

Table 22: Subgroup Summary: Efficacy Variables by Baseline Seizure Rate^a
(All Randomized Subject; Protocols YTC and YTC-E)

Seizure Type/ Race	Number of Subjects		Median % Seizure Rate Reduction		Percent Responders ^b	
	PL	TPM	PL	TPM	PL	TPM
PGTC Seizures	41	31	29.1	63.9	29	61
<4 PGTC seizures	39	47	22.5	51.6	26	51
All Seizures	41	39	21.0	51.6	22	51
<17 seizures	40	40	-1.9	18.6	15	35

^a Rate per 28 days; monthly rate based on prospective seizure data.
^b Defined as ≥50% reduction in seizure rate relative to baseline.
 Key: PL = placebo; TPM = topiramate

Table 23: Subgroup Summary: Efficacy Variables by Region and Baseline PGTC Seizure Rate
(All Randomized Subject; Protocols YTC and YTC-E)

Region	Protocol YTC						Protocol YTC-E					
	No. of Subjects		Median % Seizure Rate Reduction		Percent Responder ^a		No. of Subjects		Median % Seizure Rate Reduction		Percent Responder ^a	
	PL	TPM	PL	TPM	PL	TPM	PL	TPM	PL	TPM	PL	TPM
United States	17	15	27.0	52.0	24	53	10	3	42.5	63.9	40	100
<4/month	23	24	8.7	58.7	17	58	5	13	32.7	35.2	40	38
Europe	--	--	--	--	--	--	14	13	29.4	69.8	29	62
<4/month	--	--	--	--	--	--	11	10	46.6	53.0	36	50

^a Defined as ≥50% reduction in seizure rate relative to baseline.

Table 24: Subgroup Summary: Efficacy Variables by Background AED
(All Randomized Subject; Protocols YTC and YTC-E)

Seizure Type/ Background AED	Number of Subjects		Median % Seizure Rate Reduction		Percent Responders ^a	
	PLA	TPM	PLA	TPM	PLA	TPM
PGTC Seizures	43	41	22.5	51.6	26	54
Valproic acid and combinations	37	37	31.4	60.7	30	57
Other AEDs and combinations	19	16	32.7	83.0	21	78
One AED	44	41	34.4	57.1	39	54
Two AEDs	17	19	-35.7	39.7	6	37
Three or more AEDs	43	41	3.1	37.6	16	41
Valproic acid and combinations	38	38	12.4	34.4	21	45
Other AEDs and combinations	20	18	11.5	73.7	15	67
One AED	44	42	22.5	33.5	27	43
Two AEDs	17	19	-22.3	5.2	0	21

^a Defined as ≥50% reduction in seizure rate relative to baseline.
 Key: PLA = placebo; TPM = topiramate.

Table 31a: Percent Seizure Rate Reduction and Treatment Responders
by Sex and Plasma Topiramate Concentration Stratum
in Protocols YTC and YTC-E Combined
(All Subjects With Plasma Samples During Stabilization)

Seizure Type Plasma Topiramate Stratum	N	Median Percent Reduction	No. Responders	%
PGTC Seizures	10	16.5	3	30
Female	13	68.5	9	69
<5.13 µg/mL	11	44.8	5	45
5.13 to <8.53 µg/mL	6	34.9	3	50
>8.53 µg/mL	14	65.3	9	64
Male	12	44.0	5	42
<5.02 µg/mL	7	8.9	3	43
5.02 to <8.46 µg/mL	14	60.0	8	57
>8.46 µg/mL	12	50.2	6	50
All Seizures	10	2.9	2	20
Female	13	52.0	8	62
<5.13 µg/mL	11	51.5	6	55
5.13 to <8.53 µg/mL	7	8.9	3	43
>8.53 µg/mL	14	60.0	8	57
Male	12	50.2	6	50

Table 31b: Percent Seizure Rate Reduction and Treatment Responders
by Age and Plasma Topiramate Concentration Stratum
in Protocols YTC and YTC-E Combined
(All Subjects With Plasma Samples During Stabilization)

Seizure Type Plasma Topiramate Stratum	N	Median Percent Reduction	No. Responders	%
PGTC Seizures	4	-5.5	1	25
≤16 years	6	46.4	3	50
<4.09 µg/mL	5	68.5	3	60
4.09 to <8.41 µg/mL	17	46.7	8	47
>8.41 µg/mL	16	83.2	11	69
>16 years	18	44.7	8	44
<5.04 µg/mL	4	-6.9	0	0
5.04 to <8.61 µg/mL	6	37.6	3	50
>8.61 µg/mL	5	54.0	3	60
All Seizures	18	35.3	8	44
≤16 years	16	66.0	9	56
<4.09 µg/mL	18	51.5	10	56
4.09 to <8.41 µg/mL	18	35.3	8	44
>8.41 µg/mL	16	66.0	9	56
>16 years	18	51.5	10	56
<5.04 µg/mL	18	35.3	8	44
5.04 to <8.61 µg/mL	16	66.0	9	56
>8.61 µg/mL	18	51.5	10	56

BEST POSSIBLE COPY

Figure 4: Cumulative Response Rates Based on PGTC Seizures (All Randomized Subjects With PGTC Seizures; Protocols YTC and YTC-E)

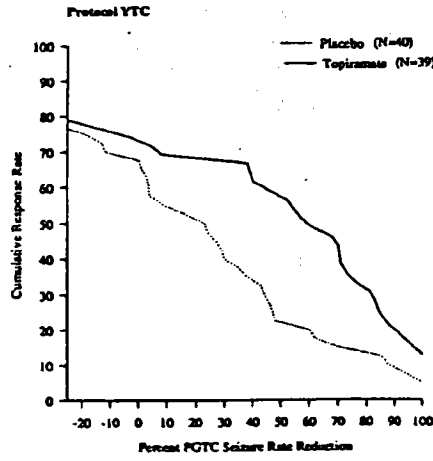
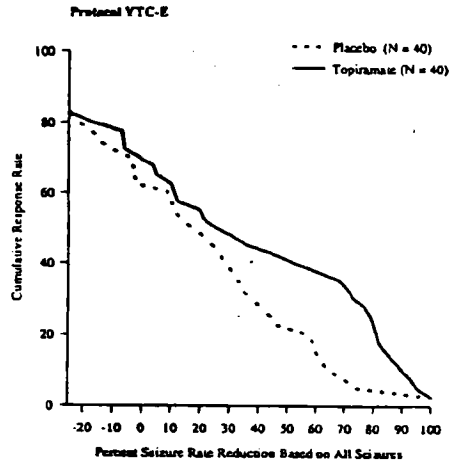
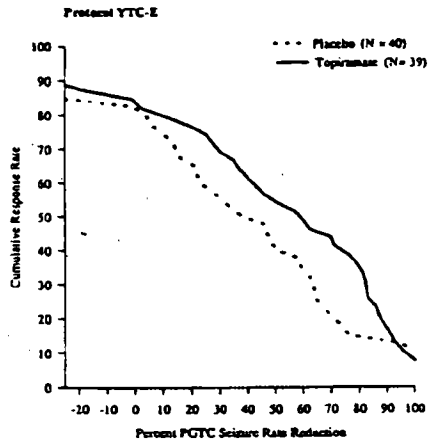
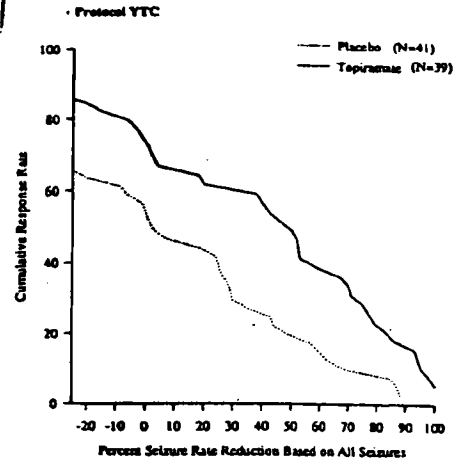
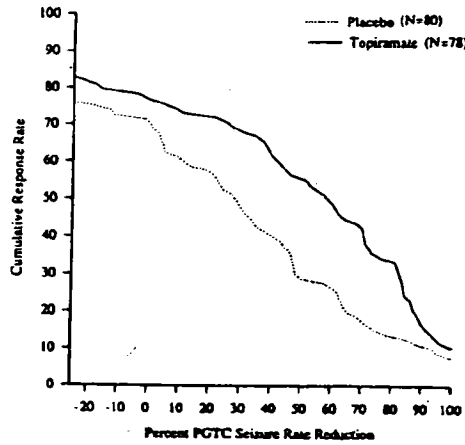


Figure 5: Cumulative Response Rate Based on All Seizures (All Randomized Subjects; Protocols YTC and YTC-E)

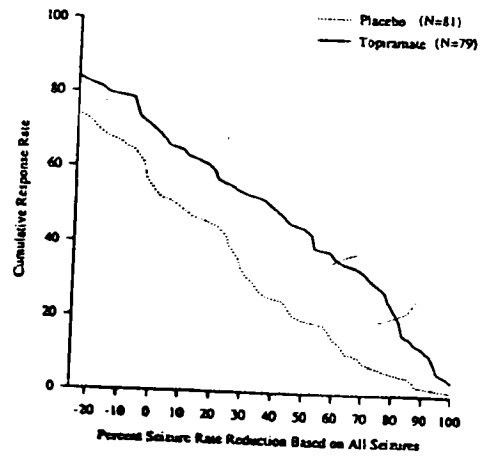


APPEARS THIS WAY ON ORIGINAL

Protocols YTC/YTC-E Combined



Protocols YTC/YTC-E Combined



BEST POSSIBLE COPY

APPEARS THIS WAY ON ORIGINAL

20 MARCH 1998 SUBMISSION

BEST POSSIBLE COPY

**Table 2: Incidence of Neuropsychiatric Adverse Events*
Comparison Between Adults and Children
% Subjects**

Adverse Event (Preferred Term)	Double-Blind				Total TPM: Double-Blind + Open-Label			
	Adults*		Children		Adults ^b		Children	
	Placebo (N=216)	TPM ^c (N=527)	Placebo (N=101)	TPM (N=98)	Adults ^d (N=1,715)	Children (N=303)	Adults ^e (N=1,845)	Children (N=310)
Dizziness	15	31	2	4	29	6	28	7
Somnolence	10	28	16	26	33	37	33	41
Headache	28	27	11	6	31	16	31	20
Fatigue	13	26	5	16	31	22	30	25
Psychomotor Slowing	2	20	2	3	22	8	21	9
Nervousness	7	19	7	14	21	17	20	21
Paresthesia	5	18	0	1	22	5	21	6
Ataxia	7	16	2	6	17	9	15	9
Difficulty with Memory	3	14	0	5	18	6	18	6
Difficulty with Concentration/Attention	1	13	2	10	15	10	14	11
Confusion	4	13	3	4	15	6	15	7
Speech Disorders/Related Speech Problems	2	13	2	4	13	6	13	7
Depression	6	12	0	0	17	2	16	3
Nystagmus	9	12	1	0	9	<1	9	<1
Diplopia	6	11	0	1	11	2	10	3
Vision Abnormal	3	11	1	2	12	1	12	2
Anorexia	4	11	15	24	21	35	21	38
Language Problems	<1	9	1	1	11	5	11	5
Tremor	6	9	1	0	11	4	9	5
Anxiety	6	9	1	0	9	<1	9	<1
Mood Problems	2	8	7	7	8	10	8	11
Insomnia	5	6	7	8	12	13	12	15
Agitation	1	4	3	2	4	5	4	5
Emotional Lability	1	2	5	5	3	4	3	4
Cognitive Problems	<1	2	2	0	2	2	3	3
Aggressive Reaction	<1	3	4	9	4	9	5	10
Personality Disorder (Behavior Problems)	0	<1	9	11	3	8	3	11

* Dose-related in adult double-blind studies.
 † Includes the 25 clinically important neuropsychiatric adverse events identified in the adult population, plus two adverse events (aggressive reaction and personality disorder/behavior problems) with a difference between topiramate and placebo in the double-blind pediatric population; adverse events are listed in order of their frequency in the adult double-blind topiramate group.
 ‡ Based on reclassified Four-Month Safety Update database for NDA 20-505 as presented in RWJPR's Response to FDA's Approvable Letter (filed 27 June 1996).
 § Based on Final Safety Update for NDA 20-505 (filed 26 September 1996).
 ¶ The total topiramate-treated group of 1,715 subjects in the Final Safety Update to NDA 20-505 includes 88 children. The total topiramate-treated group as of the 4MSU includes all 1,715 subjects from the Final Safety Update.
 †† Includes all randomized dosage groups combined (200, 400, 600, 800, and 1,000 mg/day combined).

