

**REVIEW AND EVALUATION OF CLINICAL DATA**

<b>NDA</b>	#20-505
<b>Sponsor</b>	RW Johnson Pharmaceutical Research Institute
<b>Brand Name (generic name)</b>	Topamax(topiramate)
<b>Indication</b>	Partial Onset Epilepsy
<b>NDA Classification</b>	IS
<b>Materials Received</b>	Response to Approvable Letter and Final Safety Update
<b>Original Receipt Date</b>	June 28, 1996
<b>Clinical Reviewer</b>	Cynthia G. McCormick, MD

**0.0 INTRODUCTION**

This is a review of the Final Safety Update and response to the Approvable Letter for the Topiramate NDA. The sections of the following review correspond to the outline in the original review of clinical data (NDA) dated October 11, 1995.

**1.0 MATERIALS UTILIZED IN REVIEW**

Rec'd 06/28/1996	Response to approvable letter Volumes 23.1-23
Rec'd 09/27/1996	Final Safety Update Volumes 26.1-6
Rec'd 11/08/1996	Case Report forms for discontinuations due to adverse events Volumes 27.1-28

All materials were reviewed.

## **2.0 BACKGROUND**

The NDA for Topiramate was submitted to FDA December 1994. An approveable letter was forwarded to the sponsor on completion of the review process. In this letter a series of deficiencies was cited which would have to be addressed for approval to be rendered. These issues included the following:

### **II. Those that relate to Safety**

- A-Methods for assessment of CNS adverse events.
- B-Follow-up of abnormal laboratory studies.

The sponsor has addressed these largely without the creation of new data. In addition a final safety update was submitted to the NDA incorporating some of the more specific adverse event terminology that had been developed since the original NDA was reviewed.

### **Foreign Marketing**

Since the submission of the NDA to the FDA in 12/1994, this product has become licensed in the following nations: Finland, South Africa, Sweden, Switzerland, and the United Kingdom. There have been no suspensions or withdrawals of marketing approval in any of these countries. The labeling for the product in these countries was reviewed and contains no information not previously seen in the NDA.

## **3.0 CHEMISTRY**

No new information was submitted.

## **4.0 PRECLINICAL PHARMACOLOGY**

One new study in beagle dogs was cited in the final safety update, which explored the possible interaction between topiramate and warfarin. Multiple doses of topiramate were found to induce warfarin metabolism in dogs resulting in changes in PT. It is thought that this interaction may result from induction of an isomer of cytochrome P450 not present in humans.

## 5.0 CLINICAL DATA SOURCES

The following are the key documents that contain safety data showing the cutoff dates for collection of certain data as well as the dates these documents were received by the FDA.

DOCUMENT (DATE RECEIVED)	CUTOFF DATE FOR DATA
<b>4-MONTH SAFETY UPDATE (7/14/94)</b>	
ROUTINE AE	3/31/1994
DEATHS	3/31/1994
SERIOUS AE	3/31/1994
<b>FINAL SAFETY UPDATE (9/27/1996)</b>	
ROUTINE AE	10/1/1995
DEATHS	6/30/1996
SERIOUS AE	6/30/1996
SELECTED AE'S: KIDNEY STONES PREGNANCIES	6/30/1996 7/31/1996

The final safety update included information collected in clinical studies since the cutoff date of the four month Safety Update. They are based on an overall population of 1,715 subjects (compared to 1,446 reported in the previous safety update). The studies in which the subjects included in the Final and Four-Month Safety Update analysis populations participated are indicated in Sponsor's Attachment 1a, with the 269 new subjects included in the Final Safety Update underlined. Sponsor's Attachment 1a is found on the following page.

Six new studies, ongoing when the safety update was in preparation were not included in the overall safety tables for this safety update but do contribute information on deaths and other serious adverse events. These included three non-IND Japanese studies and one study sponsored by McNeil Pharmaceuticals designed to compare the titration rates in subjects with partial onset seizures. The other two studies are RWJPR1 studies one in patients with partial seizures and the second in ,

In addition to these, any postmarketing surveillance data that were collected since the cutoff for the 4-month safety update were included and reviewed in the final safety update.

**Attachment 1a: RWJPRI-Sponsored Studies in Subjects With Epilepsy**

Study Type/Protocol	Included in Four-Month Safety Update	Included/ New in Final Safety Update
	Top*	Top*
<b>Completed, Double-Blind Studies in Subjects with Epilepsy</b>		
YD	136	136/0
YE	143	143/0
Y1	23	23/0
Y2	30	30/0
Y3	28	28/0
YF/YG	167	167/0
<b>Open-Label Studies in Subjects with Epilepsy</b>		
<b>Clinical Pharmacology</b>		
MS-215	12	12/0
MS-216	12	12/0
MS-218	12	12/0
YZL	13	13/0
YZT	8	8/0
YZW	6	6/0
MS-220	12	12/0
<b>Completed Uncontrolled-Partial Onset Seizures</b>		
YC/YCO/YCO2	23	23/0
YKP	70 (70)	70/0 (70)
YKT	224 (0)	224/0 (0)
IP	10	10/0
<b>Ongoing Uncontrolled-Partial Onset Seizures</b>		
YLT	181 (0)	181/0 (0)
YF/YG-extension	146 (33)	146/0 (33)
YOL*	275	298/23
YH*	2	2/0
YEP	69 (69)	69/0 (69)
YET	53 (0)	53/0 (0)
YLTE	31 (6)	45/14* (6)
YOLE	244	410/166
<b>Ongoing Uncontrolled-Monotherapy</b>		
*YI-extension	0	41/41 (0)*
YJ-extension	16 (0)*	86/70 (0)*
<b>Ongoing Uncontrolled-Lennox-Gastaut</b>		
YK	16	23/7
YKE	10	14/4
<b>Ongoing, Double-Blind Studies in Subjects with Epilepsy</b>		
*YI (open-label phase)	36	51/15
YJ (open-label phase)	50	86/36
<b>New Studies not included in the Four-Month Safety Update Data Base</b>		
<b>Ongoing Uncontrolled - Pediatric Partial Onset Seizures</b>		
EPPD-001	0	18/18
<b>OVERALL ANALYSIS POPULATION</b>	<b>1,446*</b>	<b>1,715*</b>

**Demographics And Baseline Characteristics**

The demographic and baseline characteristics of the 1,092 (64%) men and 623 (36%) women who were included in the 1,715-subject overall analysis population are similar to those summarized in the Four-Month Safety Update. Most (95%) of the subjects were 17 years of age or older, with a mean age of 35.2 years for the subjects ≥17 years of age. The mean age for subjects under 17 years of age was 11.5 years. Forty-two subjects were from 13 to 16 years of age, and 43 subjects were under 13 years of age.

Attachment 1b  
Demographic and Baseline Characteristics  
(All Topiramate-Treated Subjects with Epilepsy)

Patient Characteristics	Topiramate (N=1715)	
	No.	%
<b>Sex</b>		
Male	1092	63.6
Female	623	36.3
<b>Race</b>		
White	1525	88.9
Black	91	5.3
Other	89	5.2
Unknown	10	0.5
<b>Age (years)</b>		
<b>Pediatric:</b>		
0-3	1	0.1
4-12	42	2.4
13-16	42	2.4
Range	3.0-16.0	
Mean(SD)	11.5 (4.0)	
<b>Adult:</b>		
17-29	561	32.7
30-39	542	31.6
40-49	346	20.1
50-59	136	7.9
>=60	45	2.6
Range	17.0-74.0	
Mean(SD)	35.2 (11.0)	
<b>Weight (lbs)</b>		
N	1651	
Mean(SD)	162.3	(42.0)
Median	159.5	
Range	29.8-343.0	

### Extent of exposure

The distribution of subjects is summarized by topiramate treatment duration interval cross-classified with maximum dosage in Sponsor's Table 1 (on the next page). The intervals used to classify the subject's maximum dosages are <200, 200 to 399, 400 to 599, 600 to 799, 800 to 999, and ≥1,000 mg/day. As of October 1, 1995, 741 (43%) of the 1,715 subjects in the overall analysis population either remained on topiramate therapy in ongoing studies or had completed study participation, while 974 (57%) subjects had discontinued therapy prematurely. Of the 1,715 topiramate-treated subjects, 1,395 (81%) completed at least three months of therapy, 1,181 (69%) completed at least six months, 926 (54%) completed at least one year, 495 (29%) completed at least two years, 250 (15%) completed at least three years, 160 (9%) completed at least four years, 128 (7%) completed at least five years, and 80 (5%) completed at least six years. This represents 2,796 subject-years of exposure (compared with 1,756 subject-years of exposure reported in the 4 month safety update).

For the 926 subjects who completed at least one year of therapy, the mean maximum topiramate dosage ranged from 829 to 1,231 mg/day for the duration intervals beyond one year in Table 1. Overall, 634 (37%) of the 1,715 topiramate-treated subjects received a maximum dosage of at least 1,000 mg/day, of whom 476 received topiramate for at least one year. ( Seen in Sponsor's Attachment 3, next page).

**Table 1: Distribution of Subjects by Duration of Therapy and Maximum Topiramate Dosage as of October 1, 1995**

Duration:	Maximum Topiramate Daily Dosage (mg/day)										Overall Maximum Topiramate Dose								
	< 200		200-399		400-599		600-799		800-999		≥1000		Total:	Mean (SD)	Median	Min	Max		
	N	%	N	%	N	%	N	%	N	%	N	%						N	%
0 - 3 months	118	(7)	99	(6)	49	(3)	27	(2)	14	(1)	13	(1)	320	(19)	300	(256.89)	200	25	1600
3 - 6 months	7	(<1)	43	(3)	44	(3)	4	(2)	29	(2)	50	(3)	214	(12)	643	(384.28)	600	100	3200
6 - 12 months	9	(1)	35	(2)	45	(3)	44	(3)	27	(2)	95	(6)	255	(15)	789	(442.74)	700	100	1800
1 - 2 years	24	(1)	61	(4)	63	(4)	65	(4)	49	(3)	189	(10)	431	(25)	829	(506.22)	800	100	2600
2 - 3 years	1	(<1)	10	(1)	24	(1)	35	(2)	28	(2)	147	(9)	245	(14)	1060	(448.54)	1100	100	2400
3 - 4 years	0	(0)	1	(<1)	5	(<1)	6	(1)	15	(1)	61	(4)	90	(5)	1187	(442.71)	1200	300	2800
4 - 5 years	0	(0)	1	(<1)	1	(<1)	5	(<1)	7	(<1)	18	(1)	32	(2)	1091	(416.10)	1000	300	1700
5 - 6 years	0	(0)	0	(0)	7	(<1)	3	(<1)	4	(<1)	34	(2)	48	(3)	1231	(533.22)	1200	400	2400
>6 years	0	(0)	3	(<1)	0	(0)	16	(1)	14	(1)	47	(3)	80	(5)	1079	(397.36)	1000	200	1600
<b>Total</b>	<b>159</b>	<b>(9.3)</b>	<b>253</b>	<b>(14.8)</b>	<b>238</b>	<b>(13.9)</b>	<b>244</b>	<b>(14.2)</b>	<b>187</b>	<b>(10.9)</b>	<b>634</b>	<b>(37.0)</b>	<b>1715</b>	<b>(100.0)</b>	<b>781</b>	<b>(508.33)</b>	<b>700</b>	<b>25</b>	<b>3200</b>
Mean	118		286		410		615		729		861		595		--		--	--	--
SD	201.19		361.29		424.58		631.93		679.14		656.67		618.04		--		--	--	--
Median	14		129		266.5		427		525		705		408		--		--	--	--
Range(Min, Max)	1 to 910		2 to 2,442		9 to 2,159		32 to 2,659		45 to 3,043		39 to 3,038		1 to 3,043		--		--	--	--

NOTE: Each subject is counted once, i.e., in the duration range corresponding to the subject's total treatment duration.

