p>			
<p><b>PHARMACOKINETIC RESULTS:</b> The mean (±SD) topiramate single dose plasma pharmacokinetic parameters are summarized below.</p>			
<p style="text-align: center;"><u>Single Dose Plasma Topiramate Pharmacokinetic Parameters (Protocol TOPMAT-PHI-357)</u></p>			
<p><b>Topiramate Parameters*</b></p>			
	<u>Tablet</u>	<u>9% Coated Sprinkle</u>	<u>13% Coated Sprinkle</u>
$C_{max}$ (µg/mL)	1.80 (0.31)	1.81 (0.24)	1.79 (0.22)
$t_{max}$ (h)	1.6 (0.8)	1.9 (0.6)	1.8 (0.4)
AUC (0-*) (µg·h/mL)	51.2 (7.6)	52.2 (6.6)	50.6 (7.3)
AUC (0-∞) (µg·h/mL)	64.8 (12.0)	64.7 (9.0)	60.6 (9.4)
$t_{1/2}$ (h)	32.1 (5.6)	31.2 (4.2)	27.3 (4.8)
$k_e$ (h <sup>-1</sup> )	0.0223 (0.0042)	0.0225 (0.0028)	0.0262 (0.0048)
CL/F (mL/min)	26.5 (5.2)	26.2 (3.7)	28.3 (5.8)
<p>a Data are the mean (±SD), N=8. * AUC calculated to the last measured concentration.</p>			

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SYNOPSIS (Continued)

<p><b>NAME OF SPONSOR/COMPANY:</b> The R.W. Johnson Pharmaceutical Research Institute</p> <p><b>NAME OF FINISHED PRODUCT:</b> TOPAMAX® (topiramate)</p> <p><b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3:4,5-bis-O-(1-methylethylidene) β-D-fructopyranose sulfamate</p>			
<p>The mean (±SD) <math>C_{max}</math>, AUC (0-∞), and AUC (0-t) ratios from the sprinkle formulation relative to the tablet are 1.021 (0.164), 1.03 (0.11), and 1.02 (0.15), respectively. The corresponding ratios from the sprinkle formulation were 1.007 (0.138), 0.99 (0.14), and 0.96 (0.20). There was a slight trend toward decreased AUC with higher bead coating indicating decreased topiramate absorption.</p> <p><b>SAFETY RESULTS:</b> Three subjects experienced a total of seven adverse events. All four reports of headache (two reports in one subject and one report each in two subjects), which was the most common adverse event and occurred following all three treatments, were evaluated by the investigator to be possibly related to study drug. The other three adverse events -- pallor (general disorder), dizziness (nervous system), and nausea (gastrointestinal system) -- were reported by one subject on the same day as his headache (nervous system) following the administration of the sprinkle formulation. They were evaluated by the investigator as unlikely to be related to study drug. All adverse events were of mild severity and resolved spontaneously within one day. There were no deaths or serious adverse events during the study. There were no clinically noteworthy treatment-emergent abnormalities in clinical laboratory analyte values, physical or neurologic examination evaluations, vital sign measurements, or ECG measurements.</p> <p><b>CONCLUSION:</b> The results indicate that both the _____ sprinkle _____ formulations of topiramate are likely to be bioequivalent to the topiramate reference tablet.</p> <p>A single, oral 100-mg dose of topiramate in healthy male subjects was tolerated well whether administered as a market-image tablet, or as a _____, prototype sprinkle formulation. All subjects completed all three treatments. Only headache was reported by more than one subject (there were four reports of headaches of mild severity in three subjects) and was evaluated by the investigator as possibly related to topiramate treatment. No deaths or serious or potentially serious adverse events were reported. There were no clinically noteworthy treatment-emergent abnormalities in clinical laboratory analyte values, physical or neurologic examination evaluations, vital sign measurements, or ECG measurements.</p> <p><del>Data of this report</del> 17 Feb 1997</p>			

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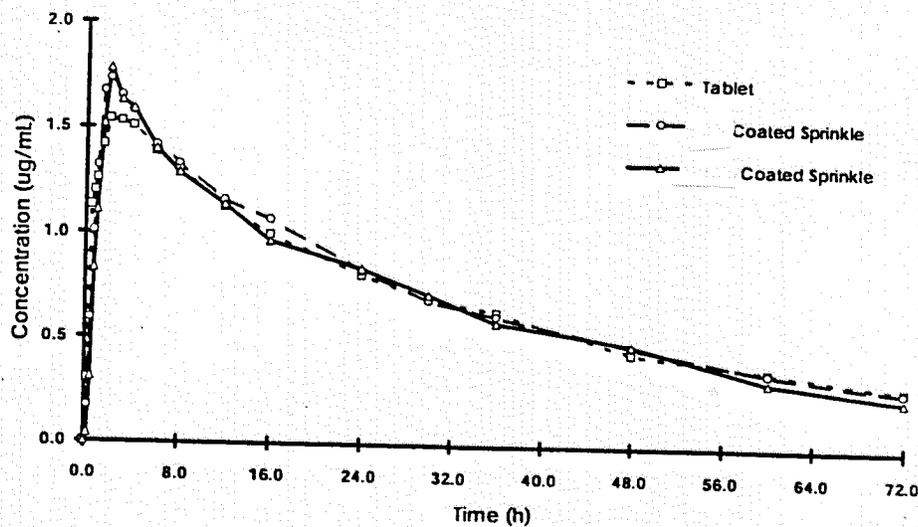
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**Table 3: Single Dose Plasma Topiramate Pharmacokinetic Parameters (Protocol TOPMAT-PHI-357)**

