Migraine

The results of 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials established the effectiveness of TOPAMAX® in the prophylactic treatment of migraine headache. The design of both trials (one study was conducted in the U.S. and one study was conducted in the U.S. and Canada) was identical, enrolling patients with a history of migraine, with or without aura, for at least 6 months, according to the International Headache Society diagnostic criteria. Patients with a history of cluster headaches or basilar, ophthalmoplegic, hemiplegic, or transformed migraine headaches were excluded from the trials. Patients were required to have completed up to a 2 week washout of any prior migraine preventive medications before starting the baseline phase.

Patients who experienced 3 to 12 migraine headaches over the 4-weeks in the baseline phase were equally randomized to either TOPAMAX® 50 mg/day, 100 mg/day, 200 mg/day, or placebo and treated for a total of 26 weeks (8-week titration period and 18-week maintenance period). Treatment was initiated at 25 mg/day for one week, and then the daily dosage was increased by 25-mg increments each week until reaching the assigned target dose or maximum tolerated dose (administered twice daily).

Effectiveness of treatment was assessed by the reduction in migraine headache frequency, as measured by the change in 4-week migraine rate from the baseline phase to double-blind treatment period in each TOPAMAX® treatment group compared to placebo in the intent to treat (ITT) population.

In the first study a total of 469 patients (416 females, 53 males), ranging in age from 13 to 70 years, were randomized and provided efficacy data. Two hundred sixty five patients completed the entire 26-week double-blind phase. The median average daily dosages were 47.8 mg/day, 88.3 mg/day, and 132.1 mg/day in the target dose groups of TOPAMAX® 50, 100, and 200 mg/day, respectively.

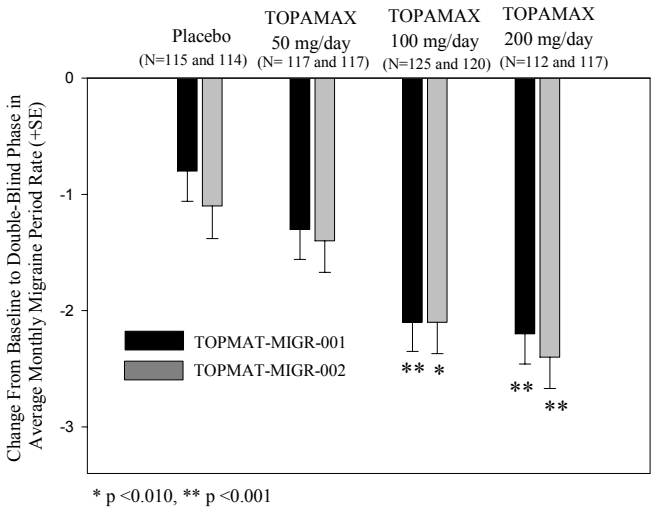
The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches/28 days and was similar across treatment groups. The change in the mean 4-week migraine headache frequency from baseline to the double-blind phase was -1.3, -2.1, and -2.2 in the TOPAMAX® 50, 100, and 200 mg/day groups, respectively, versus -0.8 in the placebo group (see Figure 2). The differences between the TOPAMAX® 100 and 200 mg/day groups versus placebo were statistically significant ($p<0.001$ for both comparisons).

In the second study a total of 468 patients (406 females, 62 males), ranging in age from 12 to 65 years, were randomized and provided efficacy data. Two hundred fifty five patients completed the entire 26-week double-blind phase. The median average daily dosages were 46.5 mg/day, 85.6 mg/day, and 150.2 mg/day in the target dose groups of TOPAMAX® 50, 100, and 200 mg/day, respectively.

The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches/28 days and was similar across treatment groups. The change in the mean 4-week migraine headache period frequency from baseline to the double-blind phase was -1.4, -2.1, and -2.4 in the TOPAMAX® 50, 100, and 200 mg/day groups, respectively, versus –1.1 in the placebo group (see Figure 2). The differences between the TOPAMAX® 100 and 200 mg/day groups versus placebo were statistically significant (p=0.008 and <0.001, respectively).

In both studies, there were no apparent differences in treatment effect within age, or gender, subgroups. Because most patients were Caucasian, there were insufficient numbers of patients from different races to make a meaningful comparison of race.

Figure 2: Reduction in 4-Week Migraine Headache Frequency (Studies TOPMAT-MIGR-001 and TOPMAT-MIGR-002)



* p <0.010, ** p <0.001

physician. Other measures, in conjunction with discontinuation of TOPAMAX®, may be helpful.

Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.

Oligohidrosis and Hyperthermia

Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with TOPAMAX® use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures.

The majority of the reports have been in children. Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TOPAMAX® is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

Withdrawal of AEDs

Antiepileptic drugs, including TOPAMAX®, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Cognitive/Neuropsychiatric Adverse Events

Adults

Adverse events most often associated with the use of TOPAMAX® were related to the central nervous system and were observed in both the epilepsy and migraine populations. In adults, the most frequent of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g. confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g. depression or mood problems); and 3) Somnolence or fatigue.