Age distribution in years - SNDA Pediatric subjects

AGE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
2	5	1.7	5	1.7
3	10	3.3	15	5.0
4	15	5.0	30	9.9
5	27	8.9	57	18.8
6	27	8.9	84	27.7
7	16	5.3	100	33.0
8	24	7.9	124	40.9
9	21	6.9	145	47.9
10	17	5.6	162	53.5
11	27	8.9	189	62.4
12	26	8.6	215	71.0
13	10	3.3	225	74.3
14	26	8.6	251	82.8
15	31	10.2	282	93.1
16	21	6.9	303	100.0

Age distribution in years - 4 month safety update Pediatric subjects

AGE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
2	5	1.6	5	1.6
3	10	3.2	15	4.8
4	17	5.5	32	10.3
5	28	9.0	60	19.4
6	28	9.0	88	28.4
7	17	5.5	105	33.9
8	24	7.7	129	41.6
9	21	6.8	150	48.4
10	17	5.5	167	53.9
11	27	8.7	194	62.6
12	27	8.7	221	71.3
13	11	3.5	232	74.8
14	26	8.4	258	83.2
15	31	10.0	289	93.2
16	21	6.8	310	100.0

Appendix 2: Average and M¹ Daily Dosage and Duration of Treatment

	Double-Blind						Total TPM		
	Placebo			TPM			4MSU		
	Pediatrics (N=101)	Adults (N=75)	Adults (N=70)	Pediatrics (N=98)	Adults (N=70)	Adults (N=105)	Pediatrics (N=303)	Adults (N=310)	Adults (N=132)
Average Daily Dosage* (mg/kg/day)									
Double-Blind Phase									
N	101	75	98	70	70	105	308*	132	
Mean (SD)	5.0 (0.95)	3.6 (1.42)	4.9 (1.23)	3.4 (1.33)	-	-	-	-	-
Median	5.2	3.7	4.9	3.5	-	-	-	-	-
Range	1.4-7.3	0.5-6.7	1.1-10.7	0.6-6.3	-	-	-	-	-
Stabilization Period									
N	99*	70*	97*	68*	300*	105	308*	132	
Mean (SD)	6.2 (1.09)	5.0 (1.59)	6.0 (1.69)	4.6 (1.61)	8.1 (4.51)	5.2 (2.95)	9.5 (5.24)	6.0 (3.42)	
Median	6.0	5.2	6.0	4.9	7.1	4.4	8.6	5.5	
Range	2.3-9.1	0.9-9.0	0.9-14.0*	0.8-8.5*	1.3-32.9	0.6-16.3	1.3-32.9	0.6-19.9	
Maximum Daily Dosage* (mg/kg/day)									
Double-Blind Phase									
N	101	75	98	70	70	105	308*	132	
Mean (SD)	6.3 (1.28)	5.1 (1.74)	6.3 (1.58)	5.0 (2.09)	-	-	-	-	-
Median	6.0	5.3	6.0	5.1	-	-	-	-	-
Range	1.4-10.0	0.5-9.1	2.3-14.2*	0.6-14.1*	-	-	-	-	-
Stabilization Period									
N	99*	70*	97*	68*	300*	105	308*	132	
Mean (SD)	6.3 (1.10)	5.3 (1.51)	6.2 (1.70)	5.1 (1.98)	12.0 (7.62)	7.8 (50.0)	14.0 (8.74)	8.7 (5.24)	
Median	6.0	5.4	6.0	5.2	9.6	6.2	11.4	7.3	
Range	3.6-10.0	1.5-9.1	0.9-14.2*	0.8-14.1*	1.3-45.9	0.6-26.6	1.3-55.3	0.6-27.7	
Duration of Therapy (days)									
N	101	75	98	70	303	105	310	132	
Mean (SD)	106.1 (29.59)	124.4 (38.51)	107.0 (26.27)	127.6 (35.41)	376.7 (310.42)	264.6 (205.31)	540.6 (364.15)	450.7 (280.58)	
Median	112.0	140.0	112.0	141.0	271.0	174.0	470.0	437.5	
Range	14-176	1-176	48-169	24-197	4-1340	17-970	22-1616	14-1057	

* Double-blind phase and stabilization period refers to double-blind data only. Data for total TPM group is based on the average or maximum daily dosage for the entire period of topiramate exposure in double-blind and open-label studies.

† Subjects who were missing a baseline weight measurement were not included in the calculation of average and maximum daily dosages.

‡ Five subjects in Protocol YTCE (14, 24, 217, 222, and 257) received greater than the protocol-specified doses based on their weights.

Appendix 3: Distribution of Subjects by Duration of Treatment

	Double-Blind						Total Topiramate									
	Placebo			Topiramate			sNDA			4MSU						
	Pediatrics (N=101)	Adults (N=75)	Adults (N=70)	Pediatrics (N=98)	Adults (N=70)	Adults (N=105)	Pediatrics (N=303)	Adults (N=105)	Adults (N=310)	Pediatrics (N=310)	Adults (N=132)					
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)				
0-90 days	43	(42.6)	16	(21.3)	38	(38.8)	16	(22.9)	49	(16.2)	18	(17.1)	25	(8.1)	12	(9.1)
91-180 days	58	(57.4)	59	(78.7)	60	(61.2)	52	(74.3)	57	(18.8)	36	(34.3)	32	(10.3)	18	(13.6)
181-270 days	0	0	0	0	0	(2.9)	2	(2.9)	45	(14.9)	13	(12.4)	18	(5.8)	15	(11.4)
271-365 days	0	0	0	0	0	0	0	0	34	(11.2)	9	(8.6)	38	(12.3)	15	(11.4)
1-2 years	0	0	0	0	0	0	0	0	75	(24.8)	24	(22.9)	112	(36.1)	46	(34.9)
2-3 years	0	0	0	0	0	0	0	0	33	(10.9)	5	(4.8)	59	(19.0)	26	(19.7)
3-4 years	0	0	0	0	0	0	0	0	10	(3.3)	0	0	19	(6.2)	0	0
4-5 years	0	0	0	0	0	0	0	0	0	0	0	0	7	(2.3)	0	0
Total	101	(100.0)	75	(100.0)	98	(100.0)	70	(100.0)	303	(100.0)	105	(100.0)	310	(100.0)	132	(100.0)

BEST POSSIBLE COPY

Table : Incidence of Treatment Emergent Adverse Events

APPENDIX 42

Supplemental NDA

	Double Blind Studies						4 Month Safety Update					
	Placebo		Topiramate		Total Topiramate		Placebo		Topiramate		Total Topiramate	
	Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)
APPLICATION SITE DISORDERS	2 (2.0)	-	-	-	3 (1.0)	-	5 (1.6)	3 (2.3)	-	-	-	
CELLULITIS	-	-	-	-	-	-	-	-	-	-	-	
INJECTION SITE INFLAMMATION	-	-	-	-	-	-	-	-	-	-	-	
INJECTION SITE REACTION	-	-	-	-	-	-	-	-	-	-	-	
OTITIS EXTERNA	-	-	-	-	-	-	-	-	-	-	-	
SKIN NODULE	-	-	-	-	-	-	-	-	-	-	-	
AUTONOMIC NERVOUS SYSTEM DISORDERS	-	-	-	-	-	-	-	-	-	-	-	
VASODILATION	-	-	-	-	-	-	-	-	-	-	-	
BODY AS A WHOLE - GENERAL DISORDERS	44 (43.6)	34 (45.3)	51 (52.0)	31 (44.3)	180 (59.4)	54 (51.4)	213 (68.7)	81 (61.4)	-	-	-	
ABDOMEN ENLARGED	-	-	-	-	-	-	-	-	-	-	-	
ALLERGIC REACTION	1 (1.0)	1 (1.3)	2 (2.0)	1 (1.4)	2 (0.7)	1 (1.0)	2 (0.6)	1 (0.8)	-	-	-	
ALLERGY	-	3 (4.0)	-	-	3 (1.0)	-	3 (1.0)	3 (2.3)	-	-	-	
ASTHMA	1 (1.0)	-	2 (2.0)	2 (2.9)	2 (0.7)	3 (2.9)	2 (0.6)	2 (1.5)	-	-	-	
BACK PAIN	-	3 (4.0)	1 (1.0)	3 (4.3)	2 (0.7)	6 (5.7)	3 (1.0)	3 (2.3)	-	-	-	
CHEST PAIN	-	4 (5.3)	-	2 (2.9)	2 (0.7)	4 (3.8)	2 (0.6)	6 (4.5)	-	-	-	
CONDITION AGGRAVATED	1 (1.0)	1 (1.3)	1 (1.0)	1 (1.4)	4 (1.3)	4 (3.8)	4 (1.3)	4 (3.0)	-	-	-	
DRUG LEVEL INCREASED	-	-	-	-	-	-	-	-	-	-	-	
BODY AS A WHOLE - GENERAL DISORDERS (Continued)	44 (43.6)	34 (45.3)	51 (52.0)	31 (44.3)	180 (59.4)	54 (51.4)	213 (68.7)	81 (61.4)	-	-	-	
FATIGUE	5 (5.0)	10 (13.3)	16 (16.3)	14 (20.0)	67 (22.1)	18 (17.1)	77 (24.8)	24 (18.2)	-	-	-	
FEVER	26 (23.7)	4 (5.3)	24 (24.5)	3 (4.3)	65 (21.5)	9 (8.6)	87 (28.1)	12 (9.1)	-	-	-	
HOT FLUSHES	1 (1.0)	-	-	-	1 (0.3)	-	1 (0.3)	-	-	-	-	
HYPOTHERMIA	-	-	-	-	-	-	-	-	-	-	-	
INFLUENZA-LIKE SYMPTOMS	12 (11.9)	11 (14.7)	7 (7.1)	2 (2.9)	34 (11.2)	8 (7.6)	44 (14.2)	15 (11.4)	-	-	-	
INJURY	13 (12.9)	-	14 (14.3)	6 (8.6)	72 (23.8)	21 (20.0)	87 (28.1)	34 (25.8)	-	-	-	
LEG PAIN	-	-	-	-	4 (1.3)	-	4 (1.3)	4 (3.0)	-	-	-	
MALJAISE	2 (2.0)	-	2 (2.0)	1 (1.4)	8 (2.6)	1 (1.0)	11 (3.5)	4 (3.0)	-	-	-	
OEDEMA	1 (1.0)	2 (2.7)	2 (2.0)	1 (1.4)	7 (2.3)	1 (1.0)	8 (2.6)	2 (1.5)	-	-	-	
OEDEMA GENITAL	-	-	-	-	-	-	-	-	-	-	-	
OEDEMA PERIPHERAL	-	-	-	-	-	-	-	-	-	-	-	
PAIN	2 (2.0)	1 (1.3)	2 (2.0)	3 (4.3)	19 (6.3)	11 (10.5)	30 (9.7)	2 (1.5)	-	-	-	
PALLOR	-	-	1 (1.0)	-	4 (1.3)	2 (1.9)	5 (1.6)	2 (1.5)	-	-	-	
RITORS	-	-	-	-	-	-	-	-	-	-	-	
SUDDEN DEATH*	-	-	-	-	-	-	-	-	-	-	-	
THERAPEUTIC RESPONSE INCREASED	-	-	-	-	-	-	-	-	-	-	-	
TOLERANCE DECREASED	-	-	-	-	-	-	-	-	-	-	-	

* Sudden death in a pediatric subject (Subject 49 in Protocol YL extension) was coded as cardiac arrest in the clinical study database.

