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 PL | Number of Subjects TPM | Median % Seizure Rate Reduction PL | Median % Seizure Rate Reduction TPM | Percent Responders[b] PL | Percent Responders[b] TPM |
|---|---|---|---|---|---|---|
| **PGTC Seizures** | | | | | | |
| < 4 PGTC seizures | 41 | 31 | 29.1 | 63.9 | 29 | 61 |
| ≥ 4 PGTC seizures | 39 | 47 | 22.5 | 51.6 | 26 | 51 |
| **All Seizures** | | | | | | |
| < 17 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 Subjects; Protocols YTC and YTC-E)

| | 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] | |
| Region | PL | TPM | PL | TPM | PL | TPM | PL | TPM | PL | TPM | PL | TPM |
| **United States** | | | | | | | | | | | | |
| <4/month | 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** | | | | | | | | | | | | |
| <4/month | -- | -- | -- | -- | -- | -- | 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 PLA | Number of Subjects TPM | Median % Seizure Rate Reduction PLA | Median % Seizure Rate Reduction TPM | Percent Responders[a] PLA | Percent Responders[a] TPM |
|---|---|---|---|---|---|---|
| **PGTC Seizures** | | | | | | |
| Valproic acid and combinations | 43 | 41 | 22.5 | 51.6 | 26 | 54 |
| Other AEDs and combinations | 37 | 37 | 31.4 | 60.7 | 30 | 57 |
| One AED | 19 | 18 | 32.7 | 83.0 | 21 | 78 |
| Two AEDs | 44 | 41 | 34.4 | 57.1 | 39 | 54 |
| Three or more AEDs | 17 | 19 | -35.7 | 39.7 | 6 | 37 |
| **All Seizures** | | | | | | |
| Valproic acid and combinations | 43 | 41 | 3.1 | 37.6 | 16 | 41 |
| Other AEDs and combinations | 38 | 38 | 12.4 | 34.4 | 21 | 45 |
| One AED | 20 | 18 | 11.5 | 73.7 | 15 | 67 |
| Two AEDs | 44 | 42 | 22.3 | 33.5 | 27 | 43 |
| Three or more 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.

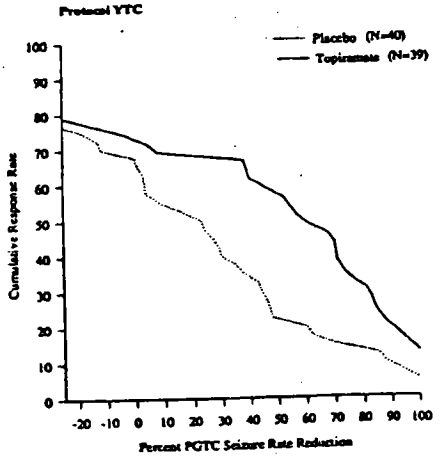
Table 31a: Percent Seizure Rate Reduction and Treatment Responders
by Sex and Plasma Topiramate Concentration Stratum
in Protocols YTC and YTC-E Combined
(All Subjects With Plasma Samples During Stabilization)

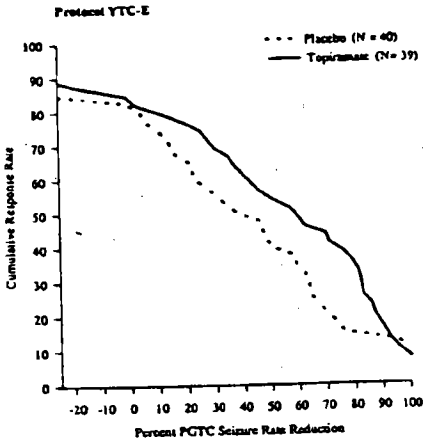
| Seizure Type Plasma Topiramate Stratum | N | Median Percent Reduction | Responders No. | Responders % |
|---|---|---|---|---|
| **PGTC Seizures** | | | | |
| Female | | | | |
| <5.13 µg/mL | 10 | 16.5 | 3 | 30 |
| 5.13 to <8.53 µg/mL | 13 | 68.5 | 9 | 69 |
| ≥8.53 µg/mL | 11 | 44.8 | 5 | 45 |
| Male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

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 | Responders No. | Responders % |
|---|---|---|---|---|
| **PGTC Seizures** | | | | |
| ≤16 years | | | | |
| <4.09 µg/mL | 4 | -5.5 | 1 | 25 |
| 4.09 to <8.41 µg/mL | 6 | 46.4 | 3 | 50 |
| ≥8.41 µg/mL | 5 | 68.5 | 3 | 60 |
| >16 years | | | | |
| <5.04 µg/mL | 17 | 46.7 | 8 | 47 |
| 5.04 to <8.61 µg/mL | 16 | 83.2 | 11 | 69 |
| ≥8.61 µg/mL | 18 | 44.7 | 8 | 44 |
| **All Seizures** | | | | |
| ≤16 years | | | | |
| <4.09 µg/mL | 4 | -6.9 | 0 | 0 |
| 4.09 to <8.41 µg/mL | 6 | 37.6 | 3 | 50 |
| ≥8.41 µg/mL | 5 | 54.0 | 3 | 60 |
| >16 years | | | | |
| <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 |

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



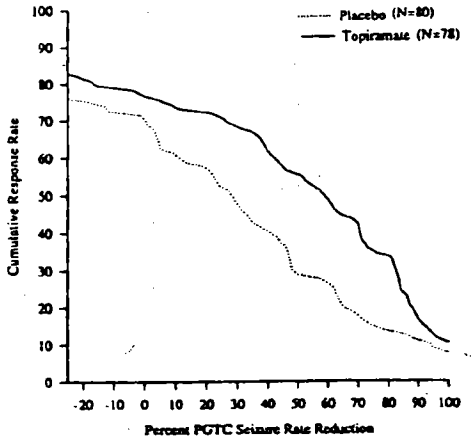
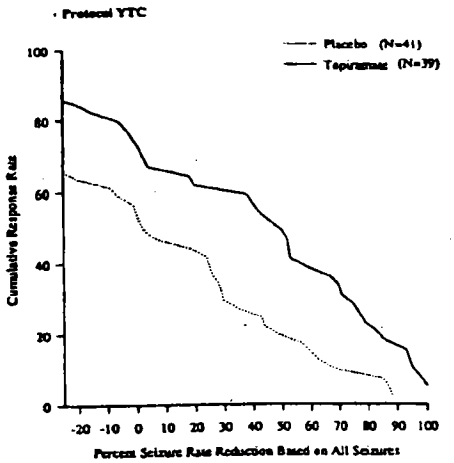
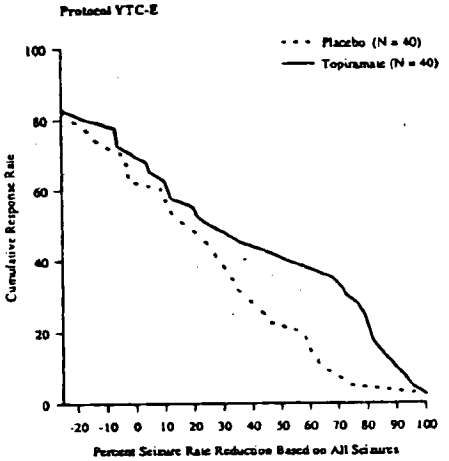
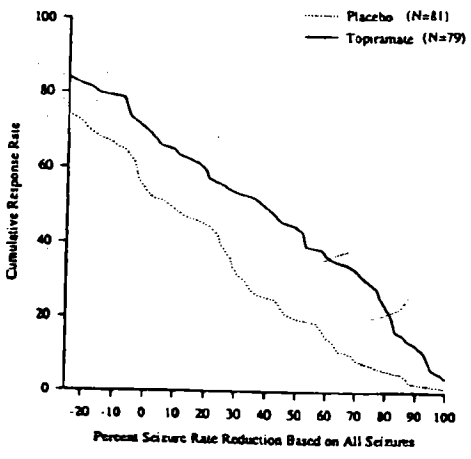




Figure 5: Cumulative Response Rate Based on All Seizures
(All Randomized Subjects; Protocols YTC and YTC-E)



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Age distribution in years - SNDA
Pediatric subjects

AGE

| 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

| 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 |

Table 2: Incidence of Neuropsychiatric Adverse Events[a]: Comparison Between Adults and Children

| | % Subjects | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Double-Blind | | | | Total TPM: Double-Blind + Open-Label | | | |
| | Adults[b] | | Children | | sNDA | | 4MSU | |
| Adverse Event (Preferred Term) | Placebo (N=216) | TPM[e] (N=527) | Placebo (N=101) | TPM (N=98) | Adults[c,d] (N=1,715) | Children (N=303) | Adults[d] (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.