KEY: N = number; SD = standard deviation; Min = minimum; Max = maximum.

Cross-reference: Attachment 3.

ATTACHMENT 3

DISTRIBUTION OF SUBJECTS BY DURATION OF TOPIRAMATE THERAPY AND  
MEAN DOSAGE AS OF OCTOBER 1, 1995  
(ALL TOPIRAMATE-TREATED SUBJECTS ≥19 YEARS OF AGE WITH EPILEPSY)

Duration	Mean Topiramate Daily Dosage <sup>a,b</sup> (mg/day)										Overall Mean Topiramate Dose		
	< 200	200-399	400-599	600-799	800-999	>=1000	Total	Mean(SD)	Median	Min	Max		
0 - 3 MONTHS	211 (12.4)	79 (4.6)	25 (1.5)	2 (0.1)	1 (0.1)	0 (0.0)	320 (18.7)	192.08(127.624)	148.14	25.00	848.571		
3 - 6 MONTHS	36 (2.1)	77 (4.5)	55 (3.2)	37 (2.3)	7 (0.4)	2 (0.1)	216 (12.5)	414.65(211.701)	387.49	52.58	1050.00		
6 - 12 MONTHS	32 (1.9)	75 (4.4)	51 (3.0)	51 (3.0)	27 (1.6)	19 (1.1)	255 (14.9)	520.75(285.242)	472.28	96.86	1245.35		
1 - 3 YEARS	61 (3.6)	92 (5.4)	90 (5.2)	76 (4.4)	48 (2.8)	64 (3.7)	431 (25.1)	593.84(342.479)	541.51	98.30	1955.47		
2 - 3 YEARS	10 (0.6)	29 (1.7)	49 (2.9)	34 (2.0)	41 (2.4)	82 (4.8)	245 (14.3)	807.32(367.403)	811.89	82.75	1503.58		
3 - 4 YEARS	0 (0.0)	8 (0.5)	14 (0.8)	16 (0.9)	23 (1.3)	29 (1.7)	90 (5.2)	892.93(385.552)	847.43	210.52	2190.84		
4 - 5 YEARS	0 (0.0)	4 (0.2)	4 (0.2)	11 (0.6)	4 (0.2)	9 (0.5)	32 (1.9)	831.81(338.770)	772.78	200.94	1472.58		
5 - 6 YEARS	0 (0.0)	6 (0.3)	9 (0.5)	7 (0.4)	8 (0.5)	18 (1.0)	48 (2.8)	886.18(402.202)	875.27	223.90	1545.75		
>6 YEARS	2 (0.1)	6 (0.3)	21 (1.2)	17 (1.0)	13 (0.8)	21 (1.2)	80 (4.7)	795.06(345.820)	750.08	153.30	1513.80		
Total	354 (20.6)	376 (21.9)	318 (18.5)	251 (14.6)	172 (10.0)	244 (14.2)	1715 (100.0)	593.85(372.737)	479.80	25.00	2190.84		
Mean	186.84	405.84	660.86	720.39	891.85	1047.58	593.85						
SD	291.234	482.144	645.218	659.350	634.822	613.814	618.038						
Median	49.50	232.00	476.00	515.00	756.50	977.00	406.00						
Range(Min,Max)	1.2407	2.2526	39.3038	62.3043	88.2644	156.2616	3.3043						

<sup>a</sup> Counts were obtained by associating the mean dose for each subject with the duration of topiramate treatment for that same subject. Therefore, subjects are counted only once.

<sup>b</sup> Subjects with all dosage information missing are not included in this summary table.  
KEY: N = Number; SD = standard deviation; Min. = minimum; Max. = maximum.

### **Postmarketing Experience**

Topiramate has been approved for marketing in 5 countries. Based on the estimated dose per prescription and the total amount of drug sold, the number of topiramate prescriptions in the UK and Sweden, the first two countries where topiramate was approved, from product launch to June 30, 1996 is thought to be approximately 1,091,000. Other approvals occurred so close in time to the June 1996 cutoff that no data were available from these countries. Only six spontaneous reports of ADRS have been received from these countries.

### **6.0 PHARMACOKINETICS**

One new study was cited which explored the possible interaction between topiramate and probenecid. These results were summarized in the clinical materials and no significant interaction was demonstrated.

### **7.0 EFFICACY**

All issues relating to efficacy were handled in the "Response to the Approvable Letter" dated June 18, 1996.

submitted.

**New Efficacy Data: none**

**New Analyses: none**

**Sponsor's Discussion** The sponsor continues to assert that its previously submitted analyses are fully supportive of the claim that it has requested, that is, topiramate is effective for the "treatment of adults with partial onset seizures

The sponsor is trying to make a semantic point, not a clinical or statistical one by focusing on the population studied rather than the condition.

**Comments**

Indeed the population studied did include some patients with just as it did include some patients who had simple partial seizures, and probably some who even had . These other seizure types do not appear in the sponsor's approved labeling, however. This highlights the message that emerges from the sponsor's proposed labeling

3

10

A compromise position might be considered here. While the term patients with partial onset seizures prominence is not afforded to a seizure type that has unproven efficacy. Therefore it would not be unreasonable to recommend to the sponsor that the following be accepted as a compromise: "Topiramate is effective for the treatment of adults with partial onset epilepsy". As before, the sponsor is invited to perform the same analyses that were required of other sponsors who have received such a claim if it is so desired.

**Recommendations**

**New Efficacy Data: none**

**New Analyses:**

The sponsor reiterates the data previously submitted from the 6 multicenter add-on trials (YD, YE, Y1, Y2, Y3, YF/G) and states that topiramate/s efficacy was consistent across all trials. Plasma samples of concomitant AEDs were obtained to ascertain whether topiramate's efficacy may have been mediated through a pharmacokinetic interaction with background AEDs.

Sponsor's table 3 on the next two pages (data submitted in the 4 month Safety Update) shows the mean change in plasma AED concentration in placebo vs. the combined topiramate treatment groups for each of the six add-on trials. From this table there appeared to be little change in background AEDs across studies for each of the 5 major AEDs. In studies Y1, Y2, and Y3 the valproate levels tended to be higher in the treatment groups as compared to placebo and there was a greater positive mean change in the treatment groups indicating a greater increase in valproate levels compared to the placebo. Statistically significant between group differences in the mean change in AED levels were seen for CBZ in protocols YE, Y2 and YF/G in the magnitude of 5-10% reduction, and similarly for phenytoin in study Y2.

**Sponsor's Discussion**

The sponsor makes three points regarding the efficacy (and safety) of topiramate

**Table 3: Change in Plasma Concentrations ( $\mu\text{g/mL}$ ) of Concomitant Antiepileptic Drugs (AEDs) from the Baseline Phase to the Double-Blind Phase<sup>a,b</sup> (Continued)  
(Randomized Subjects With Plasma Concentration Data Available: Protocols YD, YE, Y1, Y2, Y3, and YF/YG)**

Concomitant AED	Protocol Y2						Protocol Y3						Protocol YF/YG					
	Baseline		Mean Change		Baseline		Mean Change		Baseline		Mean Change		Baseline		Mean Change			
	PLA	TOP	PLA	TOP	PLA	TOP	PLA	TOP	PLA	TOP	PLA	TOP	PLA	TOP	PLA	TOP		
Carbamazepine	8.6 (24)	8.9 (20)	0.2 (24)	-0.7 <sup>c</sup> (20)	7.4 (23)	8.3 (23)	-0.2 (23)	0.1 (23)	9.8 (30)	9.9 (122)	0.3 (30)	-1.3 <sup>d</sup> (122)						
Phenytoin	16.8 (6)	17.0 (12)	1.7 (6)	-1.2 <sup>e</sup> (12)	21.7 (8)	18.5 (5)	-6.5 (8)	-1.2 (5)	16.1 (12)	17.0 (43)	-0.9 (12)	0.5 (43)						
Valproic Acid	60.5 (1)	49.8 (2)	-2.6 (1)	6.3 (2)	42.2 (6)	63.4 (4)	1.8 (5)	8.2 (4)										
Phenobarbital	20.1 (10)	21.6 (8)	1.2 (10)	1.6 (8)	22.8 (4)	13.5 (3)	-1.0 (4)	2.0 (3)										
Primidone	16.2 (4)	9.5 (5)	-0.7 (3)	-0.7 (5)	10.1 (5)	10.4 (2)	-2.2 (5)	-0.2 (2)										

<sup>a</sup> Topiramate dosage groups combined for Protocols YD and YE.

<sup>b</sup> Number of subjects receiving concomitant AED and contributing data to the analysis is shown in parentheses below mean values.

<sup>c</sup> Statistically significant difference in mean change relative to placebo group,  $p=0.015$ .

<sup>d</sup> Statistically significant difference in mean change relative to placebo group,  $p=0.001$ .

<sup>e</sup> Statistically significant difference in mean change relative to placebo group,  $p=0.039$ .

Key: PLA = placebo; TOP = topiramate.

Cross-reference: Table 41 of Four-Month Safety Update submitted July 13, 1995; Volume 1 Page 09 00195.

**Table 3: Change in Plasma Concentrations (µg/mL) of Concomitant Antiepileptic Drugs (AEDs) from the Baseline Phase to the Double-Blind Phase<sup>a,b</sup>  
(Randomized Subjects With Plasma Concentration Data Available: Protocols YD, YE, Y1, Y2, Y3, and YF/YG)**

Concomitant AED	Protocol YD				Protocol YE				Protocol Y1					
	PLA	TOP	PLA	TOP	PLA	TOP	PLA	TOP	PLA	TOP	PLA	TOP	PLA	TOP
Carbamazepine	9.0 (36)	8.8 (130)	-0.7 (36)	-0.7 (96)	9.4 (31)	9.3 (107)	-0.2 (30)	-0.7 <sup>c</sup> (101)	7.6 (16)	6.7 (16)	0.2 (13)	-0.4 (16)		
Phenytoin	19.6 (17)	15.5 (53)	-0.5 (16)	0.4 (51)	17.4 (16)	16.5 (50)	0.5 (17)	1.0 (50)	15.1 (10)	17.9 (8)	1.0 (10)	1.3 (8)		
Valproic Acid	67.5 (13)	59.5 (39)	-1.9 (13)	-2.6 (39)	70.0 (10)	70.6 (42)	-1.5 (9)	0.0 (42)	39.5 (4)	52.2 (3)	-2.0 (4)	-1.5 (3)		
Phenobarbital	22.3 (5)	22.4 (17)	0.2 (5)	-0.1 (17)	22.9 (5)	18.8 (15)	1.8 (5)	0.6 (13)	22.2 (5)	24.8 (6)	-2.3 (5)	0.1 (6)		
Primidone	7.0 (4)	9.1 (18)	0.4 (4)	-0.2 (18)	7.8 (8)	10.6 (16)	-0.3 (8)	-0.3 (16)	8.1 (2)	9.1 (3)	-1.2 (2)	-0.4 (3)		

<sup>a</sup> Topiramate dosage groups combined within Protocols YD and YE.  
<sup>b</sup> Number of subjects receiving concomitant AED and contributing data to the analysis is shown in parentheses below mean values.  
<sup>c</sup> Statistically significant difference in mean change relative to placebo group, p=0.029.

Key: PLA = placebo; TOP = topiramate.

Cross-reference: Table 41 of Four-Month Safety Update submitted July 13, 1995; Volume 1 Page 09 00195.

(Continued)

### **FDA Comments**

Discussing the sponsor's points in order, first, the lack of pharmacokinetic interaction across treatment groups.