Topiramate Parameters*	Tablet	Coated Sprinkle	Coated Sprinkle
$C_{max}$ ( $\mu\text{g/mL}$ )	1.80 (0.31)	1.81 (0.24)	1.79 (0.22)
$t_{max}$ (h)	1.6 (0.8)	1.9 (0.6)	1.8 (0.4)
AUC (0-*) ( $\mu\text{g}\cdot\text{h/mL}$ )	51.2 (7.6)	52.2 (6.6)	50.6 (7.3)
AUC (0- $\infty$ ) ( $\mu\text{g}\cdot\text{h/mL}$ )	64.8 (12.0)	64.7 (9.0)	60.6 (9.4)
$t_{1/2}$ (h)	32.1 (5.6)	31.2 (4.2)	27.3 (4.8)
$k_e$ ( $\text{h}^{-1}$ )	0.0223 (0.0042)	0.0225 (0.0028)	0.0262 (0.0048)
CL/F ( $\text{mL/min}$ )	26.5 (5.2)	26.2 (3.7)	28.3 (5.8)

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**Figure 1: Mean Topiramate Plasma Concentration vs. Time Profiles from Nine Healthy Male Subjects Following a Single Oral 100 mg Dose of Topiramate (Protocol TOPMAT-PHI-357)**



Study # 2

SYNOPSIS

<p><b>NAME OF SPONSOR/COMPANY:</b> The R.W. Johnson Pharmaceutical Research Institute [and Janssen-Cilag]</p> <p><b>NAME OF FINISHED PRODUCT:</b> Topamax® (topiramate) market-image tablet and sprinkle formulations</p> <p><b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3:4,5-Bis-O-(1-methylethylidene)β-D-fructopyranose sulfamate</p>	<p><b>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</b></p> <p>Volume: Page:</p>	<p><b>(FOR NATIONAL AUTHORITY USE ONLY)</b></p>
<p><b>Protocol No.:</b> TOPMAT-PHI-359 <b>Title of Study:</b> Comparative bioavailability of topiramate (RWJ-17021 from a 100 mg market-image tablet and a sprinkle formulation administered as a 100 mg single oral dose in the fasted state to healthy subjects</p>		
<p><b>Investigator:</b></p>		
<p><b>Study Centre:</b></p>		
<p><b>Publication (Reference):</b> None</p>		
<p><b>Studied Period (years):</b> 29 February 1996 - 11 April 1996</p>	<p><b>Phase of development:</b> 1</p>	
<p><b>Objectives:</b> The objective of this study was to compare the bioavailability of topiramate from a 100 mg coated-bead sprinkle formulation with that from a 100 mg market-image tablet formulation administered as the contents of two 50 mg capsules mixed with applesauce in healthy subjects in the fasted state.</p>		
<p><b>Methodology:</b> This was an open-label, randomized, complete two-way crossover study. Eighteen healthy subjects were randomly assigned to one of two treatment sequence groups. Each subject received a single 100 mg oral dose of topiramate administered as one 100 mg market-image tablet and a 100 mg oral dose of a _____ sprinkle formulation administered as the contents of two 50 mg capsules mixed with two tablespoons of applesauce. Each treatment was administered after an overnight fast with a minimum three-week washout period between treatments. Following each treatment, 19 blood samples (5 mL) were collected at protocol-specified timepoints for 72 hours</p>		
<p><b>Number of Subjects (planned and analyzed):</b> 18 (16 for pharmacokinetic results)</p>		
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Male and female subjects, ages 18 to 40, were eligible to be enrolled in this study. Only subjects considered to be healthy based on a detailed medical history, physical examination, and clinical laboratory evaluation and those who were within 15% of their ideal weight were included in the study.</p>		
<p><b>Test Product, Dose and Mode of Administration, Batch No.:</b> Topiramate was supplied as a 100 mg market-image tablet formulation (Batch R5772) and as 50 mg capsules of topiramate-sprinkle formulation (Batch R6290). Topiramate was administered orally.</p>		
<p><b>Duration of Treatment:</b> Single dose of each formulation.</p>		
<p><b>Reference Therapy, Dose and Mode of Administration, Batch No.:</b> Not Applicable</p>		
<p><b>Criteria for Evaluation:</b> <b>Pharmacokinetics:</b> The pharmacokinetic profile of each formulation was based on the following parameters: peak concentration (<math>C_{max}</math>), time to peak concentration (<math>t_{max}</math>), area under the concentration-time curve (AUC) to the last measurable concentration (<math>AUC_{0-\infty}</math>) and to infinity (<math>AUC_{0-\infty}</math>), oral plasma clearance (CL/F), elimination half-life (<math>t_{1/2}</math>), and elimination rate constant (<math>k_e</math>). <b>Safety:</b> Safety was evaluated by reported adverse events, clinical laboratory tests, vital sign measurements, and physical examinations</p>		

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SYNOPSIS (Continued)

<b>NAME OF SPONSOR/COMPANY:</b> The R.W. Johnson Pharmaceutical Research Institute [and Janssen-Cilag]	<b>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</b> Volume: Page:	<b>(FOR NATIONAL AUTHORITY USE ONLY)</b>
<b>NAME OF FINISHED PRODUCT:</b> Topamax® (topiramate) market-image tablet and sprinkle formulations		
<b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3:4,5-Bis-O-(1-methylethylidene)β-D-fructopyranose sulfamate		

**Statistical Methods:**

**Pharmacokinetics:** Pharmacokinetic parameters were calculated for each subject. The pharmacokinetic parameters ( $C_{max}$ ,  $AUC_{0-\infty}$ , and  $AUC_{0-t}$ ) were compared by analysis of ln-transformed parameters. For  $C_{max}$ ,  $AUC_{0-\infty}$ , and  $AUC_{0-t}$ , analysis of variance models were fit to the data with the ln-transformed parameter as the dependent variable and the effects due to treatment sequence group, subjects nested within the sequence groups, treatment and period as predictors. For  $t_{max}$ , analysis of variance models were fit to the data with the ranked parameter and raw  $t_{max}$  data as the dependent variable. Analysis of variance models were also fit to the plasma elimination rate constant ( $k_e$ ) data. Tests for the treatment sequence group effect, period effect, and treatment effect were also performed. The estimated least squares and intrasubject variability from the above model were used to construct 90% confidence intervals for the ratio of the mean bioavailability parameter ( $C_{max}$ ,  $AUC_{0-\infty}$ , and  $AUC_{0-t}$ ) before and after normalizing for treatment formulation potency for the sprinkle formulation treatment to the 100 mg market-image tablet treatment using the classical (corresponding to Schuirmann's two one-sided test procedure) confidence interval approach.