Cognitive-Related Dysfunction

The majority of cognitive-related adverse events were mild to moderate in severity, and they frequently occurred in isolation. Rapid titration rate and higher initial dose were associated with higher incidences of these events. Many of these events contributed to withdrawal from treatment [see **ADVERSE REACTIONS, Table 4, Table 6, and Table 10**].

In the original add-on epilepsy controlled trials (using rapid titration such as 100-200 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse events was 42% for 200 mg/day, 41% for 400 mg/day, 52% for 600 mg/day, 56% for 800 and 1000 mg/day, and 14% for placebo. These dose-related adverse reactions began with a similar frequency in the titration or in the maintenance phase, although in some patients the events began during titration and persisted into the maintenance phase. Some patients who experienced one or more cognitive-related adverse events in the titration phase had a dose-related recurrence of these events in the maintenance phase.

In the monotherapy epilepsy controlled trial, the proportion of patients who experienced one or more cognitive-related adverse events was 19% for TOPAMAX® 50 mg/day and 26% for 400 mg/day.

In the 6-month migraine prophylaxis controlled trials using a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse events was 19% for TOPAMAX® 50 mg/day, 22% for 100 mg/day, 28% for 200 mg/day, and 10% for placebo. These dose-related adverse reactions typically began in the titration phase and often persisted into the maintenance phase, but infrequently began in the maintenance phase. Some patients experienced a recurrence of one or more of these cognitive adverse events and this recurrence was typically in the titration phase. A relatively small proportion of topiramate-treated patients experienced more than one concurrent cognitive adverse event. The most common cognitive adverse events occurring together included difficulty with memory along with difficulty with concentration/attention, difficulty with memory along with language problems, and difficulty with concentration/attention along with language problems. Rarely, topiramate-treated patients experienced three concurrent cognitive events.

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (depression or mood problems) were dose-related for both the epilepsy and migraine populations.

Somnolence/Fatigue

Somnolence and fatigue were the adverse events most frequently reported during clinical trials of TOPAMAX® for adjunctive epilepsy. For the adjunctive epilepsy population, the incidence of somnolence did not differ substantially between 200 mg/day and 1000 mg/day, but the incidence of fatigue was dose-related and increased

Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.

Reproductive Disorders, Male: *Infrequent:* ejaculation disorder, breast discharge.

Skin and Appendages Disorders: *Infrequent:* urticaria, photosensitivity reaction, abnormal hair texture. *Rare:* chloasma.

Special Senses Other, Disorders: *Infrequent:* taste loss, parosmia.

Urinary System Disorders: *Infrequent:* urinary retention, face edema, renal pain, albuminuria, polyuria, oliguria.

Vascular (Extracardiac) Disorders: *Infrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.

Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, strabismus. *Rare:* mydriasis, iritis.

White Cell and Reticuloendothelial System Disorders: *Infrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia. *Rare:* lymphocytosis.

Migraine

In the four multicenter, randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials, most of the adverse events with topiramate were mild or moderate in severity. Most adverse events occurred more frequently during the titration period than during the maintenance period.

Table 10 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in any topiramate treatment group was at least 2% and was greater than that for placebo patients.

Table 10: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Migraine Trials Where Rate Was ≥2 % in Any Topiramate Group and Greater than the Rate in Placebo-Treated Patients [a]

	TOPAMAX® Dosage (mg/day)			
Body System/ Adverse Event	Placebo (N=445)	50 (N=235)	100 (N=386)	200 (N=514)
Body as a Whole-General Disorders				
Fatigue	11	14	15	19
Injury	7	9	6	6
Asthenia	1	<1	2	2
Fever	1	1	1	2
Influenza-Like Symptoms	<1	<1	<1	2
Allergy	<1	2	<1	<1
Central & Peripheral Nervous System Disorders				
Paresthesia	6	35	51	49
Dizziness	10	8	9	12
Hypoaesthesia	2	6	7	8
Language Problems	2	7	6	7
Involuntary Muscle Contractions	1	2	2	4
Ataxia	<1	1	2	1
Speech Disorders/Related Speech Problems	<1	1	<1	2
Gastro-Intestinal System Disorders				
Nausea	8	9	13	14
Diarrhea	4	9	11	11
Abdominal Pain	5	6	6	7
Dyspepsia	3	4	5	3
Dry Mouth	2	2	3	5
Vomiting	2	1	2	3
Gastroenteritis	1	3	3	2
Hearing and Vestibular Disorders				
Tinnitus	1	<1	1	2
Metabolic and Nutritional Disorders				
Weight Decrease	1	6	9	11
Thirst	<1	2	2	1
Musculoskeletal System Disorders				
Arthralgia	2	7	3	1
Neoplasms				
Neoplasm NOS	<1	2	<1	<1
Psychiatric Disorders				
Anorexia	6	9	15	14
Somnolence	5	8	7	10
Difficulty with Memory NOS	2	7	7	11
Difficulty with Concentration/Attention	2	3	6	10
Insomnia	5	6	7	6
Anxiety	3	4	5	6
Mood Problems	2	3	6	5
Depression	4	3	4	6
Nervousness	2	4	4	4
Confusion	2	2	3	4
Psychomotor Slowing	1	3	2	4
Libido Decreased	1	1	1	2
Aggravated Depression	1	1	2	2
Agitation	1	2	2	1
Cognitive Problems NOS	1	<1	2	2
Reproductive Disorders, Female				
Menstrual Disorder	2	3	2	2
Reproductive Disorders, Male				
Ejaculation Premature	0	3	0	0
Resistance Mechanism Disorders				
Viral Infection	3	4	4	3
Otitis Media	<1	2	1	1
Respiratory System Disorders				
Upper Respiratory Tract Infection	12	13	14	12
Sinusitis	6	10	6	8
Pharyngitis	4	5	6	2
Coughing	2	2	4	3