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

Supplemental NDA

4 Month Safety Update

	Double Blind Studies						Total Topiramate						
	Placebo			Topiramate			Total Topiramate			Total Topiramate			
	Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)					
CARDIOVASCULAR DISORDERS, GENERAL													
CYANOSIS	-	-	1 (1.0)	1 (1.4)	5 (1.7)	2 (1.9)	8 (2.6)	3 (2.3)					
ECG ABNORMAL	-	-	-	-	1 (0.3)	-	1 (0.3)	-					
HEART DISORDER	-	-	-	-	1 (0.3)	-	4 (1.3)	1 (0.8)					
HEART VALVE DISORDERS	-	-	-	-	-	1 (1.0)	1 (0.3)	1 (0.8)					
HYPERTENSION	-	-	1 (1.0)	1 (1.4)	1 (0.3)	-	1 (0.3)	-					
OEDEMA DEPENDENT	-	-	-	-	1 (0.3)	1 (1.0)	1 (0.3)	1 (0.8)					
CENTR & PERIPH NERV SYST DISORDERS	28 (27.7)	33 (44.0)	36 (36.7)	39 (55.7)	154 (50.8)	63 (60.0)	182 (58.7)	90 (68.2)					
ABSCENCES	2 (2.0)	4 (5.3)	6 (6.1)	5 (7.1)	26 (8.6)	10 (9.5)	28 (9.0)	1 (0.8)					
ATAXIA	-	1 (1.3)	-	-	3 (1.0)	-	4 (1.3)	16 (12.1)					
AUTOPTISM	-	-	-	-	-	-	2 (0.6)	1 (0.8)					
CONVULSIONS	3 (3.0)	6 (8.0)	3 (3.1)	3 (4.3)	23 (7.6)	4 (3.8)	30 (9.7)	9 (6.8)					
CONVULSIONS AGGRAVATED	-	-	1 (1.0)	1 (1.4)	6 (2.0)	2 (1.9)	11 (3.5)	3 (2.3)					
CONVULSIONS GRAND MAL	3 (3.0)	1 (1.3)	1 (1.0)	1 (1.4)	10 (3.3)	4 (3.8)	12 (3.9)	4 (3.0)					
COORDINATION ABNORMAL	-	-	-	-	-	1 (1.0)	-	1 (0.8)					
CRAMPS LEGS	2 (2.0)	11 (14.7)	4 (4.1)	13 (18.6)	19 (6.3)	17 (16.2)	22 (7.1)	21 (15.9)					
DIZZINESS	-	1 (1.3)	-	-	1 (0.3)	-	1 (0.3)	-					
DYSKINESIA	-	-	-	-	3 (1.0)	-	3 (1.0)	-					
DYSTONIA	-	-	-	-	1 (0.3)	-	1 (0.3)	-					
EEG ABNORMAL	-	-	-	-	-	-	-	-					
CENTR & PERIPH NERV SYST DISORDERS	78 (27.7)	33 (44.0)	36 (36.7)	39 (55.7)	154 (50.8)	63 (60.0)	182 (58.7)	90 (68.2)					
(Continued)													
ENCEPHALOPATHY	-	-	1 (1.0)	-	2 (0.7)	-	2 (0.6)	-					
FAECAL INCONTINENCE	-	-	8 (8.2)	3 (4.3)	24 (7.9)	8 (7.6)	31 (10.0)	11 (8.3)					
GAIT ABNORMAL	5 (5.0)	1 (1.3)	6 (6.1)	15 (21.4)	48 (15.8)	25 (23.8)	61 (19.7)	40 (30.3)					
HEADACHE	11 (10.9)	16 (21.3)	-	-	1 (0.3)	-	1 (0.3)	-					
HEMIPLEGIA	4 (4.0)	2 (2.7)	5 (5.1)	-	15 (5.0)	2 (1.9)	18 (5.8)	3 (2.3)					
HYPERTONIA	-	-	-	1 (1.4)	2 (0.7)	-	2 (0.6)	5 (3.8)					
HYPERTONIA	-	-	-	-	3 (1.0)	-	4 (1.3)	-					
HYPERTONIA	-	-	2 (2.0)	-	3 (1.0)	-	5 (1.6)	-					
HYPERTONIA	-	-	-	-	3 (1.0)	-	17 (5.5)	12 (9.1)					
HYPERTONIA	-	-	-	-	16 (5.3)	5 (4.8)	1 (0.3)	-					
HYPERTONIA	1 (1.0)	2 (2.7)	1 (1.0)	4 (5.7)	1 (0.3)	-	5 (1.6)	7 (5.3)					
LANGUAGE PROBLEMS	-	-	-	2 (2.9)	5 (1.7)	5 (4.8)	2 (0.6)	3 (2.3)					
MIGRAINE	-	-	-	1 (1.4)	2 (0.7)	2 (1.9)	2 (0.6)	-					
MUSCLE CONTRACTIONS INVOLUNTARY	1 (1.0)	-	-	-	1 (0.3)	-	1 (0.3)	-					
NYSTAGMUS	-	-	-	3 (4.3)	15 (5.0)	7 (6.7)	19 (6.1)	11 (8.3)					
OEDEMA CEREBRAL	-	1 (1.3)	1 (1.0)	-	-	-	1 (0.3)	1 (0.8)					
PARALYSIS	-	-	-	-	1 (0.3)	-	2 (0.6)	-					
PARALYSIS	-	-	-	-	1 (0.3)	-	1 (0.3)	1 (0.8)					
PARESIS	-	-	-	-	19 (6.3)	7 (6.7)	21 (6.8)	11 (8.3)					
SENSORY DISTURBANCE	-	1 (1.3)	4 (4.1)	5 (7.1)	19 (6.3)	7 (6.7)	21 (6.8)	5 (3.8)					
SPEECH DISORDERS/RELATED SPEECH PROBLEMS	2 (2.0)	-	-	2 (2.9)	-	3 (2.9)	-	-					
STUPOR	-	-	-	-	-	-	-	-					

BEST POSSIBLE COPY

Table . incidence of Treatment Emergent Adverse Events

Supplemental NDA

Double Blind Studies

4 Month Safety Update

	Placebo				Topiramate				Total Topiramate				Total Topiramate			
	Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)		
CENTR & PERIPH NERV SYST DISORDERS (Continued)	28(27.7)	33(44.0)	36(36.7)	39(55.7)	134(50.8)	63(60.0)	182(58.7)	90(68.2)								
TREMOR	1(1.0)	5(6.7)	-	4(5.7)	13(4.3)	8(7.6)	16(5.2)	17(12.9)								
VERTIGO	-	1(1.3)	-	1(1.4)	-	1(1.0)	1(0.3)	2(1.5)								
VISUAL FIELD DEFECT	-	-	-	1(1.4)	1(0.3)	1(1.0)	1(0.3)	1(0.8)								
ENDOCRINE DISORDERS	-	1(1.3)	-	-	2(0.7)	-	2(0.6)	2(1.5)								
GLUCOCORTICOIDS INCREASED	-	-	-	-	-	-	-	-								
HYPOTHYROIDISM	-	1(1.3)	-	-	2(0.7)	-	2(0.6)	1(0.8)								
PUBERTY PRECOCIOUS	-	-	-	-	-	-	-	-								
FOETAL DISORDERS	-	-	-	-	-	-	1(0.3)	-								
NAEVUS	-	-	-	-	-	-	-	1(0.3)								
GASTRO-INTESTINAL SYSTEM DISORDERS	51(50.5)	20(26.7)	39(39.8)	20(28.6)	150(49.5)	41(39.0)	188(60.6)	67(50.8)								
ABDOMINAL PAIN	6(5.9)	3(4.0)	4(4.1)	5(7.1)	19(6.3)	8(7.6)	27(8.7)	14(10.6)								
CONSTIPATION	4(4.0)	2(2.7)	5(5.1)	1(1.4)	25(8.3)	7(6.7)	35(11.3)	8(6.1)								
DIARRHOEA	26(25.7)	2(2.7)	9(9.2)	6(8.6)	45(14.9)	14(13.3)	68(21.9)	19(14.4)								
DYSPEPSIA	3(3.0)	4(5.3)	1(1.0)	4(5.7)	11(3.6)	8(7.6)	15(4.8)	11(8.3)								
FAECES DISCOLOURED	-	-	1(1.0)	-	2(0.7)	-	5(1.6)	1(0.8)								
FLATULENCE	-	-	-	-	1(0.3)	2(1.9)	1(0.6)	2(1.5)								
GASTRITIS	-	-	1(1.0)	-	1(0.3)	1(1.0)	2(0.6)	2(1.5)								
GASTRO-INTESTINAL DISORDER NOS	1(1.0)	1(1.3)	-	2(2.9)	8(2.6)	2(1.9)	11(3.5)	2(1.5)								
GASTROENTERITIS	2(2.0)	-	3(3.1)	2(2.9)	10(3.3)	3(2.9)	16(5.2)	6(4.5)								
GASTROESOPHAGEAL REFLUX	-	1(1.3)	1(1.0)	-	3(1.0)	1(1.0)	6(1.9)	1(0.8)								
GINGIVITIS	-	1(1.3)	1(1.0)	-	3(1.0)	1(1.0)	4(1.3)	-								
GLOSSITIS	-	1(1.3)	1(1.0)	-	1(0.3)	1(1.0)	1(0.3)	-								
GUM HYPERPLASIA	-	1(1.3)	1(1.0)	-	5(1.7)	1(1.0)	6(1.9)	2(1.5)								
HAEMATEMESIS	-	-	-	-	-	-	-	-								
HICCUP	-	-	-	-	4(1.3)	-	4(1.3)	1(0.8)								
INTESTINAL OBSTRUCTION	-	-	-	-	-	-	-	-								
INTESTINAL PERFORATION	-	-	-	-	-	-	-	-								
MELAENA	-	1(1.3)	-	-	2(0.7)	-	2(0.6)	1(0.8)								
NAUSEA	5(5.0)	8(10.7)	6(6.1)	5(7.1)	20(6.6)	10(9.5)	25(8.1)	21(15.9)								
OESOPHAGEAL STRICTURE	-	-	-	-	-	-	1(0.3)	-								
OESOPHAGEAL ULCERATION	-	-	-	-	-	-	1(0.3)	-								

Supplemental NDA

4 Month Safety Update

Double Blind Studies

Total Topiramate

Total Topiramate

BEST POSSIBLE COPY

	Placebo				Topiramate				Total Topiramate			
	Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)				
51(50.5)	20(26.7)	39(39.8)	20(28.6)	41(39.0)	150(49.5)	41(39.0)	188(60.6)	67(50.8)				
GASTRO-INTESTINAL SYSTEM DISORDERS (Continued)												
CEPHALGIA	-	-	-	-	-	1(1.0)	1(0.3)	1(0.8)				
PANCREATITIS	-	-	-	-	-	1(1.0)	-	1(0.8)				
PERIODONTAL DESTRUCTION	-	-	-	-	-	-	-	1(0.8)				
SALIVA INCREASED	4(4.0)	1(1.3)	6(6.1)	-	28(9.2)	-	33(10.6)	2(1.5)				
STOMATITIS	-	-	-	-	-	-	1(0.3)	-				
STOMATITIS APHTHOUS	-	-	-	-	-	-	1(0.3)	-				
STOMATITIS ULCERATIVE	3(3.0)	1(1.3)	-	-	2(0.7)	-	2(0.6)	1(0.8)				
TEETH-GRINDING	-	-	-	-	-	-	4(1.3)	-				
TONGUE DISCOLOURATION	-	-	-	-	-	-	-	1(0.8)				
TONGUE DISORDER	-	-	-	-	-	-	1(0.3)	-				
TOOTH ACHE	-	-	-	-	3(1.0)	-	7(2.3)	1(0.8)				
TOOTH CARIES	-	-	-	-	1(0.3)	1(1.0)	1(0.3)	-				
TOOTH DISORDER	1(1.0)	1(1.3)	1(1.0)	-	6(2.0)	3(2.9)	11(3.5)	4(3.0)				
VOMITING	23(22.8)	6(8.0)	11(11.2)	3(4.3)	50(16.5)	8(7.6)	63(20.3)	15(11.4)				