(Recall that acetazolamide is also generally considered clinically useful across groups. Sweeping claims about efficacy based on solely theoretical grounds cannot be used as a substitute for a robust effect in a well-designed clinical trial.

### **Recommendations**

It is recommended that the claim for monotherapy should not be granted.

### **7.0.3 ISSUES RELATED TO OPTIMUM DOSE**

In the approveable letter the FDA noted that doses higher than 400 mg/day did not appear to produce additional improvement when groups of subjects were compared in the double blind trials. The FDA provided wording in the labeling to suggest that 400 mg is the maximum useful topiramate dosage. The sponsor has stated in its response that there is agreement with the FDA on that point, however the sponsor has requested that the FDA consider the minimum effective dose to be 200 mg, based on study YD in which this dose was evaluated. In this study it was found that while there was not a strong statistically significant difference between the response at this dose and placebo ( $p=0.08$ ) there was

a strong trend with respect to the (percent seizure reduction), and there was a statistically significant difference between the 200 mg group and the placebo for investigator's global and patient's overall assessment.

This is based on data which were considered at the time of the previous review and no new data or analyses are provided.

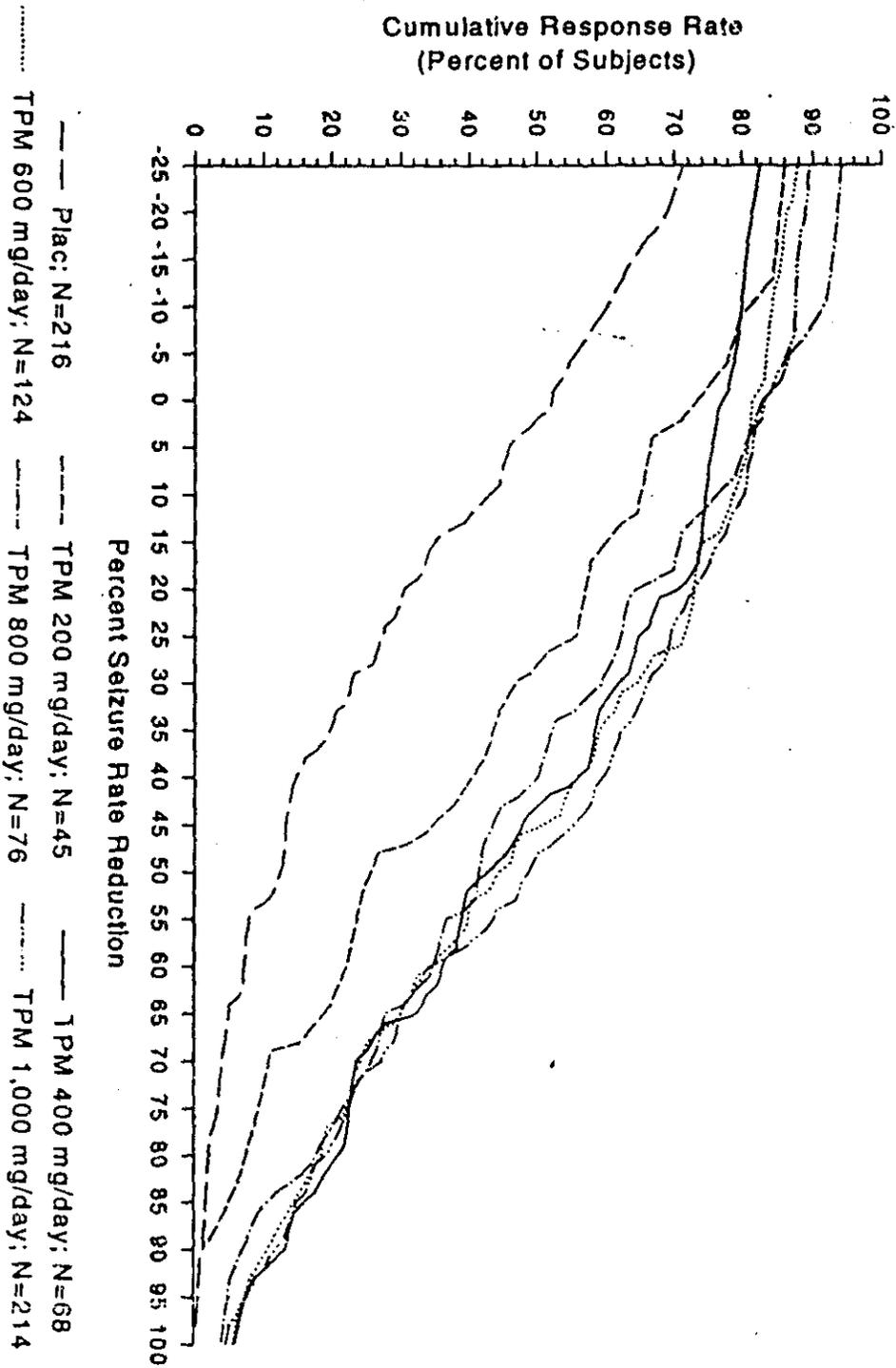
**Comment:** These are not the standards that are applied to other drug products. There is no compelling reason based on what the sponsor has presented to revise the original recommendations. It should also be pointed out that the more subjective measures on which the sponsor wishes to confer additional weight may be a function of the product's safety profile than its efficacy.

#### **7.0.4 Response to the sponsor's request for further display of data in cumulative format**

In the approveable letter the FDA noted that the sponsor provide displays of the individual patient responses in a cumulative response curve by plotting the decrease in seizures frequency from baseline (as percent reduction, from smallest to largest) against the number of subjects with a response at least as good. The sponsor has provided these for studies YD, YE, Y1, Y2, Y3 and YF/G. This includes all randomized subjects in adjunctive therapy trials for topiramate. Cumulative plots by individual study were also provided.

In the combined data set, responses at 400 through 1000 mg/day were indistinguishable. The placebo curve can clearly be distinguished from the treatment curve. As seen in the calculated response presented in tabular form in the NDA, more patients receiving topiramate had (25% and 50%) improvement in their seizures compared to placebo patients, but also more treated patients had worsening of their seizures (25 % displayed) compared to those on placebo. Similar patterns have been noted with gabapentin. This is the same phenomenon, but displayed graphically. It is not obvious from the data which patients are at risk to worsen under treatment. This degree of analysis has not been carried out.

**Figure 1: Cumulative Percent Seizure Rate Reduction From Baseline During the Double-Blind Phase<sup>3</sup>**  
 (All Randomized Subjects; Protocols YD, YE, Y1, Y2, Y3, and YF/YG)



Key: Plac = Placebo; TPM = Topiramate  
 Cross-reference: Attachments 1a and 1b.

## 8.0 SAFETY

### 8.1 ORIGINS OF SAFETY DATA (METHODS)

#### Background

The sponsor has made an effort to reevaluate the Topiramate clinical safety database to better characterize and describe the neuropsychiatric adverse effects associated with topiramate, to provide follow-up on abnormal laboratory data and to provide a better correlation between adverse events and actual doses received by patients. The reassessment took five separate and independent steps to the existing information in the NDA ostensibly guided by the December 29, 1995 Approvable Letter as well as in subsequent meetings with RWJPRI. These five steps included (1) a reanalysis of the neuropsychiatric ADRs and retabulation of the results in the 4-Month Safety Update (2) a retrospective reevaluation of the neuropsychiatric adverse events using investigator questionnaires (3) A prospective evaluation of the cognitive effects of topiramate, (4) follow-up information on markedly abnormal laboratory abnormalities that had not resolved at the time of the 4-month safety update and (5) evaluation of the adverse event profile of topiramate. The information obtained through each of these approaches was not integrated. These will be discussed in the pages that follow in the context of the specific requirements outlined by the FDA in the Approvable Letter.

#### I. Reanalysis of Neuropsychiatric adverse events.

##### FDA REQUEST:

The FDA indicated to the sponsor that the raw data from case report forms should be reexamined for the purpose of reclassifying the neuropsychiatric adverse events which occurred in topiramate-treated patients in a clear manner that would be unambiguous, nonduplicative and recognizable by clinicians expert in mental status assessment. Once done, then retabulation of incidence rates examining dose response effects (by actual doses received) should be done. The sponsor was told that if the information could not be extracted from available CRFs, alternative sources could be explored,<sup>1</sup> such as clinician interviews or

---

<sup>1</sup>First, you need to develop **standardized and validated methods to classify reports of neuropsychiatric adverse clinical events**. In some cases, it will be useful to describe and group closely related events as part of some broader category. You will need a procedure or **protocol for determining the adequacy of a case report** (i.e., whether it contains the kind of information that would allow an event to be classified). With this assessment methodology in place, a determination should then be made as to what proportion of available case report forms contain the kind of information necessary to characterize reported adverse events in language that is informative. If there are sufficient numbers of case reports containing appropriate data, especially for events associated with discontinuation or change in dosage, and those considered serious, the events reported should be classified within exclusive categories that would be readily recognizable by clinicians expert in mental status assessment. Once these classifications are completed, estimates of incidence rates for each kind of event (or related groups of events) and the relationship between incidence and dose or serum concentration, and duration of exposure, should be re-examined. Dose-response should be examined both within randomized study groups (the least confounded by time-related effects) and by actual exposure groups in the full data set.

<sup>2</sup>If the information required to classify cases cannot be extracted from available case report forms, you may

contemporaneous clinic or office records.

#### **SPONSOR'S RESPONSE**

The sponsor responded to this element by first developing a new classification system for neuropsychiatric adverse events and then retabulating them. The sponsor did not go back to the source documents as expected, but rather used the investigator's verbatim terms as a starting point. The sponsor has not provided a justification of this approach in not returning to the source documents (the case report forms) to reconstruct the safety data base. As a separate exercise the sponsor obtained information from sponsors in an effort to develop a "case definition" for some of the ADRs which on initial review appeared to be related to each other. This latter exercise was not applied to the overall retabulation of adverse events. The methods of each exercise will be described below.

#### **METHODS**

Neuropsychiatric adverse events summarized in the Four-month Safety Update for topiramate using WHOART preferred terms have been reclassified using modified terminology readily recognizable to clinicians. The basis for this reclassification is described below.

RWJPRI identified 23 WHOART terms that were used to describe adverse events associated with topiramate use:

agitation, amnesia, anorexia, anxiety, aphasia, ataxia, concentration impaired, confusion, depression, diplopia, dizziness, emotional lability, fatigue, headache, insomnia, nervousness, nystagmus, paresthesia, somnolence, speech disorder, thinking abnormal, tremor, and vision abnormal.

The investigator verbatim terms that led to these 23 terms were reexamined. Based on the recommendation of a consultant, Dr. Kimford Meador, M.D. Departments of Neurology and Pharmacology/Toxicology Medical College of Georgia, Augusta, GA, it was thought that eight were too vague to provide any useful description of all the corresponding investigator terms. These eight terms were the following:

amnesia, aphasia, impaired concentration, confusion, emotional lability, nervousness, speech disorder and abnormal thinking.

These 6 terms were reclassified as 10 "preferred WHOART terms". The remaining 15 terms were not reclassified. There came to be a total of 25 neuropsychiatric terms rather than 23. The adverse events were then retabulated accordingly.

The old and new terms are compared in Sponsor's Table 6 modified on the following page.