[a] 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.

[b] Based on reclassified Four-Month Safety Update database for NDA 20-505 as presented in RWJPRI's Response to FDA's Approvable Letter (filed 27 June 1996).

[c] Based on Final Safety Update for NDA 20-505 (filed 26 September 1996).

[d] 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

[e] Includes all randomized dosage groups combined (200, 400, 600, 800, and 1,000 mg/day combined).

## Appendix 2: Average and M[illegible] Daily Dosage and Duration of Treatment

| | Double-Blind | | | | Total TPM | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | TPM | | sNDA | | 4MSU | |
| | Pediatrics (N=101) | Adults (N=75) | Pediatrics (N=98) | Adults (N=70) | Pediatrics (N=303) | Adults (N=105) | Pediatrics (N=310) | Adults (N=132) |
| **Average Daily Dosage[a] (mg/kg/day)** | | | | | | | | |
| Double-Blind Phase | | | | | | | | |
| N | 101 | 75 | 98 | 70 | - | - | - | - |
| 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[b] | 70[b] | 97[b] | 68[b] | 300[b] | 105 | 308[b] | 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[c] | 0.8-8.5[c] | 1.3-32.9 | 0.6-16.3 | 1.3-32.9 | 0.6-19.9 |
| **Maximum Daily Dosage[a] (mg/kg/day)** | | | | | | | | |
| Double-Blind Phase | | | | | | | | |
| N | 101 | 75 | 98 | 70 | - | - | - | - |
| 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[c] | 0.6-14.1[c] | - | - | - | - |
| Stabilization Period | | | | | | | | |
| N | 99[b] | 70[b] | 97[b] | 68[b] | 300[b] | 105 | 308[b] | 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[c] | 0.8-14.1[c] | 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 |

[a] 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.

[b] Subjects who were missing a baseline wieght measurement were not included in the calculation of average and maximum daily dosages.

[c] 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) | | Pediatrics (N=98) | | Adults (N=70) | | Pediatrics (N=303) | | Adults (N=105) | | Pediatrics (N=310) | | Adult (N=132) | |
| | No. | (%) | No. | (%) | 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 | | 2 | (2.9) | 45 | (14.9) | 13 | (12.4) | 18 | (5.8) | 15 | (11.4) |
| 271-365 days | 0 | | 0 | | 0 | | 0 | | 34 | (11.2) | 9 | (8.6) | 38 | (12.3) | 15 | (11.4) |
| 1-2 years | 0 | | 0 | | 0 | | 0 | | 75 | (24.8) | 24 | (22.9) | 112 | (36.1) | 46 | (34.9) |
| 2-3 years | 0 | | 0 | | 0 | | 0 | | 33 | (10.9) | 5 | (4.8) | 59 | (19.0) | 26 | (19.7) |
| 3-4 years | 0 | | 0 | | 0 | | 0 | | 10 | (3.3) | 0 | | 19 | (6.2) | 0 | |
| 4-5 years | 0 | | 0 | | 0 | | 0 | | | | 0 | | 7 | (2.3) | 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) |

APPENDIX 4a

Table : Incidence of Treatment Emergent Adverse Events

| | Supplemental NDA | | | | | | 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 (%) |
| APPLICATION SITE DISORDERS | 2( 2.0) | - | - | - | 3( 1.0) | - | 5( 1.6) | 3( 2.3) |
| CELLULITIS | 2( 2.0) | - | - | - | 2( 0.7) | - | 3( 1.0) | 1( 0.8) |
| INJECTION SITE INFLAMMATION | - | - | - | - | - | - | - | 2( 1.5) |
| INJECTION SITE REACTION | - | - | - | - | - | - | 1( 0.3) | 1( 0.8) |
| OTITIS EXTERNA | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| SKIN NODULE | - | - | - | - | - | - | - | - |
| AUTONOMIC NERVOUS SYSTEM DISORDERS | - | - | - | - | 2( 0.7) | - | 2( 0.6) | - |
| VASODILATION | - | - | - | - | 2( 0.7) | - | 2( 0.6) | - |
| 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 | - | - | - | - | - | - | - | 1( 0.8) |
| ALLERGIC REACTION | 1( 1.0) | 1( 1.3) | 2( 2.0) | 1( 1.4) | 2( 0.7) | 1( 1.0) | 2( 0.6) | 3( 2.3) |
| ALLERGY | - | 3( 4.0) | - | 2( 2.9) | 3( 1.0) | 3( 2.9) | 7( 2.3) | 5( 3.8) |
| ASTHENIA | 1( 1.0) | - | - | 2( 2.9) | 6( 2.0) | 3( 2.9) | 6( 1.9) | 3( 2.3) |
| BACK PAIN | - | 3( 4.0) | 1( 1.0) | 3( 4.3) | 2( 0.7) | 6( 5.7) | 3( 1.0) | 16(12.1) |
| CHEST PAIN | - | 4( 5.3) | - | 2( 2.9) | 2( 0.7) | 4( 3.8) | 2( 0.6) | 6( 4.5) |
| CONDITION AGGRAVATED | - | - | - | - | - | - | - | 1( 0.8) |
| DRUG LEVEL INCREASED | 1( 1.0) | 1( 1.3) | 1( 1.0) | 1( 1.4) | 4( 1.3) | 4( 3.8) | 4( 1.3) | 4( 3.0) |

| | 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 (%) |
| 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(25.7) | 4( 5.3) | 24(24.5) | 3( 4.3) | 65(21.5) | 9( 8.6) | 87(28.1) | 12( 9.1) |
| HALITOSIS | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| HOT FLUSHES | 1( 1.0) | - | - | - | - | - | 1( 0.3) | - |
| HYPOTHERMIA | - | - | - | - | 2( 0.7) | - | 2( 0.6) | - |
| INFLUENZA-LIKE SYMPTOMS | 12(11.9) | - | 7( 7.1) | 2( 2.9) | 34(11.2) | 8( 7.6) | 44(14.2) | 15(11.4) |
| INJURY | 13(12.9) | 11(14.7) | 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) | 1( 0.8) |
| MALAISE | 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) | - | 1( 1.4) | 7( 2.3) | 1( 1.0) | 8( 2.6) | 2( 1.5) |
| OEDEMA GENITAL | - | - | - | - | - | - | 1( 0.3) | - |
| OEDEMA PERIPHERAL | - | 1( 1.3) | - | - | - | 1( 1.0) | - | 2( 1.5) |
| PAIN | 2( 2.0) | 5( 6.7) | 2( 2.0) | 3( 4.3) | 19( 6.3) | 11(10.5) | 30( 9.7) | 22(16.7) |
| PALLOR | - | - | 1( 1.0) | - | 4( 1.3) | 2( 1.9) | 5( 1.6) | 2( 1.5) |
| RIGORS | - | - | - | - | 1( 0.3) | - | 2( 0.6) | 1( 0.8) |
| SUDDEN DEATH * | - | 1( 1.3) | - | - | - | - | - | - |
| THERAPEUTIC RESPONSE INCREASED | - | - | - | 1( 1.4) | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| TOLERANCE DECREASED | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |

* 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

| | 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 (%) |
| CARDIOVASCULAR DISORDERS, GENERAL | - | - | 1( 1.0) | 1( 1.4) | 5( 1.7) | 2( 1.9) | 8( 2.6) | 3( 2.3) |
| CYANOSIS | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| ECG ABNORMAL | - | - | - | - | 1( 0.3) | - | 4( 1.3) | 1( 0.8) |
| HEART DISORDER | - | - | - | - | - | 1( 1.0) | - | 1( 0.8) |
| HEART VALVE DISORDERS | - | - | - | 1( 1.4) | 1( 0.3) | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| HYPERTENSION | - | - | 1( 1.0) | - | 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 | - | - | - | - | - | - | - | 1( 0.8) |
| ATAXIA | 2( 2.0) | 4( 5.3) | 6( 6.1) | 5( 7.1) | 26( 8.6) | 10( 9.5) | 28( 9.0) | 16(12.1) |
| AUTOMATISM | - | 1( 1.3) | - | - | 3( 1.0) | - | 4( 1.3) | - |
| CONVULSIONS | - | - | - | - | - | - | 2( 0.6) | 1( 0.8) |
| CONVULSIONS AGGRAVATED | 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 GRAND MAL | - | - | 1( 1.0) | 1( 1.4) | 6( 2.0) | 2( 1.9) | 11( 3.5) | 3( 2.3) |
| COORDINATION ABNORMAL | 3( 3.0) | 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) | - | 1( 0.8) |
| DIZZINESS | 2( 2.0) | 11(14.7) | 4( 4.1) | 13(18.6) | 19( 6.3) | 17(16.2) | 22( 7.1) | 21(15.9) |
| 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) | - |

| | 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 (%) |
|---|---|---|---|---|---|---|---|---|
| CENTR & PERIPH NERV SYST DISORDERS (Continued) | 28(27.7) | 33(44.0) | 36(36.7) | 39(55.7) | 154(50.8) | 63(60.0) | 182(58.7) | 90(68.2) |
| ENCEPHALOPATHY | - | - | - | - | 2( 0.7) | - | 2( 0.6) | - |
| FAECAL INCONTINENCE | - | - | 1( 1.0) | - | 3( 1.0) | - | 4( 1.3) | - |
| 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) |
| HEADACHE | 11(10.9) | 16(21.3) | 6( 6.1) | 15(21.4) | 48(15.8) | 25(23.8) | 61(19.7) | 40(30.3) |
| HEMIPLEGIA | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| HYPERKINESIA | 4( 4.0) | 2( 2.7) | 5( 5.1) | - | 15( 5.0) | 2( 1.9) | 18( 5.8) | 3( 2.3) |
| HYPERTONIA | - | - | - | - | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| HYPOAESTHESIA | - | - | - | 1( 1.4) | 2( 0.7) | 4( 3.8) | 2( 0.6) | 5( 3.8) |
| HYPOKINESIA | - | - | - | - | 1( 0.3) | - | - | - |
| HYPOREFLEXIA | - | - | 2( 2.0) | - | 3( 1.0) | - | 4( 1.3) | - |
| HYPOTONIA | - | - | - | - | 3( 1.0) | - | 5( 1.6) | - |
| 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) |
| MIGRAINE | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| MUSCLE CONTRACTIONS INVOLUNTARY | - | - | - | 2( 2.9) | 5( 1.7) | 5( 4.8) | 5( 1.6) | 7( 5.3) |
| NYSTAGMUS | 1( 1.0) | - | - | 1( 1.4) | 2( 0.7) | 2( 1.9) | 2( 0.6) | 3( 2.3) |
| OEDEMA CEREBRAL | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| PARAESTHESIA | - | 1( 1.3) | 1( 1.0) | 3( 4.3) | 15( 5.0) | 7( 6.7) | 19( 6.1) | 11( 8.3) |
| PARALYSIS | - | - | - | - | - | - | - | 1( 0.8) |
| PARESIS | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| SENSORY DISTURBANCE | - | - | - | - | 1( 0.3) | - | 2( 0.6) | 1( 0.8) |
| SPEECH DISORDERS/RELATED SPEECH PROBLEMS | 2( 2.0) | 1( 1.3) | 4( 4.1) | 5( 7.1) | 19( 6.3) | 7( 6.7) | 21( 6.8) | 11( 8.3) |
| STUPOR | - | - | - | 2( 2.9) | - | 3( 2.9) | - | 5( 3.8) |

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 (%) |
| CENTR & PERIPH NERV SYST DISORDERS (Continued) | 28(27.7) | 33(44.0) | 36(36.7) | 39(55.7) | 154(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 | - | - | - | - | - | - | - | 1( 0.8) |
| HYPOTHYROIDISM | - | 1( 1.3) | - | - | - | - | - | 1( 0.8) |
| PUBERTY PRECOCIOUS | - | - | - | - | 2( 0.7) | - | 2( 0.6) | - |
| FOETAL DISORDERS | - | - | - | - | - | - | 1( 0.3) | - |
| NAEVUS | - | - | - | - | - | - | 1( 0.3) | - |
| | 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 (%) |
| 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) |
| DYSPHAGIA | - | - | 1( 1.0) | - | 2( 0.7) | - | 5( 1.6) | 1( 0.8) |
| FAECES DISCOLOURED | - | - | - | - | 1( 0.3) | 2( 1.9) | 1( 0.3) | 2( 1.5) |
| FLATULENCE | - | - | 1( 1.0) | - | 1( 0.3) | - | 2( 0.6) | - |
| GASTRITIS | - | - | - | - | 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 | - | - | - | - | 3( 1.0) | - | 4( 1.3) | - |
| GLOSSITIS | - | 1( 1.3) | 1( 1.0) | - | 1( 0.3) | - | 1( 0.3) | - |
| GUM HYPERPLASIA | - | - | 1( 1.0) | - | 5( 1.7) | 1( 1.0) | 6( 1.9) | 2( 1.5) |
| HAEMATEMESIS | - | 1( 1.3) | - | - | - | - | - | - |
| HICCUP | - | - | - | - | 4( 1.3) | - | 4( 1.3) | 1( 0.8) |
| INTESTINAL OBSTRUCTION | - | - | - | - | - | - | - | 1( 0.8) |
| INTESTINAL PERFORATION | - | - | - | - | - | - | - | 1( 0.8) |
| MELAENA | - | 1( 1.3) | - | - | 2( 0.7) | - | 2( 0.6) | - |
| 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 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 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 (%) |
| GASTRO-INTESTINAL SYSTEM DISORDERS (Continued) | 51(50.5) | 20(26.7) | 39(39.8) | 20(28.6) | 150(49.5) | 41(39.0) | 188(60.6) | 67(50.8) |
| OESOPHAGITIS | - | - | - | - | - | 1( 1.0) | - | 1( 0.8) |
| PANCREATITIS | - | - | - | - | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| PERIODONTAL DESTRUCTION | - | - | - | - | - | - | - | 1( 0.8) |
| SALIVA INCREASED | 4( 4.0) | - | 6( 6.1) | - | 28( 9.2) | - | 33(10.6) | 2( 1.5) |
| STOMATITIS | - | 1( 1.3) | - | - | - | - | 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 | - | - | - | - | 2( 0.7) | - | 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 = 98 No (%) | Adult N = 70 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) | - | 2( 0.6) | 4( 3.0) |
| HEARING DECREASED | - | - | - | 1( 1.4) | 1( 0.3) | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| TINNITUS | - | 1( 1.3) | - | - | 1( 0.3) | 2( 1.9) | 1( 0.3) | 2( 1.5) |
| HEART RATE AND RHYTHM DISORDERS | - | - | 1( 1.0) | 1( 1.4) | 3( 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) | 1( 1.0) | 5( 1.6) | 4( 3.0) |
| BILIRUBINAEMIA | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| CHOLELITHIASIS | - | 1( 1.3) | - | - | - | 1( 1.0) | - | 3( 2.3) |
| GAMMA-GT INCREASED | - | - | - | - | 1( 0.3) | - | 1( 0.3) | 1( 0.8) |
| HEPATIC FUNCTION ABNORMAL | - | - | - | - | - | - | 2( 0.6) | - |
| HEPATITIS | - | - | - | - | 1( 0.3) | - | 2( 0.6) | - |