	Peds N = 101 No (%)		Adult N = 75 No (%)		Peds N = 303 No (%)		Adult N = 105 No (%)		Peds N = 310 No (%)		Adult N = 132 No (%)	
	HEARING AND VESTIBULAR DISORDERS	1(1.0)	3(4.0)	-	-	1(1.4)	13(4.3)	3(2.9)	12(3.9)	7(5.3)	-	-
EAR DISORDER NOS	-	-	-	-	-	10(3.3)	-	-	8(2.6)	-	-	
EARACHE	1(1.0)	2(2.7)	-	-	1(0.3)	1(0.3)	-	-	2(0.6)	-	4(3.0)	
HEARING DECREASED	-	-	-	-	1(0.3)	1(0.3)	1(1.0)	1(0.3)	1(0.3)	-	1(0.8)	
TINNITUS	-	1(1.3)	-	-	1(0.3)	1(0.3)	2(1.9)	1(0.3)	1(0.3)	-	2(1.5)	
HEART RATE AND RHYTHM DISORDERS	-	-	1(1.0)	1(1.4)	3(1.0)	3(1.0)	1(1.0)	1(1.0)	5(1.6)	-	2(1.5)	
BRADYCARDIA	-	-	1(1.0)	-	1(0.3)	-	-	-	1(0.3)	-	-	
CARDIAC ARREST a	-	-	-	-	-	-	-	-	1(0.3)	-	-	
FIBRILLATION ATRIAL	-	-	-	1(1.4)	-	-	1(1.0)	-	-	-	1(0.8)	
PALPITATION	-	-	-	-	2(0.7)	-	-	-	2(0.6)	-	1(0.8)	
TACHYCARDIA	-	-	-	-	-	-	-	-	1(0.3)	-	1(0.8)	
LIVER AND BILIARY SYSTEM DISORDERS	1(1.0)	1(1.3)	-	-	2(0.7)	2(0.7)	1(1.0)	1(1.0)	5(1.6)	-	4(3.0)	
BILIRUBINEMIA	-	-	-	-	1(0.3)	1(0.3)	-	-	1(0.3)	-	3(2.3)	
CHOLELITHIASIS	-	1(1.3)	-	-	-	-	1(1.0)	-	1(0.3)	-	1(0.8)	
GAMMA-GT INCREASED	-	-	-	-	1(0.3)	-	-	-	2(0.6)	-	-	
HEPATIC FUNCTION ABNORMAL	-	-	-	-	1(0.3)	-	-	-	2(0.6)	-	-	
HEPATITIS	-	-	-	-	-	-	-	-	-	-	-	

BEST POSSIBLE COPY

Table : Incidence of Treatment Emergent Adverse Events

		Supplemental NDA				4 Month Safety Update			
		Double Blind Studies				Total Topiramate			
		Placebo		Topiramate		Total Topiramate		Total Topiramate	
		Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)
LIVER AND BILIARY SYSTEM DISORDERS (Continued)									
HEPATOCELLULAR DAMAGE									
HEPATOMEGALY			1 (1.3)						
JAUNDICE						1 (0.3)		1 (0.3)	
SGOT INCREASED		1 (1.0)				1 (0.3)		1 (0.3)	
SGPT INCREASED		1 (1.0)							
METABOLIC AND NUTRITIONAL DISORDERS									
ACIDOSIS				11 (11.2)	10 (14.3)	48 (15.8)	19 (18.1)	69 (22.3)	32 (24.2)
ACIDOSIS LACTIC						1 (0.3)		1 (0.3)	
CACHEXIA									
CREATINE PHOSPHOKINASE INCREASED						1 (0.3)		1 (0.3)	
DEHYDRATION					1 (1.4)	7 (2.3)	1 (1.0)	15 (4.8)	1 (0.8)
HYPERCHOLESTEROLAEMIA									1 (0.8)
HYPERGLYCAEMIA									1 (0.8)
HYPERLIPAEMIA									1 (0.8)
HYPERTRIGLYCERIDAEMIA									1 (0.8)
HYPOCALCAEMIA						1 (0.3)		2 (0.6)	1 (0.8)
HYPOGLYCAEMIA				1 (1.0)		2 (0.7)		1 (0.3)	
HYPOKALAEMIA									
HYPOVITAMINOSIS									
LACTOSE INTOLERANCE									
NPV INCREASED									
OEDEMA PERIORBITAL					1 (1.4)		1 (1.0)	1 (0.3)	1 (0.8)
OSTEOALGIA						2 (0.7)		2 (0.6)	
PHOSPHATASE ALKALINE INCREASED									
SERUM IRON DECREASED									
SERUM IRON INCREASED					1 (1.4)		1 (1.0)	1 (0.3)	1 (0.8)
THIRST									
WEIGHT DECREASE		1 (1.0)	1 (1.3)	2 (2.0)		4 (1.3)	1 (1.0)	4 (1.3)	1 (0.8)
WEIGHT INCREASE		1 (1.0)	3 (4.0)	9 (9.2)	9 (12.9)	28 (9.2)	15 (14.3)	34 (11.0)	25 (18.9)
				1 (1.0)		7 (2.3)	2 (1.9)	9 (2.9)	3 (2.3)
MUSCULO-SKELETAL SYSTEM DISORDERS									
ARTHRALGIA				1 (1.0)	4 (5.7)	15 (5.0)	9 (8.6)	17 (5.5)	11 (8.3)
ARTHRITIS									
BONE DEVELOPMENT ABNORMAL			3 (4.0)			2 (0.7)		1 (0.3)	2 (1.5)
BONE DISORDER						3 (1.0)	2 (1.9)	3 (1.0)	2 (1.5)
FRACTURE PATHOLOGICAL			1 (1.3)		1 (1.4)	1 (0.3)	1 (1.0)	3 (1.0)	1 (0.8)
MUSCLE WEAKNESS									
MYALGIA		1 (1.0)	1 (1.3)	1 (1.0)		5 (1.7)	1 (1.0)	5 (1.6)	2 (1.5)
MYOPATHY					1 (1.4)	1 (0.3)	3 (2.9)	2 (0.6)	4 (3.0)

Table : Incidence of Treatment Emergent Adverse Events

Supplemental NDA

BEST POSSIBLE COPY

4 Month Safety Update

Double Blind Studies

	Placebo				Topiramate				Total Topiramate				Total Topiramate			
	Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)		
MUSCULO-SKELETAL SYSTEM DISORDERS (Continued)	1(1.0)	4(5.3)	1(1.0)	4(5.7)	15(5.0)	9(8.6)	17(5.5)	11(8.3)								
SKELETAL PAIN	-	-	-	2(2.9)	1(0.3)	2(1.9)	1(0.3)	2(1.5)								
SYNOVITIS	-	-	-	-	-	-	-	-								
NEONATAL AND INFANCY DISORDERS	-	-	-	-	-	-	-	1(0.8)								
PSYCHOMOTOR DEVELOPMENT IMPAIRED	-	-	-	-	-	-	-	-								
NEOPLASMS	-	1(1.3)	-	-	3(1.0)	2(1.9)	3(1.0)	2(1.5)								
BREAST FIBRODENSIS	-	-	-	-	-	1(1.0)	-	1(0.8)								
LIPOMA	-	-	-	-	1(0.3)	-	-	-								
NEOPLASM NOS	-	-	-	-	2(0.7)	-	-	2(0.6)								
OVARIAN CYST	-	1(1.3)	-	-	-	1(1.0)	-	1(0.8)								
UTERINE FIBROID	-	-	-	-	-	1(1.0)	-	1(0.8)								
PLATELET, BLEEDING & CLOTTING DISORDERS	5(5.0)	4(5.3)	14(14.3)	5(7.1)	35(11.6)	14(13.3)	48(15.5)	22(16.7)								
COAGULATION DISORDER	-	-	-	-	-	-	-	-								
COAGULATION TIME INCREASED	-	-	-	-	1(0.3)	-	1(0.3)	-								
EPISTAXIS	1(1.0)	2(2.7)	4(4.1)	2(2.9)	13(4.3)	3(2.9)	17(5.5)	3(2.3)								
GINGIVAL BLEEDING	-	-	-	-	3(1.0)	-	4(1.3)	1(0.8)								
HAEMATOMA	-	-	1(1.0)	-	2(0.7)	-	2(0.6)	-								
PLATELETS ABNORMAL	-	-	-	1(1.4)	-	1(1.0)	1(0.3)	-								
PROTHROMBIN DECREASED	-	-	1(1.0)	-	1(0.3)	-	1(0.3)	-								
PROTHROMBIN INCREASED	4(4.0)	1(1.3)	8(8.2)	2(2.9)	18(5.9)	8(7.6)	26(8.4)	13(9.8)								
PURPURA	-	1(1.3)	1(1.0)	-	2(0.7)	1(1.0)	3(1.0)	3(2.3)								
THROMBOCYTOPENIA	-	-	-	-	-	-	-	-								
PSYCHIATRIC DISORDERS	56(55.4)	32(42.7)	65(66.3)	42(60.0)	228(75.2)	70(66.7)	246(79.4)	102(77.3)								
AGGRESSIVE REACTION	4(4.0)	4(5.3)	9(9.2)	2(2.9)	28(9.2)	8(7.6)	32(10.3)	12(9.1)								
AGITATION	3(3.0)	3(4.0)	2(2.0)	1(1.4)	15(5.0)	1(1.0)	16(5.2)	6(4.5)								
ANOREXIA	15(14.9)	5(6.7)	24(24.5)	13(18.6)	105(35.0)	20(19.0)	118(38.1)	33(25.0)								
ANXIETY	1(1.0)	2(2.7)	2(2.0)	2(2.9)	1(0.3)	4(3.8)	2(0.6)	6(4.5)								
APATHY	3(3.0)	2(2.7)	2(2.0)	-	7(2.3)	-	10(3.2)	2(1.5)								
APPETITE INCREASED	-	-	1(1.0)	1(1.4)	5(1.7)	1(1.0)	6(1.9)	1(0.8)								
COGNITIVE PROBLEMS NOS	2(2.0)	2(2.7)	1(1.0)	5(7.1)	7(2.3)	10(9.5)	8(2.6)	11(8.3)								
CONFUSION	3(3.0)	6(8.0)	4(4.1)	10(14.3)	19(6.3)	15(14.3)	22(7.1)	26(19.7)								

Table 1: Incidence of Treatment Emergent Adverse Events

	Supplemental NDA										4 Month Safety Update	
	Double Blind Studies					Total Topiramate					Total Topiramate	
	Placebo		Topiramate		Topiramate		Topiramate		Topiramate		Topiramate	
	Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)				
PSYCHIATRIC DISORDERS (Cont. Inued)	56(55.4)	32(42.7)	65(66.3)	42(60.0)	228(75.2)	70(66.7)	246(79.4)	102(77.3)				
DELUSION	1(1.0)	-	-	-	7(2.3)	5(4.8)	9(2.9)	12(9.1)				
DEPRESSION	2(2.0)	2(2.7)	10(10.2)	2(2.9)	29(9.6)	3(2.9)	34(11.0)	16(12.1)				
DIFFICULTY WITH CONCENTRATION/ATTENTION	-	2(2.7)	5(5.1)	8(11.4)	17(5.6)	15(14.3)	18(5.8)	24(18.2)				
DIFFICULTY WITH MEMORY NOS	-	-	-	-	-	-	-	1(0.8)				
DREAMING ABNORMAL	5(5.0)	2(2.7)	5(5.1)	3(4.3)	13(4.3)	4(3.8)	13(4.2)	5(3.8)				
EMOTIONAL LABILITY	-	1(1.3)	-	-	3(1.0)	-	3(1.0)	-				
EUPHORIA	-	1(1.3)	-	-	3(1.0)	1(1.0)	4(1.3)	-				
HALLUCINATION	-	6(8.0)	8(8.2)	4(5.7)	38(12.5)	7(6.7)	46(14.8)	11(8.3)				
IMPOTENCE	-	-	-	2(2.9)	-	2(1.9)	-	2(1.5)				
INSOMNIA	7(6.9)	-	-	-	-	-	-	-				
LIBIDO DECREASED	-	-	-	-	1(0.3)	-	1(0.3)	-				
LIBIDO INCREASED	7(6.9)	2(2.7)	7(7.1)	3(4.3)	30(9.9)	7(6.7)	34(11.0)	9(6.8)				
MOOD PROBLEMS	7(6.9)	2(2.7)	14(14.3)	12(17.1)	51(16.8)	19(18.1)	65(21.0)	23(17.4)				
NEUROUSNESS	-	1(1.3)	1(1.0)	1(1.4)	2(0.7)	1(1.0)	2(0.6)	1(0.8)				
NEUROSIS	-	-	-	-	-	-	1(0.3)	1(0.8)				
PARANOID REACTION	1(1.0)	1(1.3)	-	-	-	-	1(0.3)	-				
PARANIRIA	9(8.9)	5(6.7)	11(11.2)	2(2.9)	25(8.3)	3(2.9)	33(10.6)	4(3.0)				
PERSONALITY DISORDER (BEHAVIOR PROBLEMS)	2(2.0)	2(2.7)	3(3.1)	4(5.7)	24(7.9)	8(7.6)	29(9.4)	11(8.3)				
PSYCHOPHOT SLOWING	-	1(1.3)	-	-	1(0.3)	-	-	2(1.5)				
SLEEP DISORDER	2(2.0)	1(1.3)	1(1.0)	-	5(1.7)	1(1.0)	6(1.9)	1(0.8)				
SOMNOLENCE	16(15.8)	14(18.7)	25(25.5)	19(27.1)	111(36.6)	29(27.6)	127(41.0)	49(37.1)				
SUICIDE ATTEMPT	-	-	-	-	-	-	-	1(0.8)				
RED BLOOD CELL DISORDERS	-	1(1.3)	-	1(1.4)	3(1.0)	2(1.9)	10(3.2)	2(1.5)				
ANAEMIA	-	1(1.3)	-	1(1.4)	2(0.7)	2(1.9)	8(2.6)	2(1.5)				
ANAEMIA HYPOCHROMIC	-	-	-	-	1(0.3)	-	2(0.6)	-				
REPRODUCTIVE DISORDERS, FEMALE @	3(6.0)	3(8.8)	1(2.3)	2(6.1)	5(4.0)	6(13.0)	7(5.6)	9(14.5)				
AMENORRHOEA	1(2.0)	-	-	1(3.0)	-	1(2.2)	-	1(1.6)				
BREAST ENLARGEMENT	-	1(2.9)	-	-	-	1(2.2)	-	1(1.6)				
BREAST PAIN FEMALE	-	-	-	-	-	1(2.2)	-	1(1.6)				
CERVICAL DYSPLASIA	1(2.0)	-	-	-	1(0.8)	2(4.5)	1(0.8)	2(3.2)				
DYSMENORRHOEA	1(2.0)	1(2.9)	1(2.3)	1(3.0)	1(0.8)	-	3(2.4)	-				
INTERMENSTRUAL BLEEDING	-	-	-	-	1(0.8)	-	1(0.8)	-				
LEUKORRHOEA	-	-	-	-	1(0.8)	1(2.2)	1(0.8)	2(3.2)				
MENORRHOEA	-	1(2.9)	-	-	1(0.8)	1(2.2)	1(0.8)	2(3.2)				
MENSTRUAL DISORDER	-	1(2.9)	-	-	1(0.8)	1(2.2)	1(0.8)	2(3.2)				
VAGINITIS	-	-	-	-	1(0.8)	-	1(0.8)	-				
VULVA DISORDER	-	-	-	-	1(0.8)	-	-	-				