---

*have to use alternative sources (e.g., interview clinicians who actually treated patients who participated in the development program, extract information from contemporaneous office or clinic records, etc.) to obtain it. Again, this is particularly critical for adverse events that led to change in therapy. "*

**TABLE 6 RECLASSIFICATION OF NEUROPSYCHIATRIC ADVERSE EVENTS**

<b>Original WHOART Preferred Term</b>	<b>Modified WHOART Preferred Term and Representative Investigators' Verbatim</b>
Abnormal thinking	<u>Psychomotor slowing(1)</u> delayed responses slowed thinking <u>Difficulty with concentration/attention(2)</u> difficulty with calculations transposition of numbers <u>Confusion(3)</u> repetitive thoughts <u>Language problems(4)</u> difficulty with spelling <u>Cognitive problems(5)</u>
Amnesia	<u>Difficulty with memory(6)</u> decreased recent and short term memory decreased fund of knowledge forgetfulness
Aphasia	<u>Language problems (4)</u> decreased comprehension difficulty spelling dysnomia word finding difficulty <u>Speech disorders/related speech problems(7)</u> difficulty forming words slow speech verbal repetition
Confusion	<u>Confusion(3)</u> disorientation confusion with seizures/postictal confusion <u>Psychomotor slowing(1)</u> confused (mental slowing)
Emotional Lability	<u>Emotional Lability (8)</u> emotional short-tempered <u>Mood problems(9)</u> mood swings cries easily/tearful <u>Nervousness (10)</u> mood swings/irritability
Impaired concentration	<u>Difficulty with concentration/attention (2)</u> difficulty with concentration/attention difficulty with calculation

	loss of train of thought
	<u>Language problems (4)</u>
	decreased reading comprehension, difficulty reading
Nervousness	<u>Nervousness (10)</u>
	excitability
	shakiness
	<u>Mood problems (9)</u>
	complaint of moodiness/irritable
Speech disorder	<u>Speech disorders/related speech problems (7)</u>
	dysarthria
	perseveration
	repeating self
	<u>Language problems (4)</u>
	decreased fluency of speech
	dysnomia/speech difficulty/frequent pauses

The starting point for this reclassification were the verbatim investigator terms. After reclassification of these neuropsychiatric adverse events, incidence rates of the adverse events were recalculated for the entire database, and the relationships between incidence and dosage and incidence and duration of exposure were examined. In addition, the duration and persistence of adverse events resulting in premature withdrawal of subjects from the double-blind trials were evaluated, and follow-up information was obtained for all markedly abnormal laboratory abnormalities that had not resolved as of the reporting interval covered by the Four-Month Safety Update.

Because it was difficult to determine the ultimate outcome of patients who left topiramate studies prematurely because of adverse events, the FDA requested that the entire database should be examined to determine the time course (time of onset, persistence, response to dose change, etc.) of the important adverse events. In addition, because much of the dose response information was constructed based upon doses to which patients were randomized, not on doses patients actually received the FDA requested that the adverse event data be displayed as a function of dose received, not randomized dose. This was done, in the response to the Approvable Letter and will be summarized in section 8.4 of this review, using a range of doses because many patients did not receive their target doses due to the occurrence of adverse events.

The retabulations can be found in section 8.4 of this review.

#### **B: Adequacy of Approach**

This new nomenclature is closer to the actual descriptions of the adverse events by sites than previously. The sponsor was cautioned that the source documents

would be most accurate and clearly, while there remains some ambiguity, this is closer to the ideal than the original NDA achieved.

## II RETROSPECTIVE CLINICAL ASSESSMENT OF THE EFFECTS OF TOPIRAMATE:

### Background

In an effort to better understand the nature of the neuropsychiatric adverse event profile of topiramate the FDA had recommended to the sponsor that an effort be made to review case documents, including case report forms, and if necessary, patient records or conduct physician interviews.

### FDA request (from the approveable letter)

The sponsor was advised to "develop standardized and validated methods to classify reports of neuropsychiatric adverse clinical events. In some cases, it will be useful to describe and group closely related events as part of some broader category. You will also need a procedure or protocol for determining the adequacy of a case report (i.e., whether it contains the kind of information that would allow an event to be classified)" With this assessment methodology in place, a determination should then be made as to what proportion of available case report forms contain the kind of information necessary to characterize reported adverse events in language that is informative. If there are sufficient numbers of case reports containing appropriate data, especially for events associated with discontinuation or change in dosage, and those considered serious, the events reported should be classified within exclusive categories that would be readily recognizable by clinicians expert in mental status assessment. Once these classifications are completed, estimates of incidence rates for each kind of event (or related groups of events) and the relationship between incidence and dose or serum concentration, and duration of exposure, should be reexamined...If the information required to classify cases cannot be extracted from available case report forms, you may have to use alternative sources (e.g., interview clinicians who actually treated patients who participated in the development program, extract information from contemporaneous office or clinic records, etc.) to obtain it. Again, this is particularly critical for adverse events that led to change in therapy."

### Method

RWJPRI undertook a retrospective study of neuropsychiatric AEs based on investigator's impressions of the clinical nature of these events, both individually and globally in order to ascertain if there might be a clinical syndrome associated with the use of topiramate.

Experienced investigators who had treated a minimum of 30 patients each with topiramate were selected for this study. Additional criteria included access to source documentation on the subjects involved. Six investigators met these criteria yielding a treatment sample of 264 patients.

Patients evaluated in the study included those who experienced at least one treatment emergent neuropsychiatric AE and who had data included in the 4 month safety update data base. There were, then 241 patients eligible for the study. Of these, 10 received placebo only. The sponsor therefore chose not to have an independent blinded investigator evaluate the data. The study was performed fully unblinded.

Investigators completed a patient-specific questionnaire asking details about the nature of the adverse events. Investigators reviewed source documents so as to most accurately describe the neuropsychiatric ADRs including time course and outcome. Specific questions included descriptions of the adverse events, means of assessment, and impression of the presence or absence of a symptom complex that could be considered a syndrome.

A second questionnaire (not patient specific) probing the impressions of the investigators about the overall safety profile of topiramate was completed.

An independent neurologist, Dr. James Cereghino, (formerly Chief of the Epilepsy Branch, NINDS, NIH) reviewed and summarized the results of the questionnaire.

**Results:**

In large part investigators tried to "explain away" adverse events rather than simply describe them. In many cases the adverse events were not even described. The summary below applies to those that were described. Overall no one particular syndrome emerged, however there were some commonalities which are notable in these reports. The table on the following page summarizes the common findings by investigator. These data were not applied to the reclassification of AEs described in the earlier section.

**Comment:** There is the suggestion of titration-related findings associated with the use of topiramate, specifically the one recurring theme is that patients have difficulty formulating their thoughts in language. These are consistently described, however as titration linked events, which improved with time on medication.

NEUROPSYCHIATRIC AES ASSOCIATED WITH TOPIRAMATE---RETROSPECTIVE STUDY

Abou-Khalil	Devinsky	Faught	Privitera	Rosenfeld	Sachdeo
<p>increased psychomotor retardation with topiramate titration</p>	<p>feeling mentally not so clear</p>	<p>transient global cognitive effects trouble thinking</p>	<p>slowness in thought</p>		<p>psychomotor slowing difficulty processing information fast slow in ability to process not comprehending</p>
<p>decreased fluency (unusual with other AEDs) --inability to formulate and express thoughts --slow responses and poorly articulated speech</p>	<p>--having trouble forming thoughts and expressing self --repeating phrases --slowed speech --naming difficulties</p>	<p>--transient problems with speech --"classical" TPM titration syndrome with typical features, especially (1) complaint of slowed thinking without drowsiness (2) subjective word finding difficulty or slowed speech production with no dysnomia or specific receptive/expressive deficits <u>demonstrable</u> on bedside examination (3) resolution in a few weeks --more spontaneous speech noted on discontinuation --titration-related slowing of speech --typical TPM language complaint of what sounds to me like dysnomia (and typically just by report, not demonstrable on office exam dysnomia and expressive aphasia mild <u>subjective</u> word-finding trouble and stuttering</p>	<p>Substantial complaints of word-finding problems but even detailed neuropsychological testing found little language problems baseline stuttering worse; slower verbal output by complaint and examiner impression, and test of verbal fluency word finding problems repeating self decr. with reduction of topiramate dose word-finding problem was similar to other patients receiving topiramate slowed speech output and word-finding problems, mild, resolved with time (1 week) slow verbal output</p>	<p>slowed speech speech dysfunction word finding difficulty mild repetitive speech</p>	<p>difficulty finding the right words (cleared medication) word finding difficulty and verbal repetition difficulty coming up with the right words fast</p>

decreased attention span	decreased attention and concentration			decreased concentration difficulty with numbers loss of train of thought concentration difficulties slowed mentation slowed responses slow thinking slowing of responses decreased cognition	
forgetfulness and decreased memory		--worsening of memory --titration related slowing of memory		alteration in memory mild decrease in memory forgetfulness Improved with lower dose	problem with memory
moody, easily provoked	behavior -- temper tantrums			moodiness	anxiety lost temper more often
psychosis and hallucinations		psychosis		hallucinations	
		irritability and fatigue fatigue	irritability	--irritability and depression --tiredness and irritability	irritability
			depression	depression	
sleepiness				mild fatigue sleepiness somnia	tiredness feeling tired and sleep

III **Prospective Assessment of the Cognitive Effects of Topiramate**  
Cognitive function tests, specifically testing recall, attention, and word fluency were performed by an investigator for subjects receiving topiramate in an open-label study.

**A: Methods**

A total of 15 patients participating in protocol YOL, an open label clinical study were evaluated prospectively for cognitive changes while on topiramate. The principal investigator was Michael Privitera, MD, a clinical neurologist. There was no prospective protocol for this portion of the study.

**B. Conduct of Study**

Since there was no protocol, one cannot say whether the study was conducted according to design. From the abstract and materials provided the following occurred during this study:

At a screening visit, patients

- underwent baseline cognitive assessment
- had background AEDs recorded
- had retrospective monthly seizure counts recorded

At follow-up visits, patients

- underwent cognitive assessment
- had concomitant AEDs recorded
- had retrospective monthly seizure counts recorded
- had topiramate dosage recorded

The follow-up visits occurred q1 month x6, then q3 months until exit. The duration of study YOL was undefined.

The cognitive assessment tool used was a simplification of a portion of the MMS (mini mental state), a bedside tool for an abbreviated mental status examination. The assessment consisted of three parts:

**Recall**

**Test:** Patient was asked to recall 3 objects immediately and at 3 minutes

**Scoring:** 1 point was given for recall of each object at three minutes

**Word Fluency**

**Test:** Patients were asked to name as many words as possible beginning with the letter "H", given 30 seconds for the task.

**Scoring:** 1 point was given for each correct answer.

**Attention**

**Test:** Patient was asked to perform serial 7's X 5, that is to count

backwards from 100 by 7's to 65.

**Scoring:** A perfect score was 5. Each error counted as -1.

It is important to note that the investigator took a great deal of liberty with this measure. If the patient was unable to perform serial 7's he was tested with serial 5's or serial 3's. This was done in some cases even when the baseline was performed in serial 7's.

Patients who remained in the study for  $\geq 12$  months had the 12 month evaluation used as the comparison with baseline. Patients who were in the study for  $< 12$  months usually had their assessment at the peak topiramate dose used as a comparison with baseline.

There were 15 patients studied at baseline. There were 8 men and 7 women studied. Their mean age was 35.7 years (range 21 to 59). They were followed for a mean duration of 14.9 months (range 4-24 months), although the data after 12 months was not used. The mean topiramate dose was 887 mcg/ml.<sup>2</sup> The patients were treated with 1-3 concomitant AEDs at baseline (VPA 13, CBZ 10 most commonly) and all but one patient underwent changes in these regimens during the study at some undefined time. Of these 15 patients, all but one experienced some treatment-emergent neuropsychiatric adverse event(s) during the study.

### **C: Adequacy of Approach**

There was no prospective protocol for this study, so that the criteria for the selection of these 15 patients remains unstated and unknown. There was agreement with DNDP and the sponsor that it would be of value to have a prospective evaluation of cognitive function in patients on topiramate. However the absence of any prospective guidelines in the form of a protocol makes it difficult to understand what was done and to interpret the results.