**SUMMARY - CONCLUSIONS**

**PHARMACOKINETIC RESULTS:** The mean (SD) topiramate pharmacokinetic parameters from the two treatments are summarized below. There were no statistically significant differences between the two formulations when comparing the ln-transformed pharmacokinetic parameters without normalizing for treatment formulation potency. Also, there were no statistically significant differences between the two formulations when comparing ranked  $t_{max}$ , raw  $t_{max}$ , and  $k_e$ .

Topiramate Pharmacokinetic Parameters and Results of Statistical Comparisons

Parameter	Market-Image Tablet (Treatment A; N=16)		Sprinkle (Treatment B; N=16)		% Diff <sup>a</sup>	ANOVA <sup>b</sup>
	Mean	(SD)	Mean	(SD)		
$C_{max}$ (µg/mL)	2.48	(0.60)	2.35	(0.50)	-5.3	NS
$AUC_{0-\infty}$ (µg·h/mL) <sup>c</sup>	60.2	(13.7)	57.9	(15.0)	-3.8	NS
$AUC_{0-t}$ (µg·h/mL)	70.6	(15.9)	69.2	(18.8)	-1.9	NS
$t_{max}$ (h)	1.8	(1.3)	2.1	(1.0)	17.5	NS
$k_e$ (1/h)	0.0286	(0.0071)	0.0269	(0.0054)	-5.9	NS
$t_{1/2}$ (h)	25.5	(5.5)	26.7	(5.4)	4.7	---
CL/F (mL/min)	24.7	(5.2)	25.9	(7.7)	4.9	---

<sup>a</sup> With respect to tablet, (sprinkle - tablet) X 100.  
tablet

<sup>b</sup> ANOVA model for a randomized two-way crossover design. NS = not statistically significantly different ( $p > 0.05$ ). ANOVA results for  $t_{max}$  were based on both ranked  $t_{max}$  and raw  $t_{max}$ ; both were not statistically significant.

<sup>c</sup>  $AUC_{0-\infty}$  = AUC calculated to the last concentration above the quantification limit.

The 90% confidence interval bounds with and without normalizing for treatment formulation potency for  $C_{max}$ ,  $AUC_{0-\infty}$ , and  $AUC_{0-t}$  are summarized in the following table.

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SYNOPSIS (Continued)

<b>NAME OF SPONSOR/COMPANY:</b> The R.W. Johnson Pharmaceutical Research Institute [and Janssen-Cilag]	<b>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</b>	<b>(FOR NATIONAL AUTHORITY USE ONLY)</b>
<b>NAME OF FINISHED PRODUCT:</b> Topamax® (topiramate) market-image tablet and sprinkle formulations	Volume: Page:	
<b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3:4,5-Bis-O - (1-methylethylidene)β-D-fructopyranose sulfamate		

90% Confidence Interval Bounds With and Without Normalizing for Treatment Formulation Potency			
Parameter	Estimated Ratio (%) of Geometric Means (Sprinkle/Tablets)	90% Confidence Interval for the Ratio of Means	
		Lower Bound <sup>a</sup> (% Reference)	Upper Bound <sup>a</sup> (% Reference)
<b>Without Normalizing for Treatment Formulation Potency</b>			
C <sub>max</sub>	95.33%	87.12%	104.32%
AUC <sub>0-∞</sub> <sup>b</sup>	94.16%	89.53%	99.03%
AUC <sub>0-∞</sub>	95.42%	89.62%	101.60%
<b>Normalized for Treatment Formulation Potency</b>			
C <sub>max</sub>	95.92%	87.65%	104.96%
AUC <sub>0-∞</sub> <sup>b</sup>	94.74%	90.08%	99.64%
AUC <sub>0-∞</sub>	96.01%	90.17%	102.22%

<sup>a</sup> Bounds as percent of the reference treatment (market-image tablets) geometric mean.  
<sup>b</sup> AUC<sub>0-∞</sub> = AUC calculated to the last concentration above the quantification limit.

The percent difference between the mean values of the pharmacokinetic parameters for the two treatments was less than 6%, except for t<sub>max</sub> (17.5%). Results of ANOVA indicated that there were no statistically significant differences between treatments for any of the pharmacokinetic parameters. Results before and after normalizing for treatment formulation potency gave confidence interval bounds for C<sub>max</sub>, AUC<sub>0-∞</sub>, and AUC<sub>0-∞</sub> that were within the accepted bioequivalence interval.

**SAFETY RESULTS:** Topiramate was well tolerated. The most commonly reported treatment-emergent adverse events for both formulations were CNS-related, primarily of mild severity and generally considered to be possibly related to topiramate. Only abnormal erythrocytes and anemia – the limiting adverse events – were of marked severity. These treatment-emergent adverse events were reported for the one subject who prematurely withdrew from the study because of limiting adverse events and both were considered by the investigator to be unlikely related to topiramate. No deaths or serious adverse events were reported during this study. There were no treatment-related clinically significant laboratory test results, vital sign measurements, or changes in physical examinations.

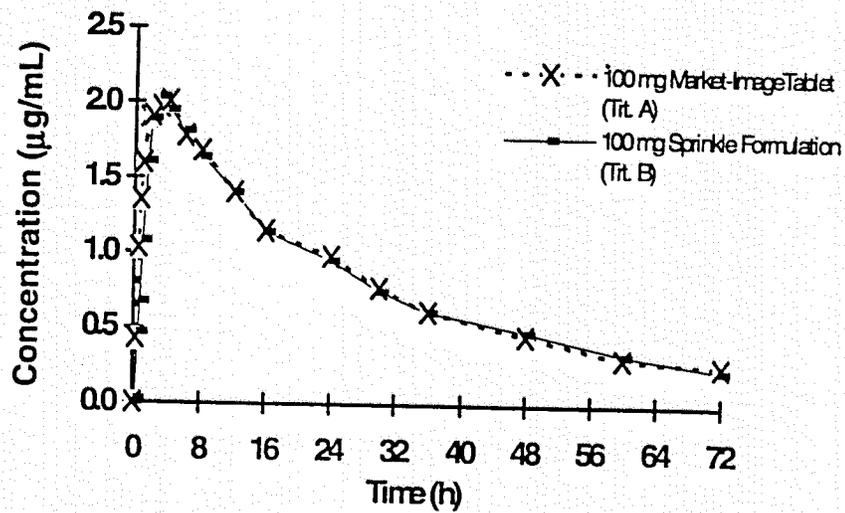
**CONCLUSION:** The pharmacokinetic results show that a 100 mg dose of the topiramate sprinkle formulation (Formula No. 17021-000-BH-34) administered as the contents of two 50 mg capsules mixed with applesauce is bioequivalent to the 100 mg market-image tablet (Formula No. 37). The 90% confidence intervals before and after normalizing for treatment formulation potency for the ratio of the means fell within the criteria for bioequivalence.