@ Percentage are based on the number of females in each group of subjects.

Double-Blind: Placebo - pediatrics: n=50, adults: n=34; Topiramate - pediatrics: n=43, adults: n=33.

Total Topiramate: SNDA - pediatrics: n=124, adults: n=46; 4MSU - pediatrics: n=126, adults: n=82.

Table 1: Incidence of Treatment Emergent Adverse Events

Supplemental NDA

	4 Month Safety Update											
	Double Blind Studies						Total Topiramate					
	Placebo		Topiramate		Total Topiramate		Placebo		Topiramate		Total Topiramate	
	Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)		Peds N = 310 No (%)	Adult N = 132 No (%)	
RESPIRATORY SYSTEM DISORDERS	60(59.4)	23(30.7)	56(57.1)	24(34.3)	200(66.0)	49(46.7)	227(73.2)	80(60.6)				
ASPIRATION	-	-	-	-	1(0.3)	-	1(0.3)	-				
ASTHMA	-	-	-	-	2(0.7)	-	2(0.6)	-				
ATELECTASIS	4(4.0)	-	1(1.0)	1(1.4)	9(3.0)	2(1.9)	16(5.2)	6(4.5)				
BRONCHITIS	1(1.0)	-	-	-	1(0.3)	-	1(0.3)	-				
BRONCHOSPASM	11(10.9)	1(1.3)	8(8.2)	4(5.7)	48(15.8)	8(7.6)	51(16.5)	13(9.8)				
COUGHING	-	1(1.3)	-	-	3(1.0)	1(1.0)	4(1.3)	3(2.3)				
DYSPNOEA	-	-	-	-	1(0.3)	-	1(0.3)	-				
HYPERVENTILATION	-	-	-	-	1(0.3)	-	1(0.3)	-				
HYPOVENTILATION	12(11.9)	1(1.3)	7(7.1)	3(4.3)	37(12.2)	6(5.7)	50(16.1)	13(9.8)				
PHARYNGITIS	-	-	-	-	-	-	-	-				
PLEURAL EFFUSION	-	-	-	-	-	-	-	-				
PLEURISY	-	-	-	-	-	-	-	-				
PNEUMONIA	1(1.0)	-	5(5.1)	-	20(6.6)	2(1.9)	29(9.4)	3(2.3)				
RESPIRATORY DEPRESSION	-	-	-	-	6(2.0)	-	7(2.3)	-				
RESPIRATORY DISORDER	8(7.9)	1(1.3)	1(1.0)	4(5.7)	50(16.5)	7(6.7)	56(18.1)	12(9.1)				
RHINITIS	16(15.8)	3(4.0)	12(12.2)	4(5.7)	55(18.2)	9(8.6)	69(22.3)	16(12.1)				
SINUSITIS	-	-	-	-	-	-	-	-				
SPUTUM INCREASED	1(1.0)	-	-	-	1(0.3)	-	3(1.0)	-				
STRIDOR	37(36.6)	16(21.3)	36(36.7)	17(24.3)	132(43.6)	34(32.4)	155(50.0)	57(43.2)				
UPPER RESP TRACT INFECTION												
REPRODUCTIVE DISORDERS, MALE @	-	1(2.4)	-	1(2.7)	-	-	-	2(2.0)				
ORCHITIS	-	-	-	-	-	-	-	-				
PROSTATIC DISORDER	-	-	-	1(2.7)	-	-	-	1(1.4)				
TESTIS DISORDER	-	1(2.4)	-	-	-	-	-	-				
RESISTANCE MECHANISM DISORDERS	24(23.8)	3(4.0)	21(21.4)	6(8.6)	88(29.0)	13(12.4)	117(37.7)	22(16.7)				
ABSCESS	-	1(1.3)	-	1(1.4)	1(0.3)	2(1.9)	4(1.3)	4(3.0)				
HEALING IMPAIRED	2(2.0)	-	-	-	1(0.3)	-	1(0.3)	-				
HERPES SIMPLEX	1(1.0)	-	-	-	2(0.7)	-	4(1.3)	-				
HERPES ZOSTER	3(3.0)	1(1.3)	3(3.1)	3(4.3)	11(3.6)	5(4.8)	16(5.2)	9(6.8)				
INFECTION	6(5.9)	-	3(3.1)	-	18(5.9)	5(4.8)	23(7.4)	11(8.4)				
INFECTION BACTERIAL	-	-	-	-	5(1.7)	2(1.9)	10(3.2)	1(0.8)				
INFECTION FUNGAL	3(3.0)	1(1.3)	7(7.1)	2(2.9)	17(5.6)	3(2.9)	30(9.7)	4(3.0)				
INFECTION VIRAL	2(2.0)	-	1(1.0)	1(1.4)	4(1.3)	3(2.9)	5(1.6)	4(3.0)				
MONILIASIS	-	-	-	-	1(0.3)	-	1(0.3)	-				
OTITIS MEDIA	13(12.9)	-	11(11.2)	1(1.4)	51(16.8)	2(1.9)	66(21.3)	5(3.8)				
SEPSIS	-	-	-	-	-	-	1(0.3)	1(0.8)				

@ Percentage are based on the number of males in each group of subjects

Double-Blind: Placebo: n=51; Topiramate: n=41; Total Topiramate: n=179

SFDA - pediatric: n=59; adults: n=164

4MSU - pediatric: n=55; adults: n=70

Table 1: Incidence of Treatment Emergent Adverse Events

Supplemental NDA

BEST POSSIBLE COPY

4 Month Safety Update

Double Blind Studies

	Placebo				Topiramate				Total Topiramate				Total Topiramate	
	Peds N=101 No (%)	Adult N=75 No (%)	Peds N=98 No (%)	Adult N=70 No (%)	Peds N=303 No (%)	Adult N=105 No (%)	Peds N=310 No (%)	Adult N=132 No (%)						
SKIN AND APPENDAGES DISORDERS	16 (15.8)	12 (16.0)	20 (20.4)	7 (10.0)	85 (28.1)	21 (20.0)	102 (32.9)	31 (23.5)						
ACNE	1 (1.0)	-	1 (1.0)	1 (1.4)	9 (3.0)	2 (1.9)	12 (3.9)	5 (3.8)						
ALOPECIA	1 (1.0)	2 (2.7)	2 (2.0)	1 (1.4)	10 (3.3)	4 (3.8)	12 (3.9)	7 (5.3)						
BULLOUS ERUPTION	1 (1.0)	-	-	-	1 (0.3)	-	2 (0.6)	-						
DERMATITIS	-	-	2 (2.0)	-	4 (1.3)	-	4 (1.3)	-						
DERMATITIS FUNGAL	1 (1.0)	-	-	-	2 (0.7)	1 (1.0)	5 (1.6)	1 (0.8)						
ECZEMA	-	-	1 (1.0)	1 (1.4)	4 (1.3)	1 (1.0)	4 (1.3)	1 (0.8)						
FOLLICULITIS	-	-	-	-	-	1 (1.0)	1 (0.3)	1 (0.8)						
HAIR TEXTURE ABNORMAL	1 (1.0)	-	2 (2.0)	1 (1.4)	2 (0.7)	-	2 (0.6)	1 (0.8)						
HYPERTRICHOSIS	-	-	-	-	1 (0.3)	-	1 (0.3)	-						
LIVEDO RETICULARIS	-	-	-	-	1 (0.3)	3 (2.9)	1 (0.3)	3 (2.3)						
NAIL DISORDER	-	-	-	-	1 (0.3)	-	1 (0.3)	-						
PHOTOSENSITIVITY REACTION	-	-	-	-	-	-	-	-						
PIGMENTATION ABNORMAL	-	-	-	-	-	-	-	-						
PILONIDAL CYST	1 (1.0)	1 (1.3)	1 (1.0)	-	11 (3.6)	1 (1.0)	13 (4.2)	1 (0.8)						
PRURITUS	-	-	-	-	-	-	-	-						
PRURITUS ANI	8 (7.9)	1 (1.3)	7 (7.1)	2 (2.9)	37 (12.2)	3 (2.9)	41 (13.2)	6 (4.5)						
RASH	-	6 (8.0)	2 (2.0)	1 (1.4)	3 (1.0)	2 (1.9)	5 (1.6)	2 (1.5)						
RASH ERYTHEMATOUS	-	1 (1.3)	-	-	3 (1.0)	1 (1.0)	5 (1.6)	1 (0.8)						
RASH MACULO-PAPULAR	-	-	1 (1.0)	-	1 (0.3)	-	1 (0.3)	-						
SEBORRHOEA	-	-	-	-	-	-	-	-						
SKIN DEPIGMENTATION	-	1 (1.3)	1 (1.0)	-	5 (1.7)	1 (1.0)	5 (1.6)	2 (1.5)						
SKIN DISCOLOURATION	-	-	-	-	-	-	-	-						
SKIN DISORDER	2 (2.0)	-	3 (3.1)	1 (1.4)	13 (4.3)	4 (3.8)	15 (4.8)	4 (3.0)						
SKIN DRY	1 (1.0)	-	-	-	4 (1.3)	1 (1.0)	5 (1.6)	-						
SKIN EXFOLIATION	1 (1.0)	-	-	-	-	-	-	-						
SKIN ULCERATION	-	-	-	-	-	-	-	-						
SWEATING INCREASED	-	1 (1.3)	-	-	4 (1.3)	-	5 (1.6)	-						
URTICARIA	1 (1.0)	-	-	-	1 (0.3)	-	1 (0.3)	-						
VERRUCA	-	-	-	-	1 (0.3)	-	1 (0.3)	-						
VESICULAR RASH	-	-	-	-	-	-	-	-						
SPECIAL SENSES OTHER, DISORDERS	-	-	-	2 (2.9)	1 (0.3)	2 (1.9)	1 (0.3)	2 (1.5)						
TASTE PERVERSION	-	-	-	2 (2.9)	1 (0.3)	2 (1.9)	1 (0.3)	2 (1.5)						
URINARY SYSTEM DISORDERS	6 (5.9)	4 (5.3)	7 (7.1)	10 (14.3)	43 (14.2)	14 (13.3)	50 (16.1)	22 (16.7)						
CREATININE CLEARANCE DECREASED	-	-	-	-	-	-	-	-						
CYSTITIS	-	-	-	1 (1.4)	1 (0.3)	1 (1.0)	1 (0.3)	1 (0.8)						
DYSURIA	1 (1.0)	-	-	-	2 (0.7)	-	3 (1.0)	1 (0.8)						
FACE OEDEMA	-	-	-	-	2 (0.7)	-	2 (0.6)	-						
HAEMATURIA	-	-	-	1 (1.4)	1 (0.3)	1 (1.0)	3 (1.0)	2 (1.5)						