The rationale for selecting these three measurements was not provided. One would have hoped that a more probative neurometric could have been used prospectively that would yield more complete information. Nevertheless, this "quick and dirty" three pronged mini-MMSE might have provided some useful information had it not been for other complicating factors.

The problems with this investigator's approach fall into three categories:

#### **1-Small N**

With a sample size of 15, the sponsor could not have hoped to learn anything but about the most frequent of events. Indeed only 14 of the patients were taking

---

<sup>2</sup>The sponsor does not state whether this represents the mean Peak topiramate dose or the mean dose at the time of assessment.

topiramate at the time when they were tested. If this small selection of patients is typical of the overall database then the results potentially reflect the overall experience with topiramate. The incidence of "impaired cognition" as reported in the placebo controlled clinical trials was 5% in the topiramate treated patients. If this is accurate, one might not expect to see cognitive impairment in any of the 14 patients studied on topiramate.

## **2- No Controls, variability of interventions**

This is the most considerable problem with a design in which an attempt is being made to correlate changes in cognitive function with dose, when so many other variables could be playing a role in the patients' mental status. Without a control group it is impossible to sort out drug effect from other effects as described below.

In this study there were numerous interventions that were varied throughout the experiment. The first is the dose of topiramate. Patients were on no topiramate at baseline (or it is presumed). During the experiment they may have been on at least two different topiramate regimens, one reflected by the peak topiramate dose and one reflected by the final topiramate dose. The dose of topiramate that corresponds to the final mental status exam is not stated, but it is presumed to be the "final dose" in the  $\geq 12$  month duration group and the "peak dose" in the  $< 12$  month exposure group. This may not be the correct assumption. Furthermore, the sponsor has not identified when in time the interventions were changed. Specifically, was the topiramate dose reduced close or distant in time to the mental status examination? Another question emerges from this, as to whether the higher doses correspond to more deteriorated mental status examinations. These data were not provided. The unexplained dose reductions in the high dose patients, if the reason for this dose reduction were provided, might give some insight into mental status changes associated with topiramate. The PI notes that two patients in the high dose group did experience decreased scores.

In addition to the variability in topiramate dosing throughout the study, the concomitant drugs and seizure rates within a test period complicated also varied considerably. While the seizure frequency was not under the control of the investigator, the variability in regimen was. Only one patient out of 15 did not have at least one medication completely discontinued, added or both during the course of the trial. The mental status changes if any occurred could be as easily attributed to change in concomitant AED regimen or seizure control as to topiramate. As in the case of topiramate dosing, the timing of these changes to drug regimen were not correlated with the timing of the mental status examination because that information was not provided.

## **3- Outcome Measures**

While the MMS is a test that has gained acceptance in the neurological community as a useful bedside assessment of cognitive function, it has its limitations (outlined in Sponsor's reference 14 provided). Nevertheless it is

far more probative than the highly abbreviated version used in this study. Neither is a substitute for a thorough mental status examination or formal validated psychometric examinations.

Even if the instrument used in this prospective study were a validated measure of mental change, the fact that the measure was altered to fit the changes in mental status in 7 cases should render it invalid. For example, patients who could not do serial 7's were allowed to do serial 5's or 3's, providing neither a valid comparison against their baseline or in comparison to the other subjects.

#### **5 "Learning" the Test**

According to the sponsor, patients returned every month for six months, then every three months for the remainder of the time on the study. The three tasks did not change at each visit. The patients could "learn" the test for at least the last two measures, serial 7's and naming "H" words. The three objects could be varied from month to month, however there is no information provided in this regard. An apparent "no change" or improvement in results could be arguably a function of learning the instrument rather than lack of drug effect.

#### **C: Results**

The results of these cognitive function tests are summarized in the table on the two pages that follow.

#### **D. Comments**

This was not a rigorous test instrument and it was not carried out rigorously. Contrary to the conclusions of the PI, that "mean scores of brief tests of cognitive function did not decrease with time", it is not possible from this experiment to draw any conclusion about mental status changes and topiramate use.

**Attachment 31: Cognitive Function Assessments: Data Listing**  
**(Subjects Who Participated in Prospective Cognitive Function Assessment Study; Protocol YOL)**

Inv/Subj No.	Gender	Age (yr)	Time on T-M (mo)	Peak TPM Dose (mg/day)	TPM Dose at FNL ASSMNT	Cognitive Test Scores										Changes from Baseline <sup>a</sup>
						BL	FNL <sup>a</sup>	CHNG	BL	FNL <sup>a</sup>	CHNG	BL	FNL <sup>a</sup>	CHNG	BL	
170/142	Male	27	24	1,000	800	1	3	+2	5	10	+5	4	8	+1	d/c CBZ	↓ 80%
170/148	Female	28	24	1,600	800	3	2	-1	12	8	-4	3	5 <sup>b</sup>	0	d/c VPA	↓ 50%
170/192	Male	51	24	1,200	800	3	3	0	14	10	-4	7	7	0	d/c CBZ	n/c
170/147	Male	41	24	1,600	700	2	3	+1	3	5	+2	5	9	0	d/c VPA	n/c
															n/c PHT	
170/146	Female	39	24	1,400	800	1	3	+2	8	3	-3	2	0	-2	d/c CBZ	↓ 50%
															n/c VPA	
															n/c CZP	
170/145	Male	41	24	1,400	1,000	3	3	0	3	4	+1	5	8 <sup>b</sup>	0	d/c CBZ	↓ 50%
															↓ VPA	
170/193	Male	30	18	700	500	1	3	+2	3	5	+2	1	6	+4	↓ VPA	SZ FREE
170/195	Female	21	14	600	400	3	3	0	8	7	-1	4	14 <sup>b</sup>	0	d/c CBZ	↑ 40%
															d/c VPA	
															add FBM	
170/150	Female	45	12	700	0 <sup>c</sup>	1	3	+2	2	7 <sup>d</sup>	+5	4	5	+1	d/c VPA	↑ 87%
															d/c CBZ	
															d/c CLZ	
															add FBM	
MEAN (212 mo)		35.9	20.9	1,133	644			+0.89			+0.33					+0.44

<sup>a</sup> For subjects treated with topiramate for <12 months, change from baseline is based on scores at month 12. For subjects treated with topiramate for <12 months, change from baseline is based on scores recorded at the peak topiramate dose.

<sup>b</sup> Subject was unable to perform serial '7's' and score was based on serial '3's'.

<sup>c</sup> Subject was discontinued because of drug inefficacy; fahamate was added as topiramate was tapered.

<sup>d</sup> Word fluency was not assessed at Month 12; change from baseline is based on Month 8 assessment. Censored at maximum score of 5 for analysis. Change adjusted if subject could not perform serial 7's.

KEY: d/c = discontinued; n/c = no change; BL = baseline; FNL = final; CHNG = change from baseline; SZ FREE = seizure free

AEDs: TPM = topiramate; CBZ = carbamazepine; VPA = valproate; PHT = phenytoin; CZP = clobazepam; FBM = felbamate; CLZ = clonazepam

(Continued)

**Attachment 31: Cognitive Function Assessments: Data Listing**  
 (Subjects Who Participated in Prospective Cognitive Function Assessment Study; Protocol YOL)

Inv/Subj No.	Gender	Age (Yr)	Time on TPM (mo)	Peak TPM Dose (mg/day)	TPM Dose at FNL ASSMNT	Cognitive Test Scores						Changes from Baseline				
						BL	FNL <sup>a</sup>	CHNG	BL	FNL <sup>a</sup>	CHNG	BL	FNL <sup>a</sup>	CHNG	In AEDs	In Seizures
170/191	Female	32	10	600	600	3	3	0	5	8	+2	4	13 <sup>b</sup>	0	d/c VPA n/c CBZ	↑ 100%
170/194	Female	29	8	700	400 <sup>c</sup>	3	3 <sup>c</sup>	0	9	12 <sup>c</sup>	+3	8	8 <sup>c</sup>	0	↓ VPA n/c CBZ	↑ 40%
170/196	Male	59	8	700	700	3	2	-1	9	4	-5	8	5 <sup>d</sup>	-1	d/c VPA add PHT	n/c
170/197	Female	34	8	400	400	3	3	0	6	9	+3	9	9 <sup>e</sup>	0 <sup>e</sup>	↓ CBZ n/c VPA	↑ 100%
170/144	Male	33	4	400	400	3	0	-3	2	0	-2	0	0 <sup>f</sup>	-5 <sup>f</sup>	↓ PHT n/c VPA	↓ 88%
170/143	Male	25	4	300	300	3	3	0	9	7	-2	9	9 <sup>g</sup>	0 <sup>g</sup>	n/c PHT n/c VPA n/c CBZ	SZ FREE
MEAN (<12 mo)		35.3	6.0	517	487			-0.67			-0.17			-1.00		
OVERALL MEAN		35.7	14.9	887	493			+0.27			+0.13			-0.13		

<sup>a</sup> For subjects treated with topiramate for ≥12 months, change from baseline is based on scores at month 12. For subjects treated with topiramate for <12 months, change from baseline is based on scores recorded at the peak topiramate dose.

<sup>b</sup> Subject was unable to perform serial '7's' and score was based on serial '3's'.

<sup>c</sup> Topiramate dose at assessment and final scores are based on Month 4 visit. Subject had increased seizures over last two months of participation and cognitive assessments were not done. Subject discontinued at Month 8 because of drug ineffectiveness.

<sup>d</sup> Subject gave five correct answers and made one error.

<sup>e</sup> Subject was unable to perform serial '5's'. The investigator noted that serial '5's' were 'OK'; no scores were given.

<sup>f</sup> Subject was unable to perform serial '7's' at baseline and was tested on serial '5's'. The subject gave no correct answers at the time of final assessment. Censored at maximum of 5 for analysis. Change adjusted if subject could not perform serial 7's.

<sup>g</sup> KEY: d/c = discontinued, n/c = no change, BL = baseline, FNL = final; CHNG = change from baseline; SZ FREE = seizure free

AEDs: TPM = topiramate; CBZ = carbamazepine; VPA = valproate; PHT = phenytoin; CZP = clobazepam; FBM = felbamate; CLZ = clonazepam

## **8.2 ASSESSMENT OF DEATHS**

The updated analysis of safety data as of October 1, 1995 for 1,715 subjects included all deaths originating from six new studies not included in the overall analysis data. These six additional studies were not included in the overall analysis because they were initiated after the October 1 1995, cutoff date, or were not sponsored by RWJPRI, or were designed to study subjects with tonic-clonic seizures.

Eight deaths were reported between the March 31, 1995 cutoff date for reporting of serious adverse events in the Four-Month Safety Update and the June 30, 1996, cutoff for this Final Safety Update and are listed in Sponsor's Table 2. Of the eight deaths, three were sudden and unexplained. This represents an incidence of 16 per 2,796 patient-years of exposure or 5.7/1000 patient years. This is still comparable to that which has been reported for other antiepileptic study populations, such as Lamictal (5.8/1000 patient years).

Of the remaining five deaths, one was accidental, and four were due to medical events, i.e., one case each of cardiac arrest, cardiac arrhythmia, aspiration during a seizure, and cerebral edema after an elective right frontal lobe resection.

The recent addition of data from the final safety update does not raise any new concerns about topiramate.