Date of the report: 20 January 1997

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Figure 1: Mean Topiramate Plasma Concentration vs. Time Profiles from Sixteen Healthy Subjects Following a Single Oral 100 mg Dose of Topiramate (Protocol TOPMAT-PHI-359)



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**ATTACHMENT 10: Statistical Analyses of  $C_{max}$ ,  $AUC_{0-\infty}$ , and  $AUC_{0-24}$ , Based on In-Transformed Results, and of Ranked  $t_{max}$ ,  $k$ , and Raw  $t_{max}$**   
 (Protocol TOPMAT-PHI-359)

Comparative Bioavailability of Topiramate (RMJ-17021-000) from a 100 mg Market-Image Tablet and a Sprinkle Formulation Administered as a 100 mg Single Oral Dose in the Fasted State to Healthy Subjects  
 Protocol TOPMAT-PHI-359

OBS	SUBJECT	GROUP	PERIOD	TREAT	P0	P0_15	P0_30	P0_45	P1	P1_30	P2	P3	P4	P6	P8	P12	P16	P24	P30	P36	P48
1	101	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	101	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	102	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	102	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5	103	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	103	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7	104	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	104	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
9	105	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	105	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
11	106	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	106	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
13	107	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	107	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
15	108	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	108	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
17	109	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	109	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
19	110	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	110	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
21	111	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	111	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
23	112	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	112	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
25	113	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26	113	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
27	114	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	114	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
29	115	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	115	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
31	118	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	118	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

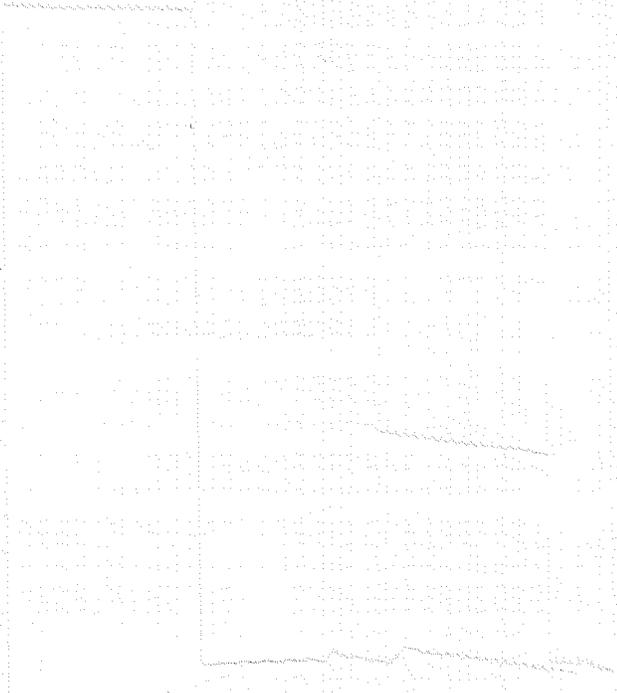
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ATTACHMENT 10: Statistical Analyses of  $C_{max}$ ,  $AUC_{0-\infty}$ , and  $AUC_{0-24}$ , Based on In-Transformed Results, and of Ranked  $t_{max}$ ,  $k_e$ , and Raw  $t_{max}$  (Protocol TOPMAT-PHI-359) (Continued)

Comparative Bioavailability of Topiramate (RWJ-17021-000) from a 100 mg Market-Image Tablet and a Sprinkle Formulation Administered as a 100 mg Single Oral Dose in the Fasted State to Healthy Subjects Protocol TOPMAT-PHI-359

OBS P60 P72 C\_MAX T\_MAX C\_MAX\_R AUC\_INF AUC\_RI CLEARI T\_HALF AUC\_LMC AUC\_RLMC CLEARLMC RTMAX LAUCI LAUCT L\_CMAX