T. Incidence of Treatment Emergent Adverse Events

BEST POSSIBLE COPY

Supplemental NDA

	Double Blind Studies						4 Month Safety Update	
	Placebo			Topiramate			Total Topiramate	
	Peds N = 101 No (%)	Adult N = 75 No (%)	Total N = 176 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Total N = 168 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)
URINARY SYSTEM DISORDERS (Continued)	6 (5.9)	4 (5.3)	7 (7.1)	10 (14.3)	43 (14.2)	14 (13.3)	50 (16.1)	22 (16.7)
MICTURITION DISORDER	-	-	-	1 (1.4)	3 (1.0)	1 (1.0)	3 (1.0)	1 (0.8)
MICTURITION FREQUENCY	-	1 (1.3)	-	1 (1.4)	6 (2.0)	2 (1.9)	7 (2.3)	2 (1.5)
NEPHROSIS	-	-	-	-	-	-	-	-
NOCTURIA	-	-	-	-	-	-	-	-
OLIGURIA	1 (1.0)	-	1 (1.0)	1 (1.4)	1 (0.3)	1 (1.0)	2 (0.6)	1 (0.8)
POLYURIA	-	-	-	-	5 (1.7)	-	5 (1.6)	1 (0.8)
PYURIA	-	-	-	-	1 (0.3)	-	1 (0.3)	-
STRANGURY	-	-	-	-	-	-	-	-
URINARY INCONTINENCE	2 (2.0)	1 (1.3)	4 (4.1)	2 (2.9)	17 (5.6)	5 (4.8)	19 (6.1)	1 (0.8)
URINARY RETENTION	1 (1.0)	2 (2.7)	1 (1.0)	3 (4.3)	2 (0.7)	-	4 (1.3)	5 (3.8)
URINARY TRACT INFECTION	1 (1.0)	-	1 (1.0)	2 (2.9)	3 (1.0)	4 (3.8)	12 (3.9)	8 (6.1)
URINE ABNORMAL	-	-	-	1 (1.4)	4 (1.3)	2 (1.9)	4 (1.3)	3 (2.3)
VASCULAR (EXTRACARDIAC) DISORDERS	-	-	-	-	-	-	-	-
FLUSHING	-	-	-	-	3 (1.0)	-	3 (1.0)	-
THROMBOHEBITIS	-	-	-	1 (1.4)	-	1 (1.0)	-	1 (0.8)
THROMBOHEBITIS DEEP	-	-	-	-	-	1 (1.0)	-	1 (0.8)
VASODILATATION	-	-	-	-	1 (0.3)	-	1 (0.3)	-
VISION DISORDERS	5 (5.0)	7 (9.3)	5 (5.1)	9 (12.9)	25 (8.3)	12 (11.4)	32 (10.3)	19 (14.4)
ANISOCORIA	-	-	-	-	-	-	-	-
CATARACT	1 (1.0)	-	-	-	1 (0.3)	-	1 (0.3)	1 (0.8)
CONJUNCTIVAL DISCOLOURATION	-	-	-	-	1 (0.3)	-	1 (0.3)	-
CONJUNCTIVAL HAEMORRAGE	-	-	-	-	1 (0.3)	-	1 (0.3)	-
CONJUNCTIVITIS	2 (2.0)	-	1 (1.0)	-	10 (3.3)	2 (1.9)	12 (3.9)	2 (1.5)
DIPLOPIA	1 (1.0)	4 (5.3)	1 (1.0)	3 (4.3)	6 (2.0)	5 (4.8)	8 (2.6)	6 (4.5)
EYE ABNORMALITY	1 (1.0)	1 (1.3)	2 (2.0)	-	1 (0.3)	1 (1.0)	2 (0.6)	1 (0.8)
EYE PAIN	1 (1.0)	1 (1.3)	-	-	1 (0.3)	-	1 (0.3)	-
KERATOCONJUNCTIVITIS	-	-	-	1 (1.4)	-	1 (1.0)	-	1 (0.8)
LACRIMATION ABNORMAL	-	-	-	-	2 (0.7)	-	2 (0.6)	-
MYOPIA	-	-	-	-	1 (0.3)	-	1 (0.3)	-
PUPILLARY REFLEX IMPAIRED	-	-	-	-	2 (0.7)	-	2 (0.6)	-
VISION ABNORMAL	1 (1.0)	1 (1.3)	2 (2.0)	7 (10.0)	1 (0.3)	1 (1.0)	1 (0.3)	-
WHITE CELL AND RES DISORDERS	1 (1.0)	2 (2.7)	3 (3.1)	1 (1.4)	7 (2.3)	3 (2.9)	8 (2.6)	6 (4.5)
GRANULOCYTOPENIA	-	1 (1.3)	-	-	1 (0.3)	-	1 (0.3)	-
GRANULOCYTOSIS	-	-	-	1 (1.4)	-	1 (1.0)	-	1 (0.8)
LEUCOPENIA	-	1 (1.3)	2 (2.0)	-	2 (0.7)	-	2 (0.6)	2 (1.5)
LEUKOCYTOSIS	-	-	-	-	-	-	-	1 (0.8)
LYMPHADENOPATHY	-	-	-	-	2 (0.7)	2 (1.9)	2 (0.6)	2 (1.5)
LYMPHOEDEMA	1 (1.0)	-	1 (1.0)	-	-	-	-	-
MONOCYTOSIS	-	-	-	-	1 (0.3)	-	1 (0.3)	-
WBC ABNORMAL NOS	-	-	-	1 (1.4)	1 (0.3)	1 (1.0)	1 (0.3)	1 (0.8)

Appendix 4b

Incidence of Treatment-Emergent Neuropsychiatric Adverse Events by Preferred Term (Double-Blind and All Topiramate-Treated Subjects in the sNDA and 4MSU)

Supplemental NDA

BEST POSSIBLE COPY

NEURO-PSYCHIATRIC DISORDERS	Double Blind Studies						4 Month Safety Update	
	Placebo		Topiramate		Total Topiramate		Total Topiramate	
	Peds N = 101 NO (%)	Adult N = 75 NO (%)	Peds N = 98 NO (%)	Adult N = 70 NO (%)	Peds N = 303 NO (%)	Adult N = 105 NO (%)	Peds N = 310 NO (%)	Adult N = 132 NO (%)
ABSCENCES	70(69.3)	47(62.7)	74(75.5)	55(78.6)	254(83.8)	86(81.9)	274(88.4)	118(89.4)
AGGRESSIVE REACTION	4(4.0)	4(5.3)	9(9.2)	2(2.9)	28(9.2)	8(7.6)	32(10.3)	1(0.8)
AGITATION	3(3.0)	3(4.0)	2(2.0)	1(1.4)	15(5.0)	1(1.0)	16(5.2)	12(9.1)
ANOREXIA	15(14.9)	5(6.7)	24(24.5)	13(18.6)	106(35.0)	20(19.0)	118(38.1)	6(4.5)
ANXIETY	1(1.0)	2(2.7)	2(2.0)	2(2.9)	1(0.3)	4(3.8)	2(0.6)	33(25.0)
APATHY	3(3.0)	2(2.7)	2(2.0)	-	7(2.3)	-	6(4.5)	6(4.5)
APPETITE INCREASED	2(2.0)	4(5.3)	1(1.0)	1(1.4)	5(1.7)	1(1.0)	10(3.2)	2(1.5)
ATAXIA	2(2.0)	1(1.3)	6(6.1)	5(7.1)	26(8.6)	10(9.5)	28(9.0)	1(0.8)
AUTISM	3(3.0)	6(8.0)	4(4.1)	5(7.1)	3(1.0)	-	4(1.3)	16(12.1)
COGNITIVE PROBLEMS NOS	3(3.0)	6(8.0)	4(4.1)	10(14.3)	19(6.3)	15(14.3)	22(7.3)	11(8.3)
CONVULSIONS	3(3.0)	6(8.0)	3(3.1)	3(4.3)	23(7.6)	4(3.8)	30(9.7)	1(0.8)
CONVULSIONS AGGRAVATED	3(3.0)	1(1.3)	1(1.0)	1(1.4)	6(2.0)	2(1.9)	13(3.5)	3(2.3)
COORDINATION ABNORMAL	1(1.0)	1(1.3)	1(1.0)	1(1.4)	10(3.3)	4(3.8)	12(3.9)	4(3.0)
CRAMPS LEGS	1(1.0)	2(2.7)	-	-	-	1(1.0)	-	1(0.8)
DEPRESSION	2(2.0)	2(2.7)	10(10.2)	1(1.4)	7(2.3)	5(4.8)	9(2.9)	12(9.1)
DIFFICULTY WITH CONCENTRATION/ATTENTION	2(2.0)	2(2.7)	5(5.1)	8(11.4)	29(9.6)	3(2.9)	34(11.0)	16(12.1)
DIFFICULTY WITH MEMORY NOS	2(2.0)	11(14.7)	4(4.1)	13(18.6)	17(5.6)	15(14.3)	18(5.8)	24(18.2)
DIZZINESS	-	-	-	-	19(6.3)	17(16.2)	22(7.1)	21(15.9)
DREAMING ABNORMAL	-	-	-	-	-	-	-	1(0.8)
DYSKINESIA	-	1(1.3)	-	-	1(0.3)	-	1(0.3)	-
DYSTONIA	-	-	-	-	3(1.0)	-	3(1.0)	-
EEG ABNORMAL	-	-	-	-	1(0.3)	-	1(0.3)	-
EMOTIONAL LABILITY	5(5.0)	2(2.7)	5(5.1)	3(4.3)	13(4.3)	4(3.8)	13(4.2)	5(3.8)
ENCEPHALOPATHY	-	-	-	-	2(0.7)	-	2(0.6)	-
EUPHORIA	-	-	-	-	3(1.0)	-	3(1.0)	-
FAECAL INCONTINENCE	-	-	-	-	3(1.0)	-	3(1.0)	-
FATIGUE	5(5.0)	10(13.3)	1(1.0)	14(20.0)	67(22.1)	18(17.1)	77(24.8)	24(18.2)
GAIT ABNORMAL	5(5.0)	1(1.3)	8(8.2)	3(4.3)	24(7.9)	8(7.6)	31(10.0)	11(8.3)
HALLUCINATION	11(10.9)	16(21.3)	5(6.1)	15(21.4)	48(15.8)	25(23.8)	61(19.7)	40(30.3)
HEADACHE	4(4.0)	2(2.7)	5(5.1)	-	15(5.0)	2(1.9)	18(5.8)	3(2.3)
HYPERTONIA	-	-	-	1(1.4)	2(0.7)	1(1.0)	3(0.9)	1(0.8)
HYPONESTHESIA	-	-	-	-	1(0.3)	4(3.8)	2(0.6)	5(3.8)
HYPOKINESIA	-	-	-	-	2(2.0)	-	2(0.6)	-
HYPOTONIA	-	-	-	-	3(1.0)	-	3(1.0)	-
IMPOTENCE	-	-	-	-	3(1.0)	-	3(1.0)	-
INSOMNIA	7(6.9)	6(8.0)	8(8.2)	4(5.7)	38(12.5)	7(6.7)	46(14.8)	11(8.3)
LANGUAGE PROBLEMS	1(1.0)	2(2.7)	1(1.0)	4(5.7)	16(5.3)	5(4.8)	17(5.5)	12(9.1)
LIBIDO DECREASED	-	-	-	2(2.9)	-	2(1.9)	-	2(1.5)