Table 2: Topiramate Clinical Study Subject Deaths Reported Between March 31, 1995, and June 30, 1996

Investigator/ Subject	Protocol No.	Age <sup>a</sup> (Yr)	Sex	Cause of Death/ Adverse Event	Day of Onset of Event <sup>b</sup>	Dosage at Onset of Event (mg/day)	Total Days of Topiramate Therapy <sup>c</sup>	Final Dosage (mg/day)	Relationship to Study Drug <sup>d</sup>	Location of Report Form Volume	Page
215/007	YI	51	F	Unexplained	968	50	968	50	Unlikely	2	12 00013
402/812	YOLE	59	M	Unexplained (probable myocardial infarction)	-660	200	-660	200	Unlikely	2	12 00262
01/005	TPS-TR	36	M	Unexplained (probable pulmonary embolism)	270	1,600	265	1,600	Unlikely	3	12 00396
NR/854	6485-9204 (Japan) <sup>e</sup>	45	F	Injury (cerebral contusion due to fall from stairs)	817	400	-620	400	Unlikely	---	---
018/008	YLT	58	M	Cardiac arrest	1,991	800	1,991	800	Unlikely	3	12 00472
345/045	YJ	43	F	Arrhythmia	791	600	791	600	Unlikely	5	12 01140
099/958	YOLE	19	F	Aspiration (during seizure)	585	800	585	600	Unlikely	8	12 01311
01/003	TPS-TR	30	M	Cerebral edema (post elective right frontal resection)	-60	200	-60	200	Unlikely	6	12 01424

<sup>a</sup> Age at study entry.

<sup>b</sup> Number of days from the beginning of the trial study until first reporting of adverse event.

<sup>c</sup> Total number of days from the beginning of the initial study until the time of death.

<sup>d</sup> Based on the investigator's assessment.

<sup>e</sup> This subject was receiving topiramate in an ongoing non-IIND study in Japan; no case report form is available. Age is at onset of event.

KEY: NR = not reported

Cross-reference: Attachment 5.

### 8.3 ASSESSMENT OF DROPOUTS

Discontinuations due to adverse events were also updated in the final safety update. They are summarized in the Sponsor's Table 3. The most common reasons for discontinuation from topiramate due to adverse events continue to be neuropsychiatric in nature: psychomotor slowing, difficulty with memory, confusion, somnolence, and difficulty with concentration/attention. The incidence of these is similar to the previous experience with the drug to the time of the 4 month safety update (and the reanalysis based on the response to the FDA Approvable letter), as expected. The only change was in the incidence of weight loss (see table).

Table 3: Incidence of the Most Common<sup>a</sup> Limiting Adverse Events

Adverse Event (Preferred Term)	4-Mo. Update Population <sup>b</sup> All Topiramate Dosages (N=1,446)		Final Update Population All Topiramate Dosages (N=1,715)	
	No.	(%)	No.	(%)
*Psychomotor slowing	60	(4.1)	70	(4.1)
*Difficulty with memory	46	(3.2)	57	(3.3)
Fatigue	44	(3.0)	57	(3.3)
*Confusion	44	(3.0)	55	(3.2)
Somnolence	51	(3.5)	55	(3.2)
*Difficulty with concentration/attention	39	(2.7)	50	(2.9)
Anorexia	31	(2.1)	49	(2.9)
Depression	38	(2.6)	45	(2.6)
Dizziness	39	(2.7)	44	(2.6)
Weight decrease	25	(1.7)	43	(2.5)
*Nervousness	27	(1.9)	38	(2.2)
Ataxia	30	(2.1)	37	(2.2)
Paraesthesia	30	(2.1)	35	(2.0)
*Language problems	25	(1.7)	34	(2.0)
*Speech disorders/related speech problems	28	(1.9)	32	(1.9)
Headache	21	(1.5)	30	(1.7)
Anxiety	20	(1.4)	26	(1.5)
*Mood problems	18	(1.2)	23	(1.3)
Nausea	18	(1.2)	23	(1.3)
Convulsions aggravated	11	(0.8)	20	(1.2)
Aggressive reaction	11	(0.8)	19	(1.1)
Psychosis	12	(0.8)	16	(0.9)
Vision abnormal	12	(0.8)	15	(0.9)
Insomnia	14	(1.0)	14	(0.8)
Tremor	10	(0.7)	13	(0.8)
Abdominal pain	9	(0.6)	12	(0.7)
Hallucination	10	(0.7)	12	(0.7)
Personality disorder	10	(0.7)	12	(0.7)
Rash	9	(0.6)	12	(0.7)
Apathy	7	(0.5)	11	(0.6)
Suicide attempt	9	(0.6)	11	(0.6)
Asthenia	8	(0.6)	10	(0.6)
Oplopia	6	(0.4)	9	(0.5)

#### **SPONTANEOUS REPORTS OF SERIOUS ADVERSE EVENTS (ASSOCIATED WITH DRUG DISCONTINUATION) FROM POSTMARKETING EXPERIENCE**

Six reports have been received from postmarketing surveillance in Europe associated with topiramate discontinuation. They are summarized below:

- **Aggravated convulsions**: patient recovered on discontinuation of topiramate 400 mg
- **Withdrawal syndrome**: patient experienced these symptoms for one week after stopping topiramate
- **Pancytopenia associated with ulcerative stomatitis** patient recovered on d/c topiramate 150 mg. This patient was also reported to have had a **withdrawal syndrome**.
- **Ataxia** not recovered on d/c topiramate 100 mg
- **Glaucoma** (transient angle closure) patient recovered after discontinuation of topiramate 100 mg/day.
- **Hallucinations, delusion, hyperkinesia**: patient recovered within days of discontinuing topiramate 400 mg.

Only glaucoma had not been previously reported in the NDA.

#### **8.4 OTHER SAFETY FINDINGS (ADR INCIDENCE TABLES)**

##### **INCIDENCE IN CONTROLLED CLINICAL TRIALS**

The table below enumerates neuropsychiatric adverse events which were treatment emergent in controlled clinical trials and which were reclassified at the request of the FDA in order to provide a clearer understanding of the occurrence and incidence of these events for the purpose of developing appropriate labeling for this product. The incidences have not been updated for the final safety update since there were no further controlled trials since the completion of the NDA.

The reclassification of neuropsychiatric adverse events resulted in removal of the term "abnormal thinking" for which a 21% incidence had been reported. The term psychomotor slowing was thought to be more accurate, and was reported in 20% of patients. It was thought to be more descriptive of the investigator term "slow thinking". The term "amnesia" (reported in 13%) was removed and the category "difficulty with memory" was added (14%). "Aphasia" was reexamined and the category "language problems", consisting primarily of word-finding difficulty, decreased fluency or spontaneous speech, and trouble reading are included. "Impaired concentration" has been replaced with "difficulty with concentration and attention", and includes investigator reports of difficulty with concentration, impaired calculation. Emotional lability (redefined) consists of reports such as temper flares and emotional swings and

outbursts. Mood problems include changes in affect or mood, but does not include reports of depression or related events.

**Reclassified Neuropsychiatric Adverse Events Based on Original WHOART Preferred terms and modified WHOART Preferred terms for all randomized subjects (YD, YE, YF/G, Y1, Y2, Y3)**

ADVERSE EVENT	4 MONTH SU		RECLASSIFIED 4 MONTH SU	
	Pbo	Tpm	Pbo	Tpm
Psychomotor slowing (new term)	--	--	5 (2%)	105 (20%)
Abnormal Thinking (old term)	5 (2%)	112 (21%)	--	--
Nervousness	16 (7%)	93 (18%)	16 (7%)	98 (19%)
Difficulty with Memory (new term)	--	--	7 (3%)	74(14%)
Amnesia (old term)	7 (3%)	69 (13%)	--	---
Difficulty with Concentration/attention (new term)	--	--	3 (1%)	69 (13%)
Impaired concentration (old term)	4 (2%)	69 (13%)	--	---
Confusion	9 (4%)	84 (16%)	9 (4%)	68(13%)
Speech Disorder (old term)	5 (2%)	53 (10%)	--	-----
Speech disorders/related speech problems (new term)	--	--	5 (2%)	66(13%)
Language problems (new term)	--	--	1(<1%)	50(9%)
Mood Problems (new term)	--	--	4 (2%)	42(8%)
Emotional lability	7 (3%)	58 (11%)	2(<1%)	13 (2%)
Cognitive problem (new term)	--	--	1(<1%)	12 (2%)
Aphasia (old term)	1(<1%)	54 (10%)	--	---

The relative contribution of drug can be estimated based on these comparisons.

The most commonly observed adverse events associated with the use of topiramate (incidence 5% or greater) at an equivalent incidence among placebo treated patients were psychomotor slowing, nervousness, difficulty with memory, difficulty with concentration/attention, confusion, speech disorders/related speech problems, language problems, mood problems, cognitive problems and emotional lability.

Treatment emergent adverse events that led to dosage reduction were summarized by the sponsor. The most common adverse events associated with dosage reduction or temporary discontinuation of therapy were fatigue, difficulty with concentration or attention, somnolence, and psychomotor slowing. Dosage reduction due to these adverse events were more likely to occur in patients randomized to 600 mg and 1000 mg/day.

#### **COMMONLY OBSERVED ADVERSE EVENTS IN CONTROLLED CLINICAL TRIALS**

The overall pattern of treatment emergent adverse events is consistent with that seen in the NDA and 4-Month Safety Update. The updated incidences are found in Sponsor's Attachment 4<sup>3</sup>. The most common treatment emergent adverse events were somnolence (32.9%), headache (30.8%), dizziness (30.8%), fatigue (30.8%), URI (27.6%), injury (23.6%), paresthesias (22.3%), weight decrease (21.7%), psychomotor slowing (21.6%), anorexia (21.1%), and nervousness (20.0%).

---

<sup>3</sup>Final safety Update, Volume 26.1

<sup>4</sup>Table 15, NDA Volume 23.4 , p. 45

<sup>5</sup>Table 19, Attachment 24 (cited in volume 23.4, page 50

## **8.5 LABORATORY FINDINGS AND VITAL SIGNS**

### **8.5.1 Clinically Important Laboratory Abnormalities Followed Up**

#### **FDA REQUEST**

The number of patients with important laboratory abnormalities has not been clearly stated, and adequate follow-up of some of these patients has not been obtained. Please reevaluate patients with clinically important abnormalities and obtain and submit detailed follow-up for this group.

#### **SPONSOR'S RESPONSE**

Follow-up laboratory test values have been obtained for subjects who had a markedly abnormal laboratory value during topiramate therapy that had not resolved by the time of the 4-month Safety Update. Follow-up laboratory test values were obtained from data on file at RWJPRI from case report forms received after the data cut-off for the Four-Month Safety Update, or from investigator's source documentation, or both.

#### **A: Methods**

Any available follow-up information was obtained through resolution<sup>6</sup> for patients with markedly abnormal laboratory values for the overall analysis population of 1,446 topiramate-treated subjects with epilepsy. Follow-up laboratory test values were obtained for subjects who had a markedly abnormal laboratory values that had not resolved by the last visit reported in the Four-Month Safety Update database.

Follow-up information was obtained by RWJPRI from case report forms received after the cut-off date for the Four-Month Safety Update (through a cut-off date of May 21, 1996). These data were referred to as "Post-4 Month Update Data". In addition some data were obtained from source documents maintained by investigators who were contacted by RWJPRI for follow-up information through May 21, 1996. The sponsor refers to these as "Follow-UpData." Investigators were contacted for follow-up information only for subjects in whom resolution of the marked abnormality of interest had not been documented based on additional data available in-house. The specific studies of clinical interest for which follow-up data were obtained by contacting investigators were: red blood cell counts, platelet counts, white blood cell counts, percentage of neutrophils, percentage of lymphocytes, hematocrit, hemoglobin, GGTP, SGOT, SGPT, LDH, and alkaline phosphatase.