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Study #3

SYNOPSIS

<p><b>NAME OF SPONSOR/COMPANY:</b> The R.W. Johnson Pharmaceutical Research Institute [and Janssen-Cilag]</p> <p><b>NAME OF FINISHED PRODUCT:</b> TOPAMAX® (topiramate)</p> <p><b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3:4,5-bis-O-(1-methylethylidene)β-D-fructopyranose sulfamate</p>	<p><b>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</b></p> <p>Volume:</p> <p>Page:</p>	<p><b>(FOR NATIONAL AUTHORITY USE ONLY)</b></p>
<p><b>Protocol No.</b> TOPMAT-PHI-360  <b>Title of Study:</b> EFFECT OF FOOD ON THE BIOAVAILABILITY OF TOPIRAMATE (RWJ-17021-000) FROM A SPRINKLE FORMULATION ADMINISTERED AS A 100 MG SINGLE DOSE TO HEALTHY SUBJECTS</p>		
<p><b>Investigator:</b></p>		
<p><b>Study Centre:</b></p>		
<p><b>Publication (Reference):</b> none</p>		
<p><b>Studied Period (years):</b> 1 April 1996 - 12 July 1996</p>		<p><b>Phase of development:</b> 1</p>
<p><b>Objectives:</b> The objective of this study was to measure the effect of food on the bioavailability of topiramate from a single 100 mg oral dose of topiramate coated-bead sprinkle formulation when administered in applesauce. The bioavailability of topiramate from a 100 mg oral dose of the coated-bead sprinkle formulation administered encapsulated in a gelatin capsule under fasted conditions was evaluated also.</p>		
<p><b>Methodology:</b> This was an open-label, randomized, three-way crossover study. Twenty-four healthy men and women, 18 to 40 years of age, were randomly assigned to one of six treatment sequences. All subjects who completed the study experienced each treatment; i.e. 100 mg topiramate sprinkle formulation in applesauce in the fasted state (Treatment A), in the fed state (Treatment B), and in a capsule in a fasted state (Treatment C). Study drug was administered after a 10-hour, overnight fast. For those subjects in Treatment B, a standard breakfast to be eaten over 15 minutes was served approximately 30 minutes before study drug was administered. Blood samples were collected at protocol specified timepoints for 72 hours after topiramate administration for determination of plasma concentrations of topiramate. There was a three-week washout between treatments.</p>		
<p>For 16 subjects a total of 400 mL of blood was collected for clinical laboratory tests and for topiramate analysis. For 8 subjects who were restarted in the study due to an error in the period 1 fed treatment, a total of 530 mL of blood was collected.</p>		
<p>Selected topiramate pharmacokinetic parameters were estimated and compared statistically to assess the bioavailability of topiramate sprinkle formulation in subjects in the fed state relative to the bioavailability in subjects in the fasted state.</p>		
<p><b>Number of Subjects (planned and analyzed):</b> 24 subjects were enrolled; 20 subjects were included in the pharmacokinetic analyses, all 24 subjects were included in the safety analyses.</p>		
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Men and women, _____ years old, were enrolled in this study. Only subjects considered to be healthy based on a detailed medical history, physical examination, and clinical laboratory evaluations were included in the study. Height and weight were required to be within 15% of limits described by Metropolitan Life Insurance Co. table. Women were postmenopausal, surgically incapable of childbearing, or were practicing an acceptable method of birth control for at least 1 month before entering and throughout the study, had normal menstrual patterns for three months before study entry, and had a negative serum pregnancy test within one week of study entry. Subjects were not allowed prescription medications for 14 days before study entry, were not allowed to consume alcohol, caffeine-containing substances, and antacids for 48 hours before study entry, and were not allowed OTC medications including vitamins and aspirin for 7 days before study entry. Subjects had to test negative for hepatitis B antigen, hepatitis C antibody, HIV antibody, and drugs of abuse, including alcohol.</p>		
<p><b>Test Product, Dose and Mode of Administration, Batch No.:</b> Topiramate was supplied as 50 mg coated-bead sprinkle formulation in a gelatin capsule, Formula No. FD 17021-000-BH-34, Batch No. R6290, for oral administration (either encapsulated or added to applesauce).</p>		
<p><b>Duration of Treatment:</b> Single-dose administered 3 or 4 times with a 3-week washout between doses</p>		
<p><b>Reference Therapy, Dose and Mode of Administration, Batch No.:</b> Not applicable</p>		

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SYNOPSIS (Continued)

<b>NAME OF SPONSOR/COMPANY</b>	<b>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</b>	<b>(FOR NATIONAL AUTHORITY USE ONLY)</b>						
The R.W. Johnson Pharmaceutical Research Institute [and Janssen-Cilag]	Volume: Page:							
<b>NAME OF FINISHED PRODUCT</b>								
TOPAMAX® (topiramate)								
<b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3:4,5-bis-O-(1-methylethylidene) $\beta$ -D-fructopyranose sulfamate								
<b>Criteria for Evaluation:</b>								
<u>Pharmacokinetics</u>								
The following plasma topiramate pharmacokinetic parameters were estimated for each subject completing the study: peak concentration ( $C_{max}$ ), time to peak concentration ( $t_{max}$ ), area under the concentration-time curve (AUC) to the last measurable concentration above the lower limit of quantitation [AUC(0-*)] and to infinity [AUC(0- $\infty$ )], oral plasma clearance (CL/F), elimination half-life ( $t_{1/2}$ ), and elimination rate constant ( $k_e$ ).								
<u>Safety</u>								
The safety assessment of topiramate included the collection of reports of treatment-emergent adverse events, and changes in clinical laboratory tests, vital signs measurements, and physical examinations.								
<b>Statistical Methods:</b>								
<u>Pharmacokinetics</u>								
Pharmacokinetic parameters were summarized by treatment. For the bioavailability pharmacokinetic parameters [ $C_{max}$ , AUC(0-*), and AUC(0- $\infty$ )] the ratios of mean parameter from applesauce/fed and capsule/fasted treatments to that from applesauce/fasted treatment were calculated for each subject. Descriptive statistics (mean, standard deviation, median, geometric mean, and range) of the pharmacokinetic parameters and parameter ratios were calculated for each treatment. The pharmacokinetic parameters [ $C_{max}$ , AUC(0-*), and AUC(0- $\infty$ )] were compared by analysis of ln-transformed parameters. For $C_{max}$ , AUC(0-*), and AUC(0- $\infty$ ), analysis of variance models were fit to the data with the ln-transformed parameter as the dependent variable and the effects due to treatment sequence group, subjects nested within the sequence groups, treatment and period as predictors. For $t_{max}$ , analysis of variance models were fit to the data with the ranked parameter and raw $t_{max}$ data as the dependent variable. Analysis of variance (ANOVA) models were also fit to the plasma elimination rate constant ( $k_e$ ) data. Test for the treatment sequence group effect, period effect, and treatment effect were carried out at 10%, 5%, and 5% levels, respectively.								
The estimated least squares and intrasubject variability from the above model were used to construct 90% confidence intervals for the ratio of the mean bioavailability parameter [ $C_{max}$ , AUC(0-*), and AUC(0- $\infty$ )] for the applesauce/fed treatment and capsule/fasted treatment to the applesauce/fasted treatment using the classical (corresponding to Schuirman's two one-sided test procedure approach) confidence interval approach.								
<b>SUMMARY - CONCLUSIONS</b>								
<u>PHARMACOKINETIC RESULTS:</u>								
The mean (SD) topiramate pharmacokinetic parameters from the two treatments are summarized in the following table.								
Plasma Topiramate Pharmacokinetic Parameters								
Parameters <sup>a</sup>	Applesauce Fasted		Applesauce Fed		% <sup>b</sup> Difference	Capsule Fasted		% <sup>b</sup> Difference
$C_{max}$ ( $\mu$ g/mL)	2.20 (0.66)	2.10 (0.61)	-4.5%	2.23 (0.59)	1.4%			
$t_{max}$ (h)	3.7 (7.6)	2.8 (0.8)	-24.3%	2.0 (0.8)	-45.9%			
AUC(0-*) ( $\mu$ g-h/mL)	60.0 (13.9)	61.1 (13.3)	1.8%	61.1 (11.8)	1.8%			
AUC(0- $\infty$ ) ( $\mu$ g-h/mL)	71.4 (14.9)	73.9 (15.9)	3.5%	72.1 (12.5)	1.0%			
$t_{1/2}$ (h)	27.2 (4.0)	28.0 (4.7)	2.9%	26.4 (4.3)	-2.9%			
$k_e$ (1/h)	0.0261 (0.0039)	0.0254 (0.0040)	-2.7%	0.0269 (0.0047)	3.1%			
CL/F (mL/min)	24.3 (4.9)	23.6 (5.3)	-2.9%	23.7 (3.9)	-2.5%			
<sup>a</sup> Data are the mean (SD), N=20.								
<sup>b</sup> With respect to Applesauce Fasted Treatment.								
<sup>*</sup> AUC calculated to the last concentration above the quantification limit.								