BEST POSSIBLE COPY

Table : Incidence of Neuro-Psychiatric Adverse Events

	Supplemental NDA						4 Month Safety Update	
	Double Blind Studies			Total Topiramate			Total Topiramate	
	Placebo	Topiramate		Total Topiramate		Total Topiramate		
	Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)
NEURO-PSYCHIATRIC DISORDERS (Continued)	70 (69.3)	47 (62.7)	74 (75.5)	55 (78.6)	254 (83.8)	86 (81.9)	274 (88.4)	118 (89.4)
LIBIDO INCREASED	-	-	-	-	1 (0.3)	-	1 (0.3)	-
MIGRAINE	7 (6.9)	2 (2.7)	7 (7.1)	3 (4.3)	1 (0.3)	4	1 (0.3)	-
MOOD PROBLEMS	-	-	-	2 (2.9)	30 (9.9)	7 (6.7)	34 (11.0)	5 (6.8)
MUSCLE CONTRACTIONS INVOLUNTARY	7 (6.9)	2 (2.7)	14 (14.3)	12 (17.1)	5 (1.7)	5 (4.8)	5 (1.6)	7 (5.3)
NERVOUSNESS	-	-	1 (1.0)	-	51 (16.8)	19 (18.1)	65 (21.0)	21 (17.4)
NEUROSIIS	1 (1.0)	-	-	1 (1.4)	2 (0.7)	1 (1.0)	2 (0.6)	1 (0.8)
OEDEMA CEREBRAL	-	-	-	-	1 (0.3)	2 (1.9)	2 (0.6)	3 (2.3)
PARAESTHESIA	-	-	1 (1.0)	3 (4.3)	15 (5.0)	7 (6.7)	19 (6.1)	11 (8.3)
PARALYSIS	-	-	-	1 (1.4)	-	1 (1.0)	1 (0.3)	1 (0.8)
PARANOID REACTION	-	-	-	-	1 (0.3)	-	1 (0.3)	-
PARESIS	-	-	-	-	-	-	-	-
PARONIRIA	1 (1.0)	1 (1.3)	-	-	1 (0.3)	-	1 (0.3)	-
PERSONALITY DISORDER (BEHAVIOR PROBLEMS)	9 (8.9)	5 (6.7)	11 (11.2)	2 (2.9)	25 (8.3)	3 (2.9)	33 (10.6)	4 (3.0)
PSYCHOMOTOR SLOWING	2 (2.0)	2 (2.7)	3 (3.1)	4 (5.7)	24 (7.9)	8 (7.6)	29 (9.4)	11 (8.2)
PSYCHOSIS	-	-	-	-	-	-	-	-
SENSORY DISTURBANCE	-	-	-	-	-	-	-	-
SLEEP DISORDER	2 (2.0)	1 (1.3)	1 (1.0)	-	1 (0.3)	-	2 (0.6)	1 (0.8)
SOMNOLENCE	16 (15.8)	14 (18.7)	25 (25.5)	19 (27.1)	5 (1.7)	1 (1.0)	6 (1.9)	1 (0.8)
SPEECH DISORDERS/RELATED SPEECH PROBLEMS	2 (2.0)	1 (1.3)	4 (4.1)	5 (7.1)	11 (3.6)	29 (27.6)	127 (41.0)	49 (37.1)
STUPOR	-	-	-	-	19 (6.3)	7 (6.7)	21 (6.8)	11 (8.3)
SUICIDE ATTEMPT	-	-	-	2 (2.9)	-	3 (2.9)	-	5 (3.8)
TREMOR	1 (1.0)	5 (6.7)	-	4 (5.7)	13 (4.3)	8 (7.6)	16 (5.2)	17 (12.9)
VERTIGO	-	1 (1.3)	-	1 (1.4)	-	1 (1.0)	1 (0.3)	2 (1.5)
VISUAL FIELD DEFECT	-	-	-	1 (1.4)	1 (0.3)	1 (1.0)	1 (0.3)	1 (0.8)

APPEARS THIS WAY
ON ORIGINAL

Appendix 4c

Incidence of Serious Adverse Events
(Double-Blind and All Topiramate-Treated Subjects in the sNDA and 4MSU)

Supplemental NDA

	Double-Blind Studies								4 Month Safety Update	
	Placebo				Topiramate				Total Topiramate	
	Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)		
APPLICATION SITE DISORDERS	-	-	-	-	-	-	-	-	-	1 (0.8)
CELLULITIS	-	-	-	-	-	-	-	-	-	1 (0.8)
BODY AS A WHOLE - GENERAL DISORDERS	-	5 (6.7)	-	1 (1.4)	5 (1.7)	4 (3.8)	8 (2.6)	8 (6.1)	-	-
ABDOMEN ENLARGED	-	1 (1.3)	-	-	-	1 (1.0)	-	-	-	1 (0.8)
CHEST PAIN	-	-	-	-	-	-	-	-	-	1 (0.8)
CONDITION AGGRAVATED	-	-	-	-	-	-	-	-	-	1 (0.8)
DRUG LEVEL INCREASED	-	-	-	-	-	-	-	-	-	1 (0.8)
FATIGUE	-	-	-	-	1 (0.3)	-	-	1 (0.3)	-	-
FEVER	-	-	-	-	2 (0.7)	-	-	4 (1.3)	-	-
HYPOTHERMIA	-	-	-	-	1 (0.3)	-	-	1 (0.3)	-	-
INJURY	-	2 (2.7)	-	-	1 (0.3)	-	-	2 (0.6)	-	4 (3.0)
PAIN	-	1 (1.3)	-	-	1 (1.0)	-	-	1 (0.3)	-	1 (0.8)
SUDDEN DEATH	-	1 (1.3)	-	-	-	-	-	-	-	1 (0.8)
THERAPEUTIC RESPONSE INCREASED	-	-	-	1 (1.4)	-	-	-	1 (0.3)	-	1 (0.8)
CENTR 6 PERIPH NERV SYST DISORDERS	2 (2.0)	4 (5.3)	1 (1.0)	3 (4.3)	14 (4.6)	3 (2.9)	28 (9.0)	9 (6.8)	-	-
ATAXIA	-	1 (1.3)	-	-	-	-	-	-	-	2 (0.6)
CONVULSIONS AGGRAVATED	2 (2.0)	4 (5.3)	1 (1.0)	-	9 (3.0)	-	-	15 (4.8)	-	5 (3.8)
CONVULSIONS GRAND MAL	-	-	-	1 (1.4)	5 (1.7)	-	-	10 (3.2)	-	2 (1.5)
DIZZINESS	-	-	-	1 (1.4)	-	-	-	1 (0.3)	-	1 (0.8)
EEG ABNORMAL	-	-	-	-	1 (0.3)	-	-	1 (0.3)	-	-
GAIT ABNORMAL	-	-	-	1 (1.4)	1 (0.3)	-	-	3 (1.0)	-	1 (0.8)
SPEECH DISORDERS/RELATED SPEECH PROBLEMS	-	-	-	1 (1.4)	-	-	-	1 (0.8)	-	1 (0.8)
STUPOR	-	-	-	-	-	-	-	-	-	1 (0.8)
TREMOR	-	-	-	1 (1.4)	-	-	-	-	-	1 (0.8)
ENDOCRINE DISORDERS	-	-	-	-	-	-	-	-	-	1 (0.8)
GLUCOCORTICIDS INCREASED	-	-	-	-	-	-	-	-	-	1 (0.8)
GASTRO-INTESTINAL SYSTEM DISORDERS	-	1 (1.3)	3 (3.1)	-	4 (1.3)	4 (3.8)	18 (5.8)	6 (4.5)	-	-
ABDOMINAL PAIN	-	-	1 (1.0)	-	1 (0.3)	1 (1.0)	1 (0.3)	2 (1.5)	-	-
CONSTIPATION	-	-	-	-	1 (0.3)	-	-	2 (0.6)	-	-
DIARRHOEA	-	-	-	-	-	-	-	4 (1.3)	-	-
DYSPHAGIA	-	-	-	-	-	-	-	2 (0.6)	-	-
GASTRITIS	-	-	-	-	-	1 (1.0)	1 (0.3)	1 (0.8)	-	-
GASTROENTERITIS	-	-	-	-	-	-	3 (1.0)	1 (0.8)	-	-
GASTROESOPHAGEAL REFLEX	-	1 (1.3)	1 (1.0)	-	1 (0.3)	-	2 (0.6)	1 (0.8)	-	-
HAEMATEMESIS	-	-	-	-	-	-	-	-	-	1 (0.8)
INTESTINAL OBSTRUCTION	-	-	-	-	-	-	-	-	-	1 (0.8)
INTESTINAL PERFORATION	-	1 (1.3)	-	-	-	-	-	-	-	1 (0.8)
NAUSEA	-	-	-	-	-	-	-	-	-	1 (0.8)
OESOPHAGEAL STRICTURE	-	-	-	-	-	1 (1.0)	1 (0.3)	1 (0.8)	-	-
PANCREATITIS	-	1 (1.3)	1 (1.0)	-	1 (0.3)	1 (1.0)	1 (0.3)	1 (0.8)	-	-
VOMITING	-	-	-	-	-	-	-	-	-	1 (0.8)

BEST POSSIBLE COPY

BEST POSSIBLE COPY

Table : Incidence of Serious Adverse Events

	Supplemental NDA											
	Double Blind Studies					Total Topiramate					4 Month Safety Update	
	Placebo		Topiramate		Total Topiramate		Peds		Adult		Total Topiramate	
Peds N = 101 No (%)	Adult N = 75 No (%)	Peds N = 98 No (%)	Adult N = 70 No (%)	Peds N = 303 No (%)	Adult N = 105 No (%)	Peds N = 310 No (%)	Adult N = 132 No (%)					
HEART RATE AND RHYTHM DISORDERS												
CARDIAC ARREST	-	-	-	-	-	-	1 (0.3)	-	-	-	-	-
LIVER AND BILIARY SYSTEM DISORDERS												
CHOLELITHIASIS	-	-	-	-	-	-	1 (1.0)	-	-	-	-	-
METABOLIC AND NUTRITIONAL DISORDERS												
ACIDOSIS LACTIC	-	-	-	-	-	6 (2.0)	1 (1.0)	-	-	-	2 (1.5)	-
DEHYDRATION	-	-	-	-	-	-	-	-	-	-	-	-
OEDEMA PERIORBITAL	-	-	-	-	-	5 (1.7)	-	-	-	-	1 (0.3)	-
OSTEOMALACIA	-	-	-	-	-	1 (0.3)	-	-	-	-	11 (3.5)	-
WEIGHT DECREASE	-	-	-	-	-	-	-	-	-	-	1 (0.3)	-
PLATELET, BLEEDING & CLOTTING DISORDERS	-	-	-	-	-	-	1 (1.0)	-	-	-	1 (0.3)	-
CONGULATION TIME INCREASED	-	-	-	-	-	-	-	-	-	-	1 (0.3)	-
PSYCHIATRIC DISORDERS												
AGGRESSIVE REACTION	-	2 (2.7)	-	-	-	-	-	-	-	-	-	-
AGITATION	-	-	-	-	-	3 (4.3)	-	-	-	-	1 (0.3)	-
ANOREXIA	-	-	-	-	-	-	-	-	-	-	-	-
APATHY	-	-	-	-	-	1 (1.4)	-	-	-	-	1 (0.3)	-
CONFUSION	-	-	-	-	-	1 (1.4)	-	-	-	-	1 (1.0)	-
DEPRESSION	-	-	-	-	-	-	-	-	-	-	1 (1.0)	-
HALLUCINATION	-	1 (1.3)	-	-	-	-	-	-	-	-	4 (1.3)	-
INSOMNIA	-	-	-	-	-	-	-	-	-	-	1 (0.3)	-
NERVOUSNESS	-	-	-	-	-	-	-	-	-	-	-	-
PERSONALITY DISORDER (BEHAVIOR PROBLEMS)	-	-	-	-	-	-	-	-	-	-	1 (0.3)	-
PSYCHOSIS	-	-	-	-	-	1 (1.4)	-	-	-	-	1 (0.8)	-
SOMNOLENCE	-	1 (1.3)	-	-	-	-	-	-	-	-	1 (0.8)	-
SUICIDE ATTEMPT	-	-	-	-	-	1 (1.4)	-	-	-	-	1 (0.8)	-
						3 (1.0)	1 (1.0)	-	-	-	6 (1.9)	-
						-	1 (1.0)	-	-	-	1 (0.8)	-
						-	-	-	-	-	10 (7.6)	-
						-	-	-	-	-	3 (2.3)	-
						-	-	-	-	-	2 (1.5)	-
						-	-	-	-	-	1 (0.8)	-
						-	-	-	-	-	2 (1.5)	-
						-	-	-	-	-	2 (1.5)	-
						-	-	-	-	-	1 (0.8)	-
						-	-	-	-	-	1 (0.8)	-
						-	-	-	-	-	1 (0.8)	-
						-	-	-	-	-	2 (1.5)	-
						-	-	-	-	-	1 (0.8)	-
						-	-	-	-	-	1 (0.8)	-