Bronchitis	2	3	3	3
Dyspnea	2	1	3	2
Rhinitis	1	1	2	2

(Continued)

Table 10: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Migraine Trials Where Rate Was ≥2 % in Any Topiramate Group and Greater than the Rate in Placebo-Treated Patients [a]

	TOPAMAX® Dosage (mg/day)			
Body System/ Adverse Event	Placebo (N=445)	50 (N=235)	100 (N=386)	200 (N=514)
Skin and Appendages Disorders				
Pruritis	2	4	2	2
Special Sense Other, Disorders				
Taste Perversion	1	15	8	12
Taste Loss	<1	1	1	2
Urinary System Disorders				
Urinary Tract Infection	2	4	2	4
Renal Calculus	0	0	1	2
Vision Disorders				
Vision Abnormal	<1	1	2	3
Blurred Vision [b]	2	4	2	4
Conjunctivitis	1	1	2	1

[a] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

[b] Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for > 50 % of events coded as vision abnormal, a preferred term.

Of the 1,135 patients exposed to topiramate in the placebo-controlled studies, 25% discontinued due to adverse events, compared to 10% of the 445 placebo patients. The adverse events associated with discontinuing therapy in the topiramate-treated patients included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%).

Patients treated with topiramate experienced mean percent reductions in body weight that were dose-dependent. This change was not seen in the placebo group. Mean changes of 0%, –2%, – 3%, and – 4% were seen for the placebo group, topiramate 50, 100, and 200 mg groups, respectively.

Table 11 shows adverse events that were dose-dependent. Several central nervous system adverse events, including some that represented cognitive dysfunction, were dose-related. The most common dose-related adverse events were paresthesia, fatigue, nausea, anorexia, dizziness, difficulty with memory, diarrhea, weight decrease, difficulty with concentration/attention, and somnolence.

Table 11: Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Migraine Trials[a]

			TOPAMAX® Dosage (mg/day)	
Adverse Event	Placebo (N =445)	50 (N = 235)	100 (N = 386)	200 (N = 514)
Paresthesia	6	35	51	49
Fatigue	11	14	15	19
Nausea	8	9	13	14
Anorexia	6	9	15	14
Dizziness	10	8	9	12
Weight decrease	1	6	9	11
Difficulty with Memory NOS	2	7	7	11
Diarrhea	4	9	11	11
Difficulty with Concentration/Attention	2	3	6	10
Somnolence	5	8	7	10
Hypoaesthesia	2	6	7	8
Anxiety	3	4	5	6
Depression	4	3	4	6
Mood Problems	2	3	6	5
Dry Mouth	2	2	3	5
Confusion	2	2	3	4
Involuntary Muscle Contractions	1	2	2	4
Abnormal Vision	<1	1	2	3
Renal Calculus	0	0	1	2

[a] The incidence rate of the adverse event in the 200 mg/day group was ≥2% than the rate in both the placebo group and the 50 mg/day group.

Other Adverse Events Observed During Migraine Clinical Trials

Topiramate, for the treatment of prophylaxis of migraine headache, has been administered to 1,367 patients in all clinical studies (includes double-blind and open-label extension). During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology.

The following additional adverse events that were not described earlier were reported by greater than 1% of the 1,367 topiramate-treated patients in the controlled clinical trials:

Body as a Whole: Pain, chest pain, allergic reaction.

Central & Peripheral Nervous System Disorders: Headache, vertigo, tremor, sensory disturbance, migraine aggravated.

Gastrointestinal System Disorders: Constipation, gastroesophageal reflux, tooth disorder.

Musculoskeletal System Disorders: Myalgia.

Platelet, Bleeding, and Clotting Disorders: Epistaxis.

Reproductive Disorders, Female: Intermenstrual bleeding.

Resistance Mechanism Disorders: Infection, genital moniliasis.

Respiratory System Disorders: Pneumonia, asthma.

Skin and Appendages Disorders: Rash, alopecia.

Vision Disorders: Abnormal accommodation, eye pain.

Postmarketing and Other Experience

In addition to the adverse experiences reported during clinical testing of TOPAMAX®, the following adverse experiences have been reported worldwide in patients receiving topiramate post-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: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, pancreatitis, pemphigus, and renal tubular acidosis.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of TOPAMAX® has not been evaluated in human studies.

OVERDOSAGE

Overdoses of TOPAMAX® have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-drug overdoses involving TOPAMAX®.

Topiramate overdose has resulted in severe metabolic acidosis (see **WARNINGS**).

A patient who ingested a dose between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.