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SYNOPSIS (Continued)

<p><u>NAME OF SPONSOR/COMPANY</u> The R.W. Johnson Pharmaceutical Research Institute [and Janssen-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:</p> <p>Page:</p>	<p><u>(FOR NATIONAL AUTHORITY USE ONLY)</u></p>
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**SUMMARY - CONCLUSIONS (Continued)**

The results of statistical comparison of the two treatments for the ln-transformed topiramate bioavailability pharmacokinetic parameters, ranked  $t_{max}$ , raw  $t_{max}$ , and  $k_e$  are summarized in the following table.

Parameter	ANOVA Result <sup>a</sup>	ANOVA Power <sup>b</sup>
AUC (0-∞)	NS	>0.999
AUC (0-*)	NS	>0.999
C <sub>max</sub>	NS	>0.999
Ranked $t_{max}$	SIG	--- <sup>c</sup>
Raw $t_{max}$	NS	--- <sup>c</sup>
$k_e$	NS	--- <sup>c</sup>

<sup>a</sup> Analysis of variance model for a randomized three-way crossover design. SIG = Statistically significantly different (p<0.05). NS = Not statistically significantly different (p>0.05).

<sup>b</sup> Power to detect a difference of ln(1.25) in the means on the log scale.

<sup>c</sup> ANOVA power and confidence intervals not calculated.

The percent difference of the mean pharmacokinetic parameter values for the applesauce/fed and capsule/fasted treatments from the applesauce/fasted treatment was less than 4.5%, except for  $t_{max}$  (45.9%). Results of ANOVA indicated that there were no statistically significant differences between treatments for any of the pharmacokinetic parameters, except  $t_{max}$ . The time to maximum concentration was longer for the applesauce/fed treatment than the other two treatments. Results from the two one-sided tests gave confidence interval bounds, relative to the applesauce/fasted treatment, for C<sub>max</sub>, AUC(0-\*), and AUC(0-∞) that were within the criteria for bioequivalence (80% to 125% of the geometric mean).

**SAFETY RESULTS:**

Topiramate administered in the fed and fasted state was well tolerated during this single-dose, bioavailability study in healthy men and women. The most commonly reported treatment-emergent adverse events were CNS-related, mild in severity, possibly related to study drug, and resolved during the treatment period in which they were reported. No treatment-emergent or clinically significant changes were reported in physical findings, vital signs, or laboratory tests.

**CONCLUSION:**

Topiramate was well tolerated during this study.

The pharmacokinetic results from this study show that there is no significant effect of food on the bioavailability of topiramate from the sprinkle formulation, and the sprinkle formulation administered as intact capsules under fasted conditions is bioequivalent to the sprinkle formulation administered after sprinkling on a small amount of food. The topiramate coated-bead sprinkle formulation can be taken without regard to food.

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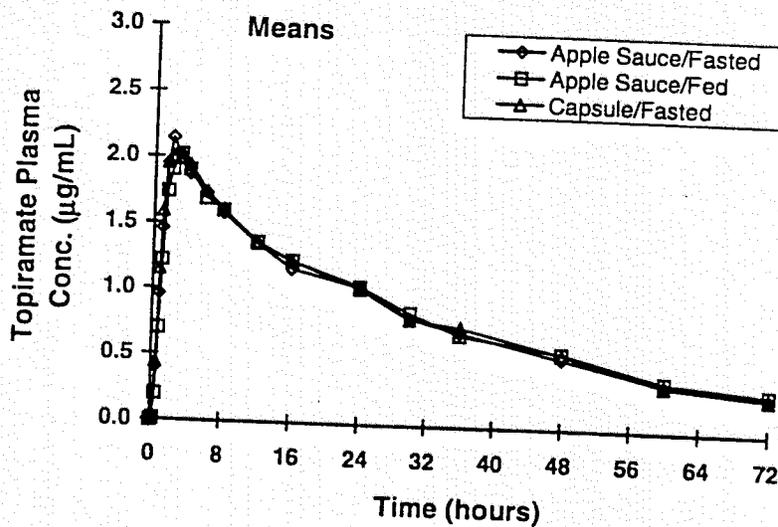
**Table 6.2: 90% Confidence Intervals for the Ratio of the Mean In-Transformed AUC (0-∞), AUC (0-\*) and C<sub>max</sub> for the Intact Capsules to Applesauce/Fasted Treatment Comparisons (All Subjects Included in Pharmacokinetic Analyses; Protocol TOPMAT-PHI-360)**