Table : Incidence of Treatment Emergent Adverse Events

| | Supplemental NDA | | | | | | 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 (%) |
| LIVER AND BILIARY SYSTEM DISORDERS (Continued) | 1( 1.0) | 1( 1.3) | - | - | 2( 0.7) | 1( 1.0) | 5( 1.6) | 4( 3.0) |
| HEPATOCELLULAR DAMAGE | - | 1( 1.3) | - | - | - | - | - | - |
| HEPATOMEGALY | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| JAUNDICE | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| SGOT INCREASED | 1( 1.0) | - | - | - | - | - | - | - |
| SGPT INCREASED | 1( 1.0) | - | - | - | - | - | - | - |
| METABOLIC AND NUTRITIONAL DISORDERS | 5( 5.0) | 4( 5.3) | 11(11.2) | 10(14.3) | 48(15.8) | 19(18.1) | 69(22.3) | 32(24.2) |
| ACIDOSIS | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| ACIDOSIS LACTIC | - | - | - | - | - | - | 1( 0.3) | - |
| CACHEXIA | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| CREATINE PHOSPHOKINASE INCREASED | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| DEHYDRATION | 1( 1.0) | - | - | - | 7( 2.3) | - | 15( 4.8) | - |
| HYPERCHOLESTEROLAEMIA | 1( 1.0) | - | - | - | - | - | - | 1( 0.8) |
| HYPERGLYCAEMIA | - | - | - | - | - | - | - | 1( 0.8) |
| HYPERLIPAEMIA | - | - | - | - | - | - | - | 1( 0.8) |
| HYPERTRIGLYCERIDAEMIA | 1( 1.0) | - | - | - | - | - | - | 1( 0.8) |
| HYPOCALCAEMIA | - | - | - | - | - | - | - | 1( 0.8) |
| HYPOGLYCAEMIA | - | - | 1( 1.0) | - | 1( 0.3) | - | 1( 0.3) | - |
| HYPOKALAEMIA | - | - | - | - | 2( 0.7) | - | 2( 0.6) | - |
| HYPOVITAMINOSIS | - | - | - | - | - | - | 1( 0.3) | - |
| LACTOSE INTOLERANCE | - | - | - | - | - | - | 1( 0.3) | - |
| NPN INCREASED | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| OEDEMA PERIORBITAL | 1( 1.0) | - | - | - | 2( 0.7) | - | 2( 0.6) | - |
| OSTEOMALACIA | - | - | - | - | - | - | 1( 0.3) | - |
| PHOSPHATASE ALKALINE INCREASED | - | - | - | - | - | - | 1( 0.3) | 1( 0.8) |
| SERUM IRON DECREASED | - | - | - | 1( 1.4) | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| SERUM IRON INCREASED | - | - | - | - | - | - | - | 1( 0.8) |
| THIRST | 1( 1.0) | 1( 1.3) | 2( 2.0) | - | 4( 1.3) | 1( 1.0) | 4( 1.3) | 1( 0.8) |
| WEIGHT DECREASE | 1( 1.0) | 3( 4.0) | 9( 9.2) | 9(12.9) | 28( 9.2) | 15(14.3) | 34(11.0) | 25(18.9) |
| WEIGHT INCREASE | - | - | 1( 1.0) | - | 7( 2.3) | 2( 1.9) | 9( 2.9) | 3( 2.3) |
| MUSCULO-SKELETAL SYSTEM DISORDERS | 1( 1.0) | 4( 5.3) | 1( 1.0) | 4( 5.7) | 15( 5.0) | 9( 8.6) | 17( 5.5) | 11( 8.3) |
| ARTHRALGIA | - | - | - | - | 2( 0.7) | - | 1( 0.3) | 2( 1.5) |
| ARTHROSIS | - | 3( 4.0) | - | - | 3( 1.0) | 2( 1.9) | 3( 1.0) | 2( 1.5) |
| BONE DEVELOPMENT ABNORMAL | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| BONE DISORDER | - | 1( 1.3) | - | 1( 1.4) | 1( 0.3) | 1( 1.0) | 3( 1.0) | 1( 0.8) |
| FRACTURE PATHOLOGICAL | - | - | - | - | - | - | 1( 0.3) | - |
| MUSCLE WEAKNESS | 1( 1.0) | 1( 1.3) | 1( 1.0) | - | 5( 1.7) | 1( 1.0) | 5( 1.6) | 2( 1.5) |
| MYALGIA | - | - | - | 1( 1.4) | 1( 0.3) | 3( 2.9) | 2( 0.6) | 4( 3.0) |
| MYOPATHY | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |

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 (%) |
| 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) | - | 2( 1.9) | - | 2( 1.5) |
| SYNOVITIS | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| NEONATAL AND INFANCY DISORDERS | - | - | - | - | - | - | - | 1( 0.8) |
| PSYCHOMOTOR DEVELOPMENT IMPAIRED | - | - | - | - | - | - | - | 1( 0.8) |
| NEOPLASMS | - | 1( 1.3) | - | - | 3( 1.0) | 2( 1.9) | 3( 1.0) | 2( 1.5) |
| BREAST FIBROADENOSIS | - | - | - | - | - | 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( 0.3) | 1( 0.8) |
| UTERINE FIBROID | - | - | - | - | - | 1( 1.0) | - | 1( 0.8) |
| | 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 (%) |
| 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 | - | - | - | - | - | - | 1( 0.3) | - |
| COAGULATION TIME INCREASED | - | - | - | - | 1( 0.3) | - | 2( 0.6) | - |
| 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( 1.0) | 1( 0.3) | 1( 0.8) |
| PROTHROMBIN DECREASED | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| PROTHROMBIN INCREASED | - | - | 1( 1.0) | - | 1( 0.3) | - | 1( 0.3) | - |
| PURPURA | 4( 4.0) | 1( 1.3) | 8( 8.2) | 2( 2.9) | 18( 5.9) | 8( 7.6) | 26( 8.4) | 13( 9.8) |
| THROMBOCYTOPENIA | - | 1( 1.3) | 1( 1.0) | - | 2( 0.7) | 1( 1.0) | 3( 1.0) | 3( 2.3) |
| 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) | 106(35.0) | 20(19.0) | 118(38.1) | 33(25.0) |
| ANXIETY | 1( 1.0) | 2( 2.7) | - | 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) | - | 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) |

