HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TOPAMAX® safely and effectively. See full prescribing information for TOPAMAX®

TOPAMAX (topiramate) TABLETS for oral use

TOPAMAX (topiramate capsules) SPRINKLE CAPSULES for oral use

Initial U.S. Approval – 1996

----------RECENT MAJOR CHANGES----------

- Indications and Usage (1.1) 07/2011
- Dosage and Administration (2.1) 07/2011
- Metabolic Acidosis (5.3) 07/2011
- Hypothermia with Concomitant Valproic Acid (VPA) Use (5.11) 07/2011

----------INDICATIONS AND USAGE----------

TOPAMAX® is an antiepileptic (AED) agent indicated for:

- Monotherapy epilepsy: Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures (1.1)
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS) (1.2)
- Migraine: Treatment for adults for prophylaxis of migraine headache (1.3)

----------DOSAGE AND ADMINISTRATION----------

See DOSAGE AND ADMINISTRATION, Epilepsy: Monotherapy and Adjunctive Therapy Use for additional details (2.1)

	Initial Dose	Titration	Recommended Dose
Epilepsy monotherapy: children 2 to <10 years (2.1)	25 mg/day administered nightly for the first week	The dosage should be titrated over 5-7 weeks	Daily doses in two divided doses based on weight (Table 2)
Epilepsy monotherapy: adults and pediatric patients ≥10 years (2.1)	50 mg/day in two divided doses	The dosage should be increased weekly by increments of 50 mg for the first 4 weeks then 100 mg for weeks 5 to 6.	400 mg/day in two divided doses
Epilepsy adjunctive therapy: adults with partial onset seizures or LGS (2.1)	25 to 50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	200-400 mg/day in two divided doses
Epilepsy adjunctive therapy: adults with primary generalized tonic-clonic seizures (2.1)	25 to 50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	400 mg/day in two divided doses
Epilepsy adjunctive therapy: pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or LGS (2.1)	25 mg/day (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week	The dosage should be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses). Dose titration should be guided by clinical outcome.	5 to 9 mg/kg/day in two divided doses
Migraine (2.2)	25 mg/day administered nightly for the first week	The dosage should be increased weekly by increments of 25 mg. Dose and titration should be guided by clinical outcome.	100 mg/day administered in two divided doses

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 25 mg, 50 mg, 100 mg, and 200 mg (3)
- Sprinkle Capsules: 15 mg and 25 mg (3)

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- Acute myopia and secondary angle closure glaucoma: Untreated elevated intraocular pressure can lead to permanent visual loss. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible (5.1)
- Oligohidrosis and hyperthermia: Monitor decreased sweating and increased body temperature, especially in pediatric patients (5.2)
- Metabolic acidosis: Baseline and periodic measurement of serum bicarbonate is recommended. Consider dose reduction or discontinuation of TOPAMAX® if clinically appropriate (5.3)
- Suicidal behavior and ideation: Antiepileptic drugs increase the risk of suicidal behavior or ideation (5.4)
- Cognitive/neuropsychiatric: TOPAMAX® may cause cognitive dysfunction. Patients should use caution when operating machinery including automobiles. Depression and mood problems may occur in epilepsy and migraine populations (5.5)
- Fetal Toxicity: TOPAMAX® use during pregnancy can cause cleft lip and/or palate (5.6)
- Withdrawal of AEDs: Withdrawal of TOPAMAX® should be done gradually (5.7)
- Hyperammonemia and encephalopathy associated with or without concomitant valproic acid use: Patients with inborn errors of metabolism or