Parameter	Geometric Mean		Estimated Ratio (%) of Geometric Mean	90% Confidence Interval for the Ratio of the Means	
	Applesauce Fasted	Capsule Fasted		Lower Bound <sup>a</sup> (% Reference)	Upper Bound <sup>a</sup> (% Reference)
AUC (0-∞)	69.98	71.10	101.60	97.41	105.98
AUC (0-*)	58.50	60.03	102.62	98.79	106.59
C <sub>max</sub>	2.11	2.16	102.38	97.96	107.00

<sup>a</sup> Bounds as percent of the reference treatment (Applesauce/fasted) geometric mean

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**Figure 1: Mean Topiramate Plasma Concentration vs. Time Profiles from Twenty Healthy Subjects Following a Single Oral 100 mg Dose of Topiramate (All Subjects Included in Pharmacokinetic Analyses; Protocol TOPMAT-PHI-360)**



Study # 4

SYNOPSIS

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<b>NAME OF SPONSOR/COMPANY:</b> The R.W. Johnson Pharmaceutical Research Institute and Janssen-Cilag		<b>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</b>  Volume:  Page:	<b>(FOR NATIONAL AUTHORITY USE ONLY)</b>
<b>NAME OF FINISHED PRODUCT:</b> TOPAMAX® (topiramate)			
<b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3:4,5-bis-O-(1-methylethylidene) B-D-fructopyranose sulfamate			
<b>Protocol No.:</b> TOPMAT-PHI-358 <b>Title of Study:</b> A double-blind, randomized study to evaluate the ability of three coated bead formulations to mask the taste of topiramate in normal male volunteers			
<b>Investigators:</b>			
<b>Study Centre(s):</b>			
<b>Publication (Reference):</b> None			
<b>Studied Period (years):</b> 11 Sept. 1995 to 30 Sept. 1995		<b>Phase of development:</b> I	
<b>Objectives:</b> The objective of this study was to determine the acceptability of each of three coating thickness levels of a topiramate bead formulation with regard to masking the bitter taste of topiramate.			
<b>Methodology:</b> This was a double-blind, randomized study conducted at a single center that evaluated the ability of each of three coating percentages to mask the bitter taste of topiramate. Forty-eight healthy men between the ages years who demonstrated sensory recognition of bitter taste were enrolled in the study and randomly assigned to one of six possible treatment sequence groups. Each subject sequentially tasted each of the three coated bead formulations with twenty minute intervals between tasting the different formulations. During each taste test, subjects first tasted a bitter standard solution consisting of 0.05% caffeine, and then tasted one of the three formulations. Subjects were asked to evaluate the taste acceptability of each formulation, to compare the bitterness intensity of each formulation with the bitterness intensity of the standard caffeine solution, and to assess the overall taste acceptability of each coated bead formulation in terms of willingness to take the study drug twice daily for the treatment of a serious illness.			
<b>Number of Subjects (planned and analyzed):</b> Forty-eight subjects were enrolled in the study and included in the analyses of taste masking and safety.			
<b>Diagnosis and Main Criteria for Inclusion:</b> Healthy men between the ages of 18 and 55 years who demonstrated sensory perception of bitter taste.			
<b>Test Product, Dose and Mode of Administration, Batch No.:</b> 50 mg topiramate with (Batch No. R6112), (Batch No. R6114), or (Batch No. R6116)			
<b>Duration of Treatment:</b> One day.			
<b>Reference Therapy, Dose and Mode of Administration, Batch No.:</b> 0.05% caffeine solution for oral administration.			
<b>Criteria for Evaluation:</b> <b>Pharmacodynamics:</b> <u>taste acceptability rating:</u> evaluated at 30 and 60 seconds, on a scale of -4 (extremely unacceptable) to 4 (extremely acceptable) with 0 being neutral; <u>bitterness intensity score:</u> evaluated at 30 and 60 seconds, on a magnitude scale in comparison to the standard caffeine solution, with the standard having a rating of 100; and <u>overall taste acceptability:</u> subject willingness to take the product as a medicine for a serious illness based on a yes/no answer, evaluated at the end of 60 seconds.			

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Study # 4

SYNOPSIS (Continued)

<p><b>NAME OF SPONSOR/COMPANY:</b> The R.W. Johnson Pharmaceutical Research Institute and Janssen-Cilag</p> <p><b>NAME OF FINISHED PRODUCT:</b> TOPAMAX® (topiramate)</p> <p><b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3:4,5-bis-O-(1-methylethylidene) β-D-fructopyranose sulfamate</p>	<p><b>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</b></p> <p>Volume:</p> <p>Page:</p>	<p><b>(FOR NATIONAL AUTHORITY USE ONLY)</b></p>
<p><b>Statistical Methods:</b> Means and standard deviations were calculated for taste acceptability ratings and bitterness intensity ratings. The effects of percentage coating on the taste acceptability and bitterness intensity ratings were analyzed using random effects models.</p>		
<p><b>SUMMARY - CONCLUSIONS</b></p>		
<p><b>PHARMACODYNAMIC RESULTS:</b> Taste acceptability was rated on a 9-point scale where 4 corresponded to Extremely Acceptable, 0 corresponded to Neutral, and -4 corresponded to Extremely Unacceptable. Mean acceptability scores ranged from _____ formulation at _____ for the _____ formulation at 60 seconds. These mean taste acceptability scores represent a rating between 0 (Neutral) and -1 (Slightly Unacceptable). Pairwise comparisons of the three coatings showed statistically significant differences in acceptability rating for the _____ versus _____ coatings at both the 30 and 60 second evaluations and for the _____ using random effects modelling. The _____ at the 60 second evaluation (<math>p \leq 0.050</math>) formulations did not differ significantly in their ability to mask the taste of topiramate.</p>		
<p>The taste acceptability increased with increasing coating percentage with only 29% of the subjects considering the _____ formulation to be acceptable and 56% considering the _____ formulation to be acceptable at the 60 second evaluation.</p>		
<p>Subjects were asked to compare the bitterness intensity of each of the three coated bead formulations with that of the standard bitterness solution (0.05% caffeine) which was assigned a bitterness intensity value of 100. Mean bitterness intensity scores were 204 for the _____ formulation, 214 for the _____ formulation, and 246 for the _____ formulation at the 60 second evaluation; these values reflect a bitterness intensity for each of the three topiramate formulations that was at least twice that of the caffeine bitterness standard solution.</p>		
<p>Subjects were asked whether they would be willing to take the study drug twice daily to treat a serious illness. Most subjects responded that they would be willing to take the drug; 73% would take _____ formulation, 87% would take _____ formulation, and 82% would take the _____ formulation.</p>		
<p><b>SAFETY RESULTS:</b> Study drug was expelled after 60 seconds, therefore subjects participating in the study were considered to be at minimal risk. Safety evaluations included reports of adverse events and vital sign measurements. Three (6%) of the 48 subjects reported adverse events; one subject reported mild asthenia and two subjects reported mild headaches.</p>		
<p><b>CONCLUSION:</b> The results of this study indicate that both the _____ formulations mask the bitter taste of topiramate to a greater extent than does the _____ formulation, and that the _____ formulations do not differ significantly from each other in their ability to mask the taste of topiramate.</p>		
<p>Date of the report: 20 January 1997</p>		