| | 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 (%) |
| PSYCHIATRIC DISORDERS (Continued) | 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) | - | - | - | - | - | - | - |
| DEPRESSION | - | 2( 2.7) | - | 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) | 10(10.2) | 2( 2.9) | 29( 9.6) | 3( 2.9) | 34(11.0) | 16(12.1) |
| DIFFICULTY WITH MEMORY NOS | - | 2( 2.7) | 5( 5.1) | 8(11.4) | 17( 5.6) | 15(14.3) | 18( 5.8) | 24(18.2) |
| DREAMING ABNORMAL | - | - | - | - | - | - | - | 1( 0.8) |
| 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) |
| EUPHORIA | - | - | - | - | 3( 1.0) | - | 3( 1.0) | - |
| HALLUCINATION | - | 1( 1.3) | - | - | 3( 1.0) | 1( 1.0) | 4( 1.3) | 5( 3.8) |
| IMPOTENCE | - | 1( 1.3) | - | - | - | - | - | - |
| 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) |
| LIBIDO DECREASED | - | - | - | 2( 2.9) | - | 2( 1.9) | - | 2( 1.5) |
| LIBIDO INCREASED | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| MOOD PROBLEMS | 7( 6.9) | 2( 2.7) | 7( 7.1) | 3( 4.3) | 30( 9.9) | 7( 6.7) | 34(11.0) | 9( 6.8) |
| NERVOUSNESS | 7( 6.9) | 2( 2.7) | 14(14.3) | 12(17.1) | 51(16.8) | 19(18.1) | 65(21.0) | 23(17.4) |
| NEUROSIS | - | - | 1( 1.0) | - | 2( 0.7) | 1( 1.0) | 2( 0.6) | 1( 0.8) |
| PARANOID REACTION | - | - | - | 1( 1.4) | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| PARONIRIA | 1( 1.0) | 1( 1.3) | - | - | - | - | 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( 8.3) |
| PSYCHOSIS | - | 1( 1.3) | - | - | - | 1( 1.0) | - | 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( 2.2) | - | - |
| BREAST PAIN FEMALE | - | 1( 2.9) | - | - | - | - | - | 1( 1.6) |
| CERVICAL DYSPLASIA | - | - | - | - | - | 1( 2.2) | - | 1( 1.6) |
| DYSMENORRHOEA | 1( 2.0) | - | - | - | 1( 0.8) | 2( 4.3) | 1( 0.8) | 2( 3.2) |
| INTERMENSTRUAL BLEEDING | 1( 2.0) | 1( 2.9) | - | - | 1( 0.8) | - | 3( 2.4) | - |
| LEUKORRHOEA | - | - | 1( 2.3) | - | 1( 0.8) | - | 1( 0.8) | - |
| MENORRHAGIA | - | - | - | 1( 3.0) | - | 1( 2.2) | - | 2( 3.2) |
| MENSTRUAL DISORDER | - | 1( 2.9) | - | - | 1( 0.8) | - | 1( 0.8) | 2( 3.2) |
| VAGINITIS | - | - | - | - | - | 1( 2.2) | 1( 0.8) | 2( 3.2) |
| 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=62

Table : Incidence of tment 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 (%) |
| 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 | - | - | - | - | 2( 0.7) | - | 2( 0.6) | - |
| BRONCHITIS | 4( 4.0) | - | 1( 1.0) | 1( 1.4) | 9( 3.0) | 2( 1.9) | 16( 5.2) | 6( 4.5) |
| BRONCHOSPASM | 1( 1.0) | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| COUGHING | 11(10.9) | 1( 1.3) | 8( 8.2) | 4( 5.7) | 48(15.8) | 8( 7.6) | 51(16.5) | 13( 9.8) |
| DYSPNOEA | - | 1( 1.3) | - | - | 3( 1.0) | 1( 1.0) | 4( 1.3) | 3( 2.3) |
| HYPERVENTILATION | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| HYPOVENTILATION | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| PHARYNGITIS | 12(11.9) | 1( 1.3) | 7( 7.1) | 3( 4.3) | 37(12.2) | 6( 5.7) | 50(16.1) | 13( 9.8) |
| PLEURAL EFFUSION | - | - | - | - | - | - | - | 1( 0.8) |
| PLEURISY | - | - | - | - | - | 1( 1.0) | - | 1( 0.8) |
| PNEUMONIA | 1( 1.0) | - | 5( 5.1) | - | 20( 6.6) | 2( 1.9) | 29( 9.4) | 3( 2.3) |
| RESPIRATORY DEPRESSION | - | - | - | - | - | - | 1( 0.3) | - |
| RESPIRATORY DISORDER | - | 1( 1.3) | 1( 1.0) | - | 6( 2.0) | - | 7( 2.3) | 3( 2.3) |
| RHINITIS | 8( 7.9) | 2( 2.7) | 5( 5.1) | 4( 5.7) | 50(16.5) | 7( 6.7) | 56(18.1) | 12( 9.1) |
| SINUSITIS | 16(15.8) | 3( 4.0) | 12(12.2) | 4( 5.7) | 55(18.2) | 9( 8.6) | 69(22.3) | 16(12.1) |
| SPUTUM INCREASED | - | - | - | - | - | - | 1( 0.3) | - |
| STRIDOR | 1( 1.0) | - | - | - | 1( 0.3) | - | 3( 1.0) | - |
| UPPER RESP TRACT INFECTION | 37(36.6) | 16(21.3) | 36(36.7) | 17(24.3) | 132(43.6) | 34(32.4) | 155(50.0) | 57(43.2) |
| | 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 (%) |
| REPRODUCTIVE DISORDERS, MALE@ | - | 1( 2.4) | - | 1( 2.7) | - | 1( 1.7) | - | 2( 2.8) |
| ORCHITIS | - | - | - | - | - | - | - | 1( 1.4) |
| PROSTATIC DISORDER | - | - | - | 1( 2.7) | - | 1( 1.7) | - | 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 | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| HERPES SIMPLEX | 2( 2.0) | - | - | - | 2( 0.7) | - | 4( 1.3) | 1( 0.8) |
| HERPES ZOSTER | 1( 1.0) | - | - | - | 1( 0.3) | - | 3( 1.0) | - |
| INFECTION | 3( 3.0) | 1( 1.3) | 3( 3.1) | 3( 4.3) | 12( 4.0) | 5( 4.8) | 16( 5.2) | 9( 6.8) |
| INFECTION BACTERIAL | 6( 5.9) | - | 3( 3.1) | - | 18( 5.9) | - | 23( 7.4) | 1( 0.8) |
| INFECTION FUNGAL | - | - | - | - | 5( 1.7) | 2( 1.9) | 10( 3.2) | 1( 0.8) |
| INFECTION VIRAL | 3( 3.0) | 1( 1.3) | 7( 7.1) | 2( 2.9) | 17( 5.6) | 3( 2.9) | 30( 9.7) | 4( 3.0) |
| MONILIASIS | 2( 2.0) | - | 1( 1.0) | 1( 1.4) | 4( 1.3) | 3( 2.9) | 5( 1.6) | 4( 3.0) |
| MONILIASIS GENITAL | - | - | - | - | 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 - pediatrics: n=51
- adults: n=41
Topiramate - pediatrics: n=55
adults n=37

Total Topiramate
SNDA - pediatrics: n=179
adults: n=59
4MSU - pediatrics: n=184
adults: n=70

Table : I: ce of Treatment Emergent Adverse Events

| | Supplemental NDA | | | | | | 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) | 1( 0.8) |
| DERMATITIS FUNGAL | 1( 1.0) | - | - | - | 2( 0.7) | 1( 1.0) | 5( 1.6) | 4( 3.0) |
| 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( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| HYPERTRICHOSIS | 1( 1.0) | - | 2( 2.0) | - | 2( 0.7) | - | 2( 0.6) | - |
| LIVEDO RETICULARIS | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| NAIL DISORDER | - | - | - | - | 1( 0.3) | 3( 2.9) | 1( 0.3) | 3( 2.3) |
| PHOTOSENSITIVITY REACTION | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| PIGMENTATION ABNORMAL | - | - | - | - | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| PILONIDAL CYST | - | - | - | - | - | 1( 1.0) | - | 1( 0.8) |
| PRURITUS | 1( 1.0) | 1( 1.3) | 1( 1.0) | - | 11( 3.6) | 1( 1.0) | 13( 4.2) | 3( 2.3) |
| PRURITUS ANI | - | 1( 1.3) | - | - | 1( 0.3) | - | - | - |
| RASH | 8( 7.9) | 6( 8.0) | 7( 7.1) | 2( 2.9) | 37(12.2) | 3( 2.9) | 41(13.2) | 6( 4.5) |
| RASH ERYTHEMATOUS | - | 1( 1.3) | 2( 2.0) | 1( 1.4) | 3( 1.0) | 2( 1.9) | 5( 1.6) | 2( 1.5) |
| RASH MACULO-PAPULAR | - | - | - | - | 3( 1.0) | 1( 1.0) | 5( 1.6) | 1( 0.8) |
| SEBORRHOEA | - | - | 1( 1.0) | - | 1( 0.3) | - | 1( 0.3) | - |
| SKIN DEPIGMENTATION | - | - | - | - | - | - | 1( 0.3) | - |
| SKIN DISCOLOURATION | - | 1( 1.3) | 1( 1.0) | - | 5( 1.7) | 1( 1.0) | 5( 1.6) | 2( 1.5) |
| 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 | - | - | - | - | - | - | 2( 0.6) | 1( 0.8) |
| SWEATING INCREASED | - | 1( 1.3) | - | - | - | - | - | - |
| URTICARIA | 1( 1.0) | - | - | - | 4( 1.3) | - | 5( 1.6) | - |
| VERRUCA | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| VESICULAR RASH | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| 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 | - | - | - | - | - | - | - | 1( 0.8) |
| 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