For subjects who required laboratory follow-up from investigators, specific data

---

<sup>6</sup>Resolution of markedly abnormal values was defined as a return to baseline status (high, low, or normal relative to the reference range), i.e., return to the normal range for values that were normal at baseline; return to a normal or low value (rather than a markedly low value) for values that were low relative to the normal range at baseline; or return to a normal or high value (rather than a markedly high value) for values that were high relative to the normal range at baseline.

collection instruments (DCIs) were designed and sent to investigators. For each subject and laboratory test specified, the investigator was asked to provide the laboratory value and date on which the study returned to baseline or normal, or, if the abnormality had not resolved, the last available value and associated date.

For completeness, subjects who had markedly abnormal laboratory test values that were no longer markedly abnormal and had returned to their baseline status (e.g., values within the normal range at baseline had now returned to the normal range) by the last visit reported in the Four-Month Safety Update were also tracked.

In the Four-Month Safety Update a difference between topiramate and placebo in the incidence of markedly low white blood cells was noted (6.1 % versus 3.3% for markedly low WBCs). RWJPRI considered this laboratory abnormality to warrant special emphasis in the review of follow-up information for markedly abnormal laboratory values. Additionally, based on the profiles of other antiepileptic drugs, RWJPRI considered platelet and red blood cell counts of particular clinical interest in assessing the effects of topiramate.

**B: Adequacy of Approach**

This was a thorough approach that conformed to FDA expectations.

**C: Results**

These subjects and all available follow-up laboratory values are listed in Sponsor's Appendix 10 and a summary is provided below, grouped by hematology and clinical chemistry.

**HEMATOLOGY:**

**Low WBC:**

Of 1294 patients with laboratory data available, 99 (7.7%) had markedly low WBCs during topiramate therapy. Based on the last visit reported in the 4-month SU, 75/99 (76%) of these abnormalities had resolved. Of the 24 patients whose laboratory studies had not resolved by the completion of the safety update, the sponsor attempted to gain further information. Eight (8) have no additional follow-up information. The remaining 15 have WBC's that have returned to normal or baseline. Based on the available data from CRFs or DCIs the following is noted:

**TABLE: FOLLOW-UP OF LOW WBC COUNTS UNRESOLVED AT TIME OF 4M SU**

	Number	Off Medication
No change		
WBC lower	2 *	
WBC low, improving	7	
Resolved	15	15

\*One of these patients was lost to follow-up since discontinuing topiramate.

Most of the unresolved low WBC counts at the time of the 4 month SU have resolved or are improving. Resolution was noted after withdrawal in all cases. Two patients who continued on drug have not shown improvement. In the 15 cases in which resolution of low WBC occurred, the median time to resolution was 3 months (range 8 days to 4.4 years).

**Low Platelet Counts**

Of 1294 patients with laboratory data available, 22 (1.7%) had markedly low platelet counts during topiramate therapy. Based on the last visit reported in the 4-month SU, 15/22 (68%) of these abnormalities resolved. Of the 7 patients whose laboratory studies had not resolved by the completion of the safety update, the sponsor has attempted to gain further information. Six (6) have additional follow-up information. Of these 5 had resolved, and one remained markedly low (47,000).

**TABLE:FOLLOW-UP OF LOW PLT COUNTS UNRESOLVED AT TIME OF 4M SU**

	Number	Off Medication
No change	none	
Plt count lower	2	1
Plt count low, improving	none	
Resolved	5	5

\*One of these patients was lost to follow-up since discontinuing topiramate. Resolution is noted after withdrawal of topiramate in all but one of the above cases. This patient has had continually dropping platelet counts over the course of 357 days and the last result was obtained at the time when the patient's topiramate dosage was 0 mg/day. The sample had "clumping" and the platelet count may not have been accurate, but it was not retested. There is no further information and this patient has been lost to follow-up. Sponsor notes that the patient did not discontinue the topiramate because of the thrombocytopenia, but rather because of paraesthesias. The failure of thrombocytopenia to resolve upon discontinuation of drug even though it was seen in only one case should be highlighted in the drug's labeling.

**Low Red Blood Cell Counts**

Of the 1278 patients who had laboratory data in the NDA and Safety Update, there were 13 (1%) who had markedly abnormally low RBC counts during topiramate therapy. At the time of the 4 month SU, 7 of these had resolved. Of the remaining 6 patients 4 had improvement or normalization of these studies on subsequent follow-up. No information is available on the remaining 2.

**TABLE:FOLLOW-UP OF LOW RBC COUNTS UNRESOLVED AT TIME OF 4M SU**

	Number	Off Medication
No change	1	

Plt count lower	none	
Plt count low, improving	2	2
Resolved	3	2

**D. Comments**

These laboratory abnormalities usually resolved spontaneously while the subject continued topiramate therapy.

**NEW MARKEDLY ABNORMAL LABORATORY STUDIES**

The number and percentage of new abnormal laboratory studies since the 4 month safety update cutoff is are tabulated in Sponsor's Table 4 (see next page). Except for the case of unresolved thrombocytopenia, there are no new findings in these data which would suggest a problem with this product or that the current FDA proposed labeling should be altered in this area.

Sponsor's Table 4 is shown on the next page.

Of the abnormal laboratory studies, only two patients discontinued treatment with adverse events associated with these studies: one patient with elevated LFTS (patient discontinued for other reasons, and the labs were not sufficiently abnormal to warrant treatment discontinuation) and another patient with severe anemia (associated with chemotherapy for breast cancer. In other words none of these abnormal lab were sufficiently abnormal by themselves to lead to the alteration of treatment.

There is one finding that bears mentioning, however, seen in the previous data but more pronounced now, that of the presence of a mild metabolic acidosis (not unexpected for a carbonic anhydrase inhibitor with patients running serum bicarbonates in the "markedly abnormal" range. Of 240 patients with markedly abnormal serum  $\text{HCO}_3$  187 (78%) had values  $\geq 17$ mmol/L, while only 6 (3%) had values  $< 15$  mmol/L. These abnormalities were not correlated with clinical manifestations of metabolic acidosis.

**Table 4: Incidence of Treatment-Emergent Markedly Abnormal Clinical Laboratory Test Values**

Analyte	Markedly Abnormal Criteria	4-Mo. Update Population <sup>a</sup> All Topiramate Dosages (N=1,446)	Final Update Population All Topiramate Dosages (N=1,715)
<b>Liver Function Tests</b>			
SGOT	>100 U/L	28/1,278 (2.2)	31/1,570 (2.0)
SGPT	>110 U/L	22/1,282 (1.7)	26/1,577 (1.6)
Alkaline Phosphatase	>300 U/L	52/1,296 (4.0)	68/1,586 (4.3)
GGTP	>120 U/L	4/453 (0.9)	9/604 (1.5)
Bilirubin	>2.5 mg/dL	2/916 (0.2)	3/1,056 (0.3)
LDH	>500 U/L	1/478 (0.2)	2/642 (0.3)
Cholesterol	<80 mg/dL	1/867 (0.1)	1/997 (0.1)
	>400 mg/dL	2/867 (0.2)	3/997 (0.3)
Albumin	<2.5 g/dL	1/874 (0.1)	1/1,006 (0.1)
	>6.0 g/dL	1/874 (0.1)	1/1,006 (0.1)
Protein	<4.0 g/dL	1/914 (0.1)	2/1,005 (0.2)
	>9.5 g/dL	1/914 (0.1)	2/1,005 (0.2)
<b>Renal Function Tests</b>			
BUN	<2 mg/dL	3/1,296 (0.2)	5/1,581 (0.3)
	>40 mg/dL	30/1,296 (2.3)	49/1,581 (3.1)
Creatinine	>2.5 mg/dL	2/1,297 (0.2)	4/1,588 (0.3)
<b>Electrolytes</b>			
Sodium	<125 mEq/L	6/1,285 (0.5)	12/1,579 (0.8)
	>154 mEq/L	11/1,285 (0.9)	13/1,579 (0.8)
Potassium	<3 mEq/L	6/1,285 (0.5)	10/1,579 (0.6)
	>6 mEq/L	37/1,285 (2.9)	42/1,579 (0.6)
Chloride	<85 mEq/L	4/1,219 (0.3)	5/1,523 (0.3)
	>119 mEq/L	21/1,219 (1.7)	43/1,523 (2.8)
Bicarbonate	<18 mmol/L	8/1,817 (0.4)	240/1,014 (23.7)
	>36 mmol/L	3/817 (0.4)	3/1,014 (0.3)
<b>Other Chemistries</b>			
Uric Acid	<1.5 mg/dL	6/907 (0.7)	9/1,047 (0.9)
	>10.0 mg/dL	5/907 (0.6)	3/1,047 (0.3)
Calcium	<7.5 mg/dL	8/912 (0.9)	8/1,065 (0.8)
	>11.6 mg/dL	7/912 (0.8)	7/1,065 (0.7)
Triglycerides	<10 mg/dL	0/511 (0.0)	0/676 (0.0)
	>600 mg/dL	0/511 (0.0)	5/676 (0.7)
Glucose	<50 mg/dL	79/1,296 (6.1)	92/1,587 (5.9)
	>200 mg/dL	4/1,296 (0.3)	4/1,587 (0.3)
Phosphorus	<2.0 mg/dL	64/740 (8.6)	67/1,018 (6.6)
	>5.3 mg/dL	37/740 (5.0)	42/1,018 (4.1)

<sup>a</sup> Corresponds to the population presented in the RWJPRI response to the FDA Approvable Letter submitted June 27, 1996.

(Continued)

Note: Values represent (Number of subjects with markedly abnormal analyte value)/(Number of subjects with analyte data available). Percent of subjects with data available who have marked abnormality is given in parentheses.

KEY: Mo. = month; N = number; SGOT = serum glutamic oxaloacetic transaminase (AST); SGPT = serum glutamic pyruvic transaminase (ALT); GGTP = gamma- glutamyl transpeptidase; LDH = lactate dehydrogenase; BUN = blood urea nitrogen.

Cross-reference: Volume 4 of 23, page 08 00163, Table 42 of the RWJPRI response to the FDA Approvable Letter submitted June 27, 1996; Attachment 7 of this document.

**ECGs AND VITAL SIGNS**

The mean change in body weight from baseline to the final measurement (last weight recorded up to 30 days after the end of therapy) for 1,319 subjects ≥19 years of age is presented by dosage group and baseline body weight in Sponsor's Table 5. Reductions in body weight appeared to be related to mean topiramate dosage as well as to baseline weight.

<b>Sponsor's Table 5: Mean Change From Baseline Weight to Final Weight by Dosage Group and Baseline Weight</b>			
<b>Parameter</b>	<b>N</b>	<b>Mean Baseline (kg)</b>	<b>Mean (%) Change From Baseline (kg)</b>
<b>Topiramate Dosage Group<sup>b</sup> (mg/day)</b>			
<200	159	71.2	-1.6 (-2.2)
200-399	285	73.5	-2.8 (-3.7)
400-599	275	74.1	-3.1 (-4.1)
600-799	218	77.7	-4.2 (-5.0)
800-999	154	76.2	-4.5 (-5.5)
≥ 1,000	228	83.0	-6.5 (-7.3)
<b>Baseline Weight (kg)</b>			
>0-60	241	53.0	-1.3 (-2.5)
>60-80	595	70.3	-3.1 (-4.4)
>80-100	356	88.3	-4.5 (-5.0)
>100	127	111.9	-9.6 (-8.4)

Mean weight loss ranged from 1.6 kg (2.2% decline) in the lowest dosage group (average dosage <200 mg/day) to 6.5 kg (7.3% decline) in the highest dosage group (average dosage ≥1,000 mg/day). However as the sponsor notes, interpretation of the relationship between weight loss and dosage is difficult because average topiramate dosage tends to increase with duration of treatment. Changes in body weight varied with initial body weight; subjects who weighed the most (>100 kg) prior to topiramate therapy showed the greatest weight loss (mean decrease 9.6 kg or 8.4%), while those in the lowest (≤60 kg) baseline weight group showed the least weight loss (mean decrease of 1.3 kg or 2.5%). These results are consistent with those of similar analyses reported in the Four-Month Safety Update for 1,236 subjects who had weight recorded at baseline and the end of therapy.