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Study #5

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**SYNOPSIS**

<b>NAME OF SPONSOR/COMPANY:</b> The R.W. Johnson Pharmaceutical Research Institute [and Janssen-Cilag]	<b>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</b>	<b>(FOR NATIONAL AUTHORITY USE ONLY)</b>
<b>NAME OF FINISHED PRODUCT:</b> TOPAMAX® (topiramate)	Volume:	
<b>NAME OF ACTIVE INGREDIENT(S):</b> 2,3: 4,5-bis-O-(1-methylethylidene)β-D-fructopyranose sulfamate	Page:	
<b>Protocol No.:</b> Amendment 1 to Protocol YP (6 February 1996) Amendment 5 to Protocol EPPD-001 (15 March 1996) <b>Title of Study:</b> Topiramate (RWJ-17021) Sprinkle Palatability Study in Pediatric Subjects with Epilepsy		
<b>Investigators:</b>		
<b>Study Centre(s):</b>		
<b>Publication (Reference):</b> None		
<b>Studied Period (years):</b> 20 May 1996 - 31 July 1996	<b>Phase of development:</b> 1	
<b>Objectives:</b> This study was designed to evaluate the palatability of a sprinkle formulation of topiramate in pediatric subjects with epilepsy who were currently receiving topiramate tablets.		
<b>Methodology:</b> This was an open-label, two-center study, involving 15 pediatric subjects (3 - 14 years of age) with epilepsy who were currently enrolled in and receiving topiramate tablets in an open-label extension study of topiramate. Topiramate sprinkle formulation replaced the morning tablet dose once daily for three days. Study drug was mixed with approximately one tablespoon of soft food such as applesauce, and administered in the investigator's office on Day 1 and in the child's home on Days 2 and 3. If the food was spit out or vomited, the subject was to be given his or her normal dose in regular tablet form. On Days 1, 2, and 3, parents recorded whether or not the child spit out the sprinkle. On Day 3, the subject completed a pictogram depicting his or her reaction to the tablet and the sprinkle, and parents or guardians performed an overall assessment.		
<b>Number of Subjects (planned and analyzed):</b> 15		
<b>Diagnosis and Main Criteria for Inclusion:</b> Male and female pediatric subjects, 3 to 12 years of age, with epilepsy, who were stabilized on topiramate tablets in an open-label extension study. Subjects were at least 14 kg (31 lbs).		
<b>Test Product. Dose and Mode of Administration, Batch No.:</b> Topiramate 25 mg and 50 mg capsules (Batches R6369 and R6290, respectively) were administered mixed with approximately 1 tablespoon of soft food such as applesauce to a maximum dosage of ≤9 mg/kg per day.		
<b>Duration of Treatment:</b> morning dose for 3 days		
<b>Reference Therapy, Dose and Mode of Administration, Batch No.:</b> none		
<b>Criteria for Evaluation:</b> <u>Palatability</u> Subject Evaluations of Palatability were based on responses to the questions "how do you like topiramate (white pills)?" and "how do you like topiramate sprinkle?" based on a scale of 1=excellent to 7=terrible. Parental Evaluations were based on i) ease of use of topiramate sprinkle rated as either easy or hard and ii) overall assessment of topiramate sprinkle compared with topiramate tablets rated as better, the same, or worse.		

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Study #5

SYNOPSIS (Continued)

<u>NAME OF SPONSOR/COMPANY:</u> The R.W. Johnson Pharmaceutical Research Institute	<u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u>  Volume:  Page:	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
<u>NAME OF FINISHED PRODUCT:</u> TOPAMAX® (topiramate)		
<u>NAME OF ACTIVE INGREDIENT(S):</u> 2,3: 4,5-bis-O-(1-methylethylidene)β- D-fructopyranose sulfamate		
<u>Criteria for Evaluation (Continued):</u> <u>Safety</u> During this 3-day study, safety data were collected and reported as part of the open-label extension study in which the child was participating and included adverse events, vital signs, physical examinations, and clinical laboratory tests.		
<u>Statistical Methods:</u> The results of the subject evaluation of palatability and parental evaluations of ease of use and overall assessment of the sprinkle vs. tablet formulations were summarized in frequency tables.		
<u>SUMMARY - CONCLUSIONS</u> The palatability of topiramate sprinkle formulation was similar to that of the topiramate tablets based on subject evaluation of palatability; 13 subjects rated the sprinkle and 12 subjects rated the tablet as average or better based on a scale of 1 (excellent) to 7 (terrible) where score of 4.0 was average. None of the 15 subjects spit out either topiramate sprinkle or tablet during the study. Fourteen of 15 parents considered topiramate sprinkle formulation easy to use. In their overall assessment of topiramate sprinkle formulation, seven parents felt that the sprinkle was worse than the tablet, five considered it the same as the tablet, two considered it better than the tablet, and one parent did not complete the evaluation.  <u>CONCLUSION:</u> In children with epilepsy who were receiving topiramate tablets, the topiramate sprinkle formulation was an acceptable substitute for the tablet in terms of palatability and ease of use.		
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Date of the report: 4 FEB 1997		

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