| | 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 (%) |
| 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 | - | - | - | - | - | - | - | 1( 0.8) |
| NOCTURIA | - | - | 1( 1.0) | 1( 1.4) | 1( 0.3) | 1( 1.0) | 2( 0.6) | 1( 0.8) |
| OLIGURIA | 1( 1.0) | - | - | - | 5( 1.7) | - | 5( 1.6) | 1( 0.8) |
| POLYURIA | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| PYURIA | - | - | - | - | - | - | 1( 0.3) | 1( 0.8) |
| STRANGURY | - | - | - | - | - | - | - | 1( 0.8) |
| URINARY INCONTINENCE | 2( 2.0) | 1( 1.3) | 4( 4.1) | 2( 2.9) | 17( 5.6) | 5( 4.8) | 19( 6.1) | 5( 3.8) |
| URINARY RETENTION | - | - | - | - | 2( 0.7) | - | 4( 1.3) | - |
| URINARY TRACT INFECTION | 1( 1.0) | 2( 2.7) | 1( 1.0) | 3( 4.3) | 9( 3.0) | 4( 3.8) | 12( 3.9) | 8( 6.1) |
| URINE ABNORMAL | 1( 1.0) | - | 1( 1.0) | 2( 2.9) | 3( 1.0) | 2( 1.9) | 4( 1.3) | 3( 2.3) |
| VASCULAR (EXTRACARDIAC) DISORDERS | - | - | - | 1( 1.4) | 4( 1.3) | 2( 1.9) | 4( 1.3) | 2( 1.5) |
| FLUSHING | - | - | - | - | 3( 1.0) | - | 3( 1.0) | - |
| THROMBOPHLEBITIS | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| THROMBOPHLEBITIS 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 | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| CATARACT | - | - | - | - | - | - | - | 1( 0.8) |
| CONJUNCTIVAL DISCOLOURATION | 1( 1.0) | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| CONJUNCTIVAL HAEMORRHAGE | - | - | - | - | 1( 0.3) | - | 1( 0.3) | 2( 1.5) |
| CONJUNCTIVITIS | 2( 2.0) | - | 1( 1.0) | - | 10( 3.3) | 2( 1.9) | 12( 3.9) | 5( 3.8) |
| DIPLOPIA | - | 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) | - | 2( 0.7) | 1( 1.0) | 2( 0.6) | 1( 0.8) |
| EYE PAIN | 1( 1.0) | 1( 1.3) | - | - | 1( 0.3) | - | 3( 1.0) | - |
| KERATOCONJUNCTIVITIS | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| LACRIMATION ABNORMAL | - | - | 1( 1.0) | - | 2( 0.7) | - | 2( 0.6) | - |
| MYOPIA | - | - | 1( 1.0) | - | 1( 0.3) | - | 1( 0.3) | - |
| PUPILLARY REFLEX IMPAIRED | - | - | - | - | 1( 0.3) | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| VISION ABNORMAL | 1( 1.0) | 1( 1.3) | 2( 2.0) | 7(10.0) | 4( 1.3) | 7( 6.7) | 5( 1.6) | 8( 6.1) |
| 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( 0.3) | 1( 0.8) |
| LYMPHADENOPATHY | 1( 1.0) | - | 1( 1.0) | - | 2( 0.7) | 2( 1.9) | 2( 0.6) | 2( 1.5) |
| LYMPHOEDEMA | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| MONOCYTOSIS | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| WBC ABNORMAL NOS | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 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 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Double Blind Studies | | | | | | 4 Month Safety Update | |
| | Placebo | | Topiramate | | Total Topiramate | | Total Topiramate | |
| NEURO-PSYCHIATRIC DISORDERS | 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 (%) |
| | 70(69.3) | 47(62.7) | 74(75.5) | 55(78.6) | 254(83.8) | 86(81.9) | 274(88.4) | 118(89.4) |
| ABSCENCES | - | - | - | - | - | - | - | 1( 0.8) |
| 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) | 106(35.0) | 20(19.0) | 118(38.1) | 33(25.0) |
| ANXIETY | 1( 1.0) | 2( 2.7) | - | 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) |
| ATAXIA | 2( 2.0) | 4( 5.3) | 6( 6.1) | 5( 7.1) | 26( 8.6) | 10( 9.5) | 28( 9.0) | 16(12.1) |
| AUTOMATISM | - | 1( 1.3) | - | - | 3( 1.0) | - | 4( 1.3) | - |
| COGNITIVE PROBLEMS NOS | 2( 2.0) | 2( 2.7) | - | 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) |
| CONVULSIONS | - | - | - | - | - | - | 2( 0.6) | 1( 0.8) |
| CONVULSIONS AGGRAVATED | 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 GRAND MAL | - | - | 1( 1.0) | 1( 1.4) | 6( 2.0) | 2( 1.9) | 11( 3.5) | 3( 2.3) |
| COORDINATION ABNORMAL | 3( 3.0) | 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) | - | 1( 0.8) |
| DELUSION | 1( 1.0) | - | - | - | - | - | - | - |
| DEPRESSION | - | 2( 2.7) | - | 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) | 10(10.2) | 2( 2.9) | 29( 9.6) | 3( 2.9) | 34(11.0) | 16(12.1) |
| DIFFICULTY WITH MEMORY NOS | - | 2( 2.7) | 5( 5.1) | 8(11.4) | 17( 5.6) | 15(14.3) | 18( 5.8) | 24(18.2) |
| DIZZINESS | 2( 2.0) | 11(14.7) | 4( 4.1) | 13(18.6) | 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 | - | - | - | - | 13( 4.3) | 4( 3.8) | 13( 4.2) | 5( 3.8) |
| ENCEPHALOPATHY | 5( 5.0) | 2( 2.7) | 5( 5.1) | 3( 4.3) | 2( 0.7) | - | 2( 0.6) | - |
| EUPHORIA | - | - | - | - | 3( 1.0) | - | 3( 1.0) | - |
| FAECAL INCONTINENCE | - | - | - | - | 3( 1.0) | - | 4( 1.3) | - |
| FATIGUE | - | - | 1( 1.0) | - | 67(22.1) | 18(17.1) | 77(24.8) | 24(18.2) |
| GAIT ABNORMAL | 5( 5.0) | 10(13.3) | 16(16.3) | 14(20.0) | 24( 7.9) | 8( 7.6) | 31(10.0) | 11( 8.3) |
| HALLUCINATION | 5( 5.0) | 1( 1.3) | 8( 8.2) | 3( 4.3) | 3( 1.0) | 1( 1.0) | 4( 1.3) | 5( 3.8) |
| HEADACHE | - | 1( 1.3) | - | - | 48(15.8) | 25(23.8) | 61(19.7) | 40(30.3) |
| HEMIPLEGIA | 11(10.9) | 16(21.3) | 6( 6.1) | 15(21.4) | 1( 0.3) | - | 1( 0.3) | - |
| HYPERKINESIA | - | - | - | - | 15( 5.0) | 2( 1.9) | 18( 5.8) | 3( 2.3) |
| HYPERTONIA | 4( 4.0) | 2( 2.7) | 5( 5.1) | - | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| HYPOAESTHESIA | - | - | - | - | 2( 0.7) | 4( 3.8) | 2( 0.6) | 5( 3.8) |
| HYPOKINESIA | - | - | - | 1( 1.4) | 1( 0.3) | - | - | - |
| HYPOREFLEXIA | - | - | - | - | 3( 1.0) | - | 4( 1.3) | - |
| HYPOTONIA | - | - | 2( 2.0) | - | 3( 1.0) | - | 5( 1.6) | - |
| IMPOTENCE | - | - | - | - | - | - | - | - |
| INSOMNIA | - | 1( 1.3) | - | - | 38(12.5) | 7( 6.7) | 46(14.8) | 11( 8.3) |
| LANGUAGE PROBLEMS | 7( 6.9) | 6( 8.0) | 8( 8.2) | 4( 5.7) | 16( 5.3) | 5( 4.8) | 17( 5.5) | 12( 9.1) |
| LIBIDO DECREASED | 1( 1.0) | 2( 2.7) | 1( 1.0) | 4( 5.7) | - | 2( 1.9) | - | 2( 1.5) |
| | - | - | - | 2( 2.9) | | | | |