BEST POSSIBLE COPY

Table . . . incidence of Serious Adverse Events

	Supplemental NDA											
	Double Blind Studies						Topiramate					
	Placebo		Adult		Peds		Adult		Peds		Total Topiramate	
	N = 101	N = 75	N = 98	N = 70	N = 303	N = 105	N = 310	No (%)	No (%)	No (%)	No (%)	
RESPIRATORY SYSTEM DISORDERS			2 (2.0)		14 (4.6)	1 (1.0)	19 (6.1)			3 (2.3)		
ASPIRATION												
ASTHMA												
ATELECTASIS					1 (0.3)		1 (0.3)					
BRONCHITIS					1 (0.3)		1 (0.3)					
DYSPNOEA					1 (0.3)		1 (0.3)					
PHARYNGITIS												
PLEURAL EFFUSION												
PNEUMONIA					4 (1.3)		4 (1.3)			1 (0.8)		
RESPIRATORY DEPRESSION			2 (2.0)		6 (2.0)	1 (1.0)	11 (3.5)			1 (0.8)		
RESPIRATORY DISORDER					1 (0.3)		1 (0.3)			2 (1.5)		
SINUSITIS			1 (1.0)		1 (0.3)		1 (0.3)					
UPPER RESP TRACT INFECTION					1 (0.3)		3 (1.0)					
SKIN AND APPENDAGES DISORDERS							2 (0.6)					
RASH					2 (0.7)		2 (0.6)					
REPRODUCTIVE DISORDERS, FEMALE @					2 (0.7)		2 (0.6)					
BREAST ENLARGEMENT												
REPRODUCTIVE DISORDERS, MALE @												
PROSTATIC DISORDER												
RESISTANCE MECHANISM DISORDERS												
ABSCESS	1 (1.0)	1 (1.3)	1 (1.0)	2 (2.9)	2 (0.7)	2 (1.9)	7 (2.3)			4 (3.0)		
INFECTION BACTERIAL												
INFECTION VIRAL												
OTITIS MEDIA												
SEPSIS			1 (1.0)		2 (0.7)		2 (0.6)			1 (0.8)		

@ Percentage are based on the number of males or females in each group of subjects

Double-Blind

Placebo - pediatrics: 51M and 50F
 adults: 41M and 34F

TPM - pediatrics: 55M and 43F
 adults: 37M and 33F

Total Topiramate

SNDA - pediatrics: 179M and 124F
 adults: 59M and 46F

4MSU - pediatrics: 184M and 126F
 adults: 70M and 62F

BEST POSSIBLE COPY

Table : Incidence of Serious Adverse Events

	Supplemental NDA																
	Double Blind Studies						Total Topiramate						4 Month Safety Update				
	Placebo		Topiramate		Total Topiramate		Peds		Adult		Total Topiramate		Peds		Adult		
N	No (%)	N	No (%)	N	No (%)	N	No (%)	N	No (%)	N	No (%)	N	No (%)	N	No (%)	N	No (%)
URINARY SYSTEM DISORDERS	-	-	-	1 (1.4)	-	1 (0.3)	1 (1.0)	-	-	-	-	2 (0.6)	-	-	-	2 (1.5)	-
MICTURITION DISORDER	-	-	-	1 (1.4)	-	-	-	-	-	-	-	-	-	-	-	-	-
OLIGURIA	-	-	-	1 (1.4)	-	-	-	-	-	-	-	-	-	-	-	-	-
URINARY INCONTINENCE	-	-	-	1 (1.4)	-	-	-	-	-	-	-	-	-	-	-	-	-
URINARY TRACT INFECTION	-	-	-	-	-	1 (0.3)	1 (1.0)	-	-	-	-	2 (0.6)	-	-	-	-	-
VASCULAR (EXTRACARDIAC) DISORDERS	-	-	-	1 (1.4)	-	-	2 (1.9)	-	-	-	-	-	-	-	-	2 (1.5)	-
THROMBOPHEBITIS	-	-	-	1 (1.4)	-	-	-	-	-	-	-	-	-	-	-	-	-
THROMBOPHEBITIS DEEP	-	-	-	1 (1.4)	-	-	1 (1.0)	-	-	-	-	-	-	-	-	1 (0.8)	-
VISION DISORDERS	-	-	-	1 (1.4)	-	-	1 (1.0)	-	-	-	-	-	-	-	-	1 (0.8)	-
VISION ABNORMAL	-	-	-	1 (1.4)	-	-	1 (1.0)	-	-	-	-	-	-	-	-	1 (0.8)	-

APPEARS THIS WAY
ON ORIGINAL

REVIEW AND EVALUATION OF CLINICAL DATA

IND (serial no.)	20,505 (006)
SPONSOR	R. W. Johnson
DRUG (generic name)	Topamax (Topiramate)
INDICATION	Epilepsy
MATERIAL SUBMITTED	Labeling change
CORRESPONDENCE DATE	3/9/99
DATE RECEIVED	3/10/99
DATE REVIEWED	3/18/99

INTRODUCTION

Topamax (TOP) was approved on December 24, 1997 as adjunctive therapy for the treatment of partial seizures in adults with epilepsy. The sponsor now proposes a change to the pregnancy section in labeling.

REVIEW

Because of four, presumably retrospective reports of hypospadias after first trimester exposure to TOP (in three of which there was also concomitant use of carbamazepine), the sponsor has elected on its own to change current labeling to reflect this information, without imputing an established causal connection. See the attached documentation.

CONCLUSION

I concur with the labeling change recommended by the sponsor.

/s/

Richard M. Tresley
Medical Reviewer

IND 20,505 (006) div file/Katz R/Ware J/Tresley R/18 March 1999

APPEARS THIS WAY
ON ORIGINAL

Joelle -
In answer to your
email question

/S/

REVIEW AND EVALUATION OF CLINICAL DATA

NDA	20,505
SPONSOR	R. W. Johnson
DRUG (generic name)	Topamax (Topiramate)
INDICATION	Epilepsy
MATERIAL SUBMITTED	Consult #3777 (Rates of hepatic and renal adverse events)
CORRESPONDENCE DATE	10/7/98
DATE RECEIVED	10/13/98
DATE REVIEWED	10/27/98

INTRODUCTION

TOPAMAX was approved as an anticonvulsant medication in 12/24/96. One postmarketing report from Norway of fulminant liver failure leading to transplant was recently received and has been published in *Lancet* (v 332, #9134 [3 Oct 1998]). Following are the questions posed and the responses:

(1) Please provide an estimate of the rate of liver disease with topiramate since its approval.

According to labeling, SGPT, SGOT, and alk phos increases occur in 1/100-1/1000 patients), GGT increases in fewer than 1/1000 patients. Estimated US exposure since approval is 20,553 person-years (median duration of therapy, 31 days; mean, 35 days; mode, 31 [range 7-100]).

The Norwegian case concerned a 39-year-old female, on CBZ x 2 years (without problem), who developed apparently acute liver failure 4 months after TOPAMAX initiation (beginning at 50 mg/day and escalating to 300 mg/day). Symptoms of fatigue, nausea, and anorexia occurred a few days after the last dose increase from 275 to 300 mg/day. Her SGPT rose to 10,000; levels of CBZ and TOPAMAX were reportedly within normal ranges; Hep, CMV, and EBV titres were negative. She became encephalopathic and developed hepatorenal syndrome.

Two cases of adverse hepatic events were recognized in the US:

(1) 8-year-old female, on TOPAMAX 100 mg/d, developed anorexia, fatigue, and weight loss, and was diagnosed with hepatitis (no Hep screens were done). Four weeks after TOPAMAX initiation, her SGOT rose to 738, SGPT to 387, and tot bili to 3.2. Hospitalization was not required, and her LFTs declined 4 days after TOPAMAX was discontinued (SGOT 140, SGPT 262, tot bili 1.5). Concomitant meds: CBZ started 6 months, and phenobarbital 3 months, prior to symptom onset).

(2) 42-year-old male, on increasing doses of TOPAMAX x 3 weeks (25 mg/d x 1 week, 50 mg/d x 1 week, 100 mg/d x 1 week), developed nausea, jaundice, and anorexia (SGPT 1464, GGT 508, tot bili 13.9). The patient was hospitalized and a liver biopsy showed "moderately severe chronic active hepatitis with cholestasis with drug reaction or viral infection." Hep screen was negative; following TOPAMAX discontinuation, his LFTs began to improve (SGOT 503, GGT 404, tot bili 11.4); no further follow-up was provided. Concomitant meds: gabapentin started about 6 months prior to symptoms and phenytoin (starting date unknown).

Based on the one hospitalized US patient, the overall reporting rate for serious hepatic events in the US was calculated at 1/20,553 person-years of exposure. For Norway, based on the case above, the reporting rate for acute liver failure among TOPAMAX users in Norway was calculated at 1/500 patient-years of exposure, much higher than the expected rate.

Because of the presence of confounders (all 3 patients were other drugs known to cause liver problems) and the small numbers of reported events (subjecting the estimated rates to considerable statistical variability), interpretation of the cases is open to some question. However,

it appears that all patients began to improve after TOPAMAX was withdrawn.

(2) Please provide an estimate of the rate of renal disease with topiramate since its approval.

Labeling ("Precautions") singles out kidney stones (increased "incidence of 2-4 times that expected in a similar untreated population"). Dosage adjustment in cases of renal impairment is recommended ("may be required").

Two postmarketing cases were recognized:

(1) US case: 11-year-old male, on TOPAMAX x 2 months (no other anticonvulsants mentioned), developed renal failure attributed to hypocalcemia and renal tubular acidosis. The patient was hospitalized, but no other information was available. Hypocalcemia is listed in labeling as an adverse event occurring in 1/100-1/1000 patients. In view of its similarity to carbonic anhydrase inhibitors (e.g., Diamox), renal tubular acidosis is a possible adverse event.

(2) Swedish case: 63-year-old diabetic female developed nephrotic syndrome after having been treated with TOPAMAX 150 mg/d x 2 months and Lamictal (start date unknown). Kidney biopsy showed membranous glomerulonephritis and nephrosclerosis "that a 'clinical expert' deemed to be a possible drug-induced reaction. The reporter was less convinced that topiramate was the etiology of the event." The patient was hospitalized and the drug discontinued, but the nephrotic syndrome reportedly has not resolved 5-6 months later.

Based on the single US case of serious renal disease, the overall estimated reporting rate was 1/20,553 person-years of exposure. No rate was provided for the Swedish case; the presence of diabetes and Lamictal as confounders, as well as the fact that the patient has not improved off TOPAMAX, makes it more difficult to implicate the drug.

From an earlier consult:

(3) Please provide an estimate of use for Topamax, as well as similar comparative data for the other recently approved anticonvulsants -- Felbamate, Gabapentin, and Lamictal.

Estimated number of prescriptions dispensed in the first 12 months of marketing:

RECOMMENDATIONS

(1) Given the uncertainty of the actual incidence of serious hepatic disease (owing to the small numbers of reported events), a postmarketing section should be added at the end of current labeling for Topamax (repeated from my review of a previous Epidemiology consult, dated 6/25/98):

Postmarketing and Other Experience: In addition to the adverse experiences reported during clinical testing of TOPAMAX, the following adverse experiences have been reported in patients receiving marketed TOPAMAX from worldwide use since approval. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: cholelithiasis, hepatic failure, hepatitis, pancreatitis, and renal tubular acidosis.

One patient, a 30-40 year-old female on a stable dose of carbamazepine for over a year, was begun on Topamax at 50 mg/day, then subsequently titrated to 300 mg/day (over 4 months). During the titration period, her liver function

tests rose 300-fold and she developed signs of hepatic encephalopathy and the hepatorenal syndrome, necessitating a liver transplant. Histopathology was "quite compatible with toxic influence."

(2) The "Warnings" section should advise regular monitoring of SGOT, SGPT, and bilirubin while patients are on TOPAMAX.

(3) Follow-up of all the above cases should be done as soon as possible and continued until the patients have returned to baseline.

(4) Expedited reporting of all cases of liver, pancreatic, gallbladder, and biliary tree disorders should be made imperative upon the sponsor.

Richard M. Tresley
Medical Reviewer

IND 20,505 div file/Katz R/Ware J/Tresley R/27 October 1998

APPEARS THIS WAY
ON ORIGINAL