Table 6 shows the change in body weight over time for all topiramate-treated

subjects  $\geq 19$  years of age regardless of total duration of topiramate therapy and for the subset of 143 subjects who remained on topiramate therapy for more than four years. The pattern of body weight change was generally similar in these two groups of subjects. Overall, weight loss was noted within the first three months of therapy and peaked at a mean of approximately six kilograms after approximately 12 to 18 months of therapy. The weight loss observed during topiramate therapy appears to be partially reversible with prolonged therapy. Thus, while mean body weight does decrease during the first 12 to 18 months of topiramate therapy, subjects who continue on topiramate therapy may tend to return toward their pretreatment weight after 18 months.

Duration of Topiramate Therapy (Months)	Any Therapy Duration <sup>a</sup>		Therapy Duration >4 Years <sup>b</sup>	
	N <sup>c</sup>	Mean Change (kg)	N <sup>c</sup>	Mean Change (kg)
>0≤1	799	-0.9	27	-0.5
>1-2	836	-1.6	28	-1.1
>2-3	793	-2.6	27	-1.6
>3-4	833	-3.1	54	-2.7
>4-5	744	-3.9	62	-3.8
>5-6	613	-4.1	38	-3.6
>6-9	626	-4.8	37	-4.7
>9-12	555	-5.2	37	-4.7
>12-15	456	-6.0	40	-6.4
>15-18	408	-5.8	47	-6.5
>18-24	411	-5.5	81	-6.1
>24-30	351	-5.0	110	-5.5
>30-36	300	-4.4	133	-4.9
>36-42	213	-4.2	138	-4.5
>42-48	164	-3.5	143	-3.7
>48-54	143	-3.5	143	-3.5
>54-60	126	-3.3	126	-3.3
>60-66	115	-2.9	115	-2.9
>66-72	90	-2.4	90	-2.4
>72	70	-1.2	70	-1.2

<sup>a</sup> Includes 1,319 subjects with weight recorded at baseline and up to 30 days after the end of topiramate therapy. Subjects <19 years of age are excluded.

<sup>b</sup> Represents a subset (N= 143) of the 1,319 subjects noted above.

<sup>c</sup> Represents all topiramate-treated subjects  $\geq 19$  years of age with weight recorded during the specified time interval; the last weight recorded in that interval is included.

## 8.6 SPECIAL STUDIES

### 8.6.1 HUMAN REPRODUCTION

One new pregnancy has been reported (7/31/1996) since the 4 month safety update. The outcome has not been determined.

### 8.6.2 RENAL CALCULI

The overall (cumulative topiramate-exposed) population was reviewed for onset of renal calculi through October 1, 1995 and followed through to June 30, 1996. The sponsor has provided annualized rates of occurrence below.

**Sponsor's Table 7:**  
Annualized Incidence Rates and Rates of  
Occurrence of Renal Calculi Over Time

Duration of Exposure <sup>a</sup>	Annualized Incidence Rate <sup>b</sup>	Annualized Rate of Occurrence <sup>c</sup>
0-1 yr	143/10,000	187/10,000
>1-2 yr	85/10,000	84/10,000
>2-3 yr	136/10,000	134/10,000
>3-4 yr	50/10,000	196/10,000
>4-5 yr	141/10,000	209/10,000

- a Beyond five years, the subject sample size was too small to make a valid estimate of the incidence rate of renal calculi.
- b Based on life table estimates of the first occurrence of a renal calculus for a subject.
- c Based on life table estimates of any occurrence of a renal calculus. Some subjects may have had more than one occurrence.

In the topiramate database there were 33 subjects who developed renal calculi. Of these, 27 were men and 6 were women. Sponsor's analyses of the covariates age, sex, mean topiramate dose, and duration of topiramated therapy showed sex to be the only covariate to be statistically associated with the risk of renal stones. This is consistent with the results previously described.

## 9.0 CONCLUSIONS

The sponsor's response to the Approvable letter, reclassification of adverse events and safety update have been reviewed. The sponsor's new appeals with regard to

The sponsor's new safety data have not produced any new concerns about the safety of this product. While the reassessment of neuropsychiatric adverse events did not fully meet the FDA's expectations based on previous discussions with the sponsor, the

response did provide sufficient clarification of adverse events necessary to develop adequate labeling.

**10.0 RECOMMENDATIONS**

This product should be approved as adjunctive therapy in patients with partial onset seizures. The recommended dose should be 400 mg/day.

*Cynthia McCormick MD*

Cynthia McCormick, MD  
Clinical Reviewer

November 18, 1996

## REVIEW AND EVALUATION OF CLINICAL DATA

<b>NDA</b>	#20-505
<b>Sponsor</b>	W Johnson Pharmaceutical Research Institute
<b>Brand Name (generic name)</b>	Topamax(topiramate)
<b>Indication</b>	Partial Onset Epilepsy
<b>NDA Classification</b>	IS
<b>Materials Received</b>	Study report and new labeling
<b>Original Receipt Date</b>	December 6, 1996
<b>Clinical Reviewer</b>	Cynthia G. McCormick, MD

### Background:

The Sponsor submitted a new study report to support a change in the labeling for Topamax (topiramate) that would justify a more conservative titration schedule. These materials along with the new proposed labeling were reviewed and are summarized in this brief addendum to the review of clinical data (response to approvable letter and final safety report) submitted in November 1996.

up DATE

The sponsor submitted data from a randomized multi center, double-blind, parallel design US trial which compared the safety profiles associated with two titration rates of Topamax--slow and rapid titration to a maximum dose of 400 mg/day in patients with partial onset seizures maintained on stable doses of either carbamazepine or phenytoin.

The group randomized to rapid titration received doses increasing from 50 mg/day to 400 mg/day over the course of 3 weeks. Their titration schedule is shown below.

<u>Days</u>	<u>Regimen</u>	<u>Total Daily Dose</u>
1-7	100 mg HS	100 mg
8-14	100 mg BID	200 mg
15-21	200 mg BID	400 mg

The group randomized to slow titration received doses increasing from 50 mg/day to 400 mg/day over the course of 8 weeks. Their titration schedule is shown below.

<u>Days</u>	<u>Regimen</u>	<u>Total Daily Dose</u>
1-7	50 mg HS	50 mg
8-14	50 mg BiD	100 mg
15-21	50 mg AM, 100 mg PM	150 mg
22-28	100 mg BID	200 mg
29-35	100 mg AM, 150 mg PM	250 mg
36-42	150 mg BID	300 mg
43-49	150 mg AM, 200 mg PM	350 mg
50-56	200 mg	400 mg

ent-emergent adverse events that were reported, particularly those which led to "study drug actions" (drug reduction, drug stopped temporarily, and drug discontinued) were collected. They were described by Kaplan-Meier estimates of cumulative incidence rates. The duration of the study included a two week baseline phase, titration schedule lasting up to 8 weeks and 4 weeks of treatment.

Patients could exit the study before completion if the investigator deemed the exit necessary or in the patient's best interest, or at the patient's request. Reasons for discontinuation included patient choice, death, loss to follow-up, adverse events, and other miscellaneous reasons not stated.

A total of 188 patients were enrolled from 16 centers and randomized to either the slow or the rapid titration group. Of these 93 were assigned to rapid titration and 95 were assigned to the slow titration group. The number of patients taking one and two antiepileptic drugs was approximately equivalent.

	Rapid Titration N=93	Slow Titration N=95
One AED	45 (48%)	44 (52%)
Two AEDs	48 (51%)	51 (49%)

The treatment groups were comparable in demographic considerations.

Results: Sponsor's table # summarizes the discontinuation information for the two groups. In the rapid titration group, the rate of discontinuation was 21/93 (22.6%) at any time during the study. In the slow titration group 16/95 (16.3%) withdrew during the study. If the withdrawal due to adverse events was separated from these rates, one could see that in the rapid titration group 17 (18.3%) of patients withdrew for adverse events, while only 10 (10.5%) in the slow titration group did so. Sponsor's Table 3 is attached to this review.

Sponsor's Table 7a (included) displays the subjects with adverse events leading to study drug action and lists those actions taken for each group. In the rapid titration group, 16% of patients had their medication reduced, and 18.28% had their medication stopped permanently, and 3.23% had a temporary cessation of treatment. In the slow titration group, 14.74% had medication reduced, 10.5% stopped permanently and no patients had their drug stopped permanently.

The Kaplan-Meier estimate of cumulative incidence rate of adverse events leading to study drug actions is significantly higher in the rapid titration group when compared to the slow titration group ( $p=0.048$ ). These results are shown in Sponsor's table 8a (included).

The adverse events leading to study drug action did not differ significantly from that which was expected, and between the two groups. Review of the sponsor's data and CRFs did not suggest any reason to doubt the conclusions.

Conclusion: While an exhaustive review of the data was not possible in the short time frame available for review, the data and analyses presented by the sponsor do support the sponsor's assertion that the slower titration rates are associated with fewer adverse events.

Recommendation: The sponsor's new labeling with regard to titration schedule for topiramate should be adopted.

*Cynthia McCormick, MD*  
Cynthia McCormick, MD  
Clinical Reviewer

December 6, 1996

Randomized, Double-Blind, Parallel-Design Multicenter Trial to Evaluate  
 Two Titration Rates of Oral Topamax (Topiramate) in Subjects with Epilepsy  
 Protocol TPS-TR  
 18141 Thursday, November 14, 1996

Table 3: Summary of Discontinuation of Double-Blind Study Drug  
 (All Randomized Subjects)

Reason for Discontinuation	Rapid Titration (N=93)		Slow Titration (N=95)	
	n	%	n	%
Adverse Event	17	18.28	10	10.53
Subject Choice	1	1.08	5	5.26
Other	3	3.23	6	6.08
Lost to Follow-Up	0	0.00	1	1.05
Total	21	22.58	16	16.84

Cross-reference: Tables 4a and 4b.

Note: Information on this table was derived from CRF page 37 which provides information regarding discontinuation of double blind drug.

Randomized, Double-Blind, Parallel-Design Multicenter Trial to Evaluate  
 Two Titration Rates of Oral Topamax (Topiramate) in Subjects with Epilepsy  
 Protocol TPS-TR  
 19:04 Thursday, November 14, 1996

Table 7a: Summary of Subjects with Adverse Events Leading to Double-Blind Drug  
 Stopped Permanently or Temporarily or Dosage Reduced  
 (All Randomized Subjects)

Action	Rapid Titration (N=93)		Slow Titration (N=96)	
	n	%	n	%
Reduced	16	16.13	14	14.74
Stopped Permanently	17	18.28	10	10.53
Stopped Temporarily	3	3.23	0	0
Total Subjects	36	37.63	24	25.26

Cross-reference: Table 13b.  
 The most severe action is counted for subjects with more than one action.

Table 0a: Kaplan-Meier Estimate of Cumulative Incidence Rate of Adverse Events  
 Leading to Study Drug Actions  
 (I.e.: Drug reduced, drug stopped temporarily or permanently)  
 (All Randomized Subjects)

Days on Drug // Rate at End of Period	Cumulative Failure Rate	
	Rapid Titration	Slow Titration
0-8	0.1507	0.1053
9-22	0.2709	0.1481
23-36	0.3158	0.230
37-57	0.3607	0.2239
58-85	0.3535	0.2572

P-value = 0.048