Table : Incidence of Neuro-PSychiatric Adverse Events

| NEURO-PSYCHIATRIC DISORDERS (Continued) | Supplemental NDA: Double Blind Studies: Placebo: Peds N = 101 No (%) | Supplemental NDA: Double Blind Studies: Placebo: Adult N = 75 No (%) | Supplemental NDA: Double Blind Studies: Topiramate: Peds N = 98 No (%) | Supplemental NDA: Double Blind Studies: Topiramate: Adult N = 70 No (%) | Supplemental NDA: Total Topiramate: Peds N = 303 No (%) | Supplemental NDA: Total Topiramate: Adult N = 105 No (%) | 4 Month Safety Update: Total Topiramate: Peds N = 310 No (%) | 4 Month Safety Update: Total Topiramate: Adult N = 132 No (%) |
|---|---|---|---|---|---|---|---|---|
| | 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 | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| MOOD PROBLEMS | 7( 6.9) | 2( 2.7) | 7( 7.1) | 3( 4.3) | 30( 9.9) | 7( 6.7) | 34(11.0) | 9( 6.8) |
| MUSCLE CONTRACTIONS INVOLUNTARY | - | - | - | 2( 2.9) | 5( 1.7) | 5( 4.8) | 5( 1.6) | 7( 5.3) |
| NERVOUSNESS | 7( 6.9) | 2( 2.7) | 14(14.3) | 12(17.1) | 51(16.8) | 19(18.1) | 65(21.0) | 23(17.4) |
| NEUROSIS | - | - | 1( 1.0) | - | 2( 0.7) | 1( 1.0) | 2( 0.6) | 1( 0.8) |
| NYSTAGMUS | 1( 1.0) | - | - | 1( 1.4) | 2( 0.7) | 2( 1.9) | 2( 0.6) | 3( 2.3) |
| OEDEMA CEREBRAL | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| PARAESTHESIA | - | 1( 1.3) | 1( 1.0) | 3( 4.3) | 15( 5.0) | 7( 6.7) | 19( 6.1) | 11( 8.3) |
| PARALYSIS | - | - | - | - | - | - | - | 1( 0.8) |
| PARANOID REACTION | - | - | - | 1( 1.4) | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| PARESIS | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| PARONIRIA | - | - | - | - | - | - | 1( 0.3) | - |
| PERSONALITY DISORDER(BEHAVIOR PROBLEMS) | 1( 1.0) | 1( 1.3) | - | - | 25( 8.3) | 3( 2.9) | 33(10.6) | 4( 3.0) |
| PSYCHOMOTOR SLOWING | 9( 8.9) | 5( 6.7) | 11(11.2) | 2( 2.9) | 24( 7.9) | 8( 7.6) | 29( 9.4) | 11( 8.3) |
| PSYCHOSIS | 2( 2.0) | 2( 2.7) | 3( 3.1) | 4( 5.7) | - | 1( 1.0) | - | 2( 1.5) |
| SENSORY DISTURBANCE | - | 1( 1.3) | - | - | 1( 0.3) | - | 2( 0.6) | 1( 0.8) |
| SLEEP DISORDER | - | - | - | - | 5( 1.7) | 1( 1.0) | 6( 1.9) | 1( 0.8) |
| SOMNOLENCE | 2( 2.0) | 1( 1.3) | 1( 1.0) | - | 111(36.6) | 29(27.6) | 127(41.0) | 49(37.1) |
| SPEECH DISORDERS/RELATED SPEECH PROBLEMS | 16(15.8) | 14(18.7) | 25(25.5) | 19(27.1) | 19( 6.3) | 7( 6.7) | 21( 6.8) | 11( 8.3) |
| STUPOR | 2( 2.0) | 1( 1.3) | 4( 4.1) | 5( 7.1) | - | 3( 2.9) | - | 5( 3.8) |
| SUICIDE ATTEMPT | - | - | - | 2( 2.9) | - | - | - | 1( 0.8) |
| TREMOR | - | - | - | - | 13( 4.3) | 8( 7.6) | 16( 5.2) | 17(12.9) |
| VERTIGO | 1( 1.0) | 5( 6.7) | - | 4( 5.7) | - | 1( 1.0) | 1( 0.3) | 2( 1.5) |
| VISUAL FIELD DEFECT | - | 1( 1.3) | - | 1( 1.4) | 1( 0.3) | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| | - | - | - | 1( 1.4) | | | | |

APPEARS THIS WAY
ON ORIGINAL

# Appendix 4c

## Incid[illegible] 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 | | 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( 0.8) |
| CHEST PAIN | - | 1( 1.3) | - | - | - | 1( 1.0) | - | - |
| CONDITION AGGRAVATED | - | - | - | - | - | - | - | 1( 0.8) |
| DRUG LEVEL INCREASED | - | - | - | - | - | - | 1( 0.3) | - |
| FATIGUE | - | - | - | - | 1( 0.3) | - | - | - |
| FEVER | - | - | - | - | 2( 0.7) | - | 4( 1.3) | - |
| HYPOTHERMIA | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| INJURY | - | 2( 2.7) | - | - | 1( 0.3) | 1( 1.0) | 2( 0.6) | 4( 3.0) |
| PAIN | - | 1( 1.3) | - | - | - | 1( 1.0) | - | 1( 0.8) |
| SUDDEN DEATH | - | 1( 1.3) | - | - | - | - | - | - |
| THERAPEUTIC RESPONSE INCREASED | - | - | - | 1( 1.4) | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| CENTR & 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) | - | - | - | - | - | - |
| CONVULSIONS | - | - | - | - | - | - | 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) | 1( 1.0) | 10( 3.2) | 2( 1.5) |
| DIZZINESS | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| EEG ABNORMAL | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| GAIT ABNORMAL | - | - | - | 1( 1.4) | 1( 0.3) | 1( 1.0) | 3( 1.0) | 1( 0.8) |
| SPEECH DISORDERS/RELATED SPEECH PROBLEMS | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| STUPOR | - | - | - | - | - | - | - | 1( 0.8) |
| TREMOR | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| ENDOCRINE DISORDERS | - | - | - | - | - | - | - | 1( 0.8) |
| GLUCOCORTICOIDS 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) | 2( 1.5) |
| CONSTIPATION | - | - | 1( 1.0) | - | 1( 0.3) | - | 2( 0.6) | - |
| DIARRHOEA | - | - | - | - | 1( 0.3) | - | 4( 1.3) | - |
| DYSPHAGIA | - | - | - | - | - | - | 2( 0.6) | - |
| GASTRITIS | - | - | - | - | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| GASTROENTERITIS | - | - | - | - | - | - | 3( 1.0) | - |
| GASTROESOPHAGEAL REFLUX | - | - | 1( 1.0) | - | 1( 0.3) | - | 2( 0.6) | 1( 0.8) |
| HAEMATEMESIS | - | 1( 1.3) | - | - | - | - | - | - |
| INTESTINAL OBSTRUCTION | - | - | - | - | - | - | - | 1( 0.8) |
| INTESTINAL PERFORATION | - | - | - | - | - | - | - | 1( 0.8) |
| NAUSEA | - | 1( 1.3) | - | - | - | 1( 1.0) | - | 1( 0.8) |
| OESOPHAGEAL STRICTURE | - | - | - | - | - | - | 1( 0.3) | - |
| PANCREATITIS | - | - | - | - | - | 1( 1.0) | 1( 0.3) | 1( 0.8) |
| VOMITING | - | 1( 1.3) | 1( 1.0) | - | 1( 0.3) | 1( 1.0) | 5( 1.6) | 1( 0.8) |

Table : Incidence of Serious 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 (%) |
| HEART RATE AND RHYTHM DISORDERS | - | - | - | - | - | - | 1( 0.3) | - |
| CARDIAC ARREST | - | - | - | - | - | - | 1( 0.3) | - |
| LIVER AND BILIARY SYSTEM DISORDERS | - | - | - | - | - | 1( 1.0) | - | 2( 1.5) |
| CHOLELITHIASIS | - | - | - | - | - | 1( 1.0) | - | 2( 1.5) |
| METABOLIC AND NUTRITIONAL DISORDERS | - | - | - | - | 6( 2.0) | 1( 1.0) | 14( 4.5) | 1( 0.8) |
| ACIDOSIS LACTIC | - | - | - | - | - | - | 1( 0.3) | - |
| DEHYDRATION | - | - | - | - | 5( 1.7) | - | 11( 3.5) | - |
| OEDEMA PERIORBITAL | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| OSTEOMALACIA | - | - | - | - | - | - | 1( 0.3) | - |
| WEIGHT DECREASE | - | - | - | - | - | 1( 1.0) | - | 1( 0.8) |
| PLATELET, BLEEDING & CLOTTING DISORDERS | - | - | - | - | - | - | 1( 0.3) | - |
| COAGULATION TIME INCREASED | - | - | - | - | - | - | 1( 0.3) | - |
| PSYCHIATRIC DISORDERS | - | 2( 2.7) | - | 3( 4.3) | 5( 1.7) | 4( 3.8) | 10( 3.2) | 10( 7.6) |
| AGGRESSIVE REACTION | - | - | - | 1( 1.4) | 1( 0.3) | 1( 1.0) | 1( 0.3) | 3( 2.3) |
| AGITATION | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 2( 1.5) |
| ANOREXIA | - | - | - | - | 1( 0.3) | - | 4( 1.3) | - |
| APATHY | - | - | - | - | 1( 0.3) | - | 1( 0.3) | 1( 0.8) |
| CONFUSION | - | 1( 1.3) | - | - | - | - | - | 2( 1.5) |
| DEPRESSION | - | - | - | - | - | 1( 1.0) | - | 2( 1.5) |
| HALLUCINATION | - | - | - | - | 1( 0.3) | - | 1( 0.3) | 1( 0.8) |
| INSOMNIA | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| NERVOUSNESS | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| PERSONALITY DISORDER (BEHAVIOR PROBLEMS) | - | - | - | - | - | 1( 1.0) | - | 1( 0.8) |
| PSYCHOSIS | - | 1( 1.3) | - | - | - | - | - | 1( 0.8) |
| SOMNOLENCE | - | - | - | 1( 1.4) | 3( 1.0) | 1( 1.0) | 6( 1.9) | 2( 1.5) |
| SUICIDE ATTEMPT | - | - | - | - | - | 1( 1.0) | - | 1( 0.8) |
| | | | | | | - | | 1( 0.8) |

Table . .cidence of Serious Adverse Events

| | Supplemental NDA | | | | | | 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 (%) |
| RESPIRATORY SYSTEM DISORDERS | - | - | 2( 2.0) | - | 14( 4.6) | 1( 1.0) | 19( 6.1) | 3( 2.3) |
| ASPIRATION | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| ASTHMA | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| ATELECTASIS | - | - | - | - | 1( 0.3) | - | 1( 0.3) | - |
| BRONCHITIS | - | - | - | - | - | - | 1( 0.3) | - |
| DYSPNOEA | - | - | - | - | - | - | - | 1( 0.8) |
| PHARYNGITIS | - | - | - | - | 4( 1.3) | - | 4( 1.3) | - |
| PLEURAL EFFUSION | - | - | 2( 2.0) | - | - | - | - | 1( 0.8) |
| PNEUMONIA | - | - | - | - | 6( 2.0) | 1( 1.0) | 11( 3.5) | 2( 1.5) |
| RESPIRATORY DEPRESSION | - | - | - | - | - | - | 1( 0.3) | - |
| RESPIRATORY DISORDER | - | - | 1( 1.0) | - | 1( 0.3) | - | 1( 0.3) | - |
| SINUSITIS | - | - | - | - | 1( 0.3) | - | 3( 1.0) | - |
| UPPER RESP TRACT INFECTION | - | - | - | - | 1( 0.3) | - | 2( 0.6) | - |
| SKIN AND APPENDAGES DISORDERS | - | - | - | - | 2( 0.7) | - | 2( 0.6) | - |
| RASH | - | - | - | - | 2( 0.7) | - | 2( 0.6) | - |
| REPRODUCTIVE DISORDERS, FEMALE @ | - | - | - | - | - | 1( 2.2) | - | - |
| BREAST ENLARGEMENT | - | - | - | - | - | 1( 2.2) | - | - |
| REPRODUCTIVE DISORDERS, MALE @ | - | - | - | 1( 2.7) | - | 1( 1.7) | - | 1( 1.4) |
| PROSTATIC DISORDER | - | - | - | 1( 2.7) | - | 1( 1.7) | - | 1( 1.4) |
| RESISTANCE MECHANISM DISORDERS | 1( 1.0) | 1( 1.3) | 1( 1.0) | 2( 2.9) | 2( 0.7) | 2( 1.9) | 7( 2.3) | 4( 3.0) |
| ABSCESS | - | 1( 1.3) | - | 1( 1.4) | - | 1( 1.0) | - | 2( 1.5) |
| INFECTION | - | - | - | - | - | - | 1( 0.3) | 1( 0.8) |
| INFECTION BACTERIAL | - | - | - | - | - | - | 1( 0.3) | 1( 0.8) |
| INFECTION VIRAL | 1( 1.0) | - | - | 1( 1.4) | - | 1( 1.0) | 2( 0.6) | 1( 0.8) |
| OTITIS MEDIA | - | - | 1( 1.0) | - | 2( 0.7) | - | 2( 0.6) | - |
| SEPSIS | - | - | - | - | - | - | 1( 0.3) | 1( 0.8) |

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

Double - Blind

Placebo - pedialrics 51M and 50F
- adults 41M and 34F

TPM - pedialrics 55M and 43F
adults 37M and 33F

Total Topiramate

SNDA - pedialrics: 179M and 124F.
adults: 59M and 46F.

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

Table : Incidence of Serious 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 (%) |
| URINARY SYSTEM DISORDERS | - | - | - | 1( 1.4) | 1( 0.3) | 1( 1.0) | 2( 0.6) | 2( 1.5) |
| MICTURITION DISORDER | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| OLIGURIA | - | - | - | - | - | - | - | 1( 0.8) |
| URINARY INCONTINENCE | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| URINARY TRACT INFECTION | - | - | - | - | 1( 0.3) | - | 2( 0.6) | - |
| VASCULAR (EXTRACARDIAC) DISORDERS | - | - | - | 1( 1.4) | - | 2( 1.9) | - | 2( 1.5) |
| THROMBOPHLEBITIS | - | - | - | 1( 1.4) | - | 1( 1.0) | - | 1( 0.8) |
| THROMBOPHLEBITIS DEEP | - | - | - | - | - | 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

Jackie -
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 phenobarbitol 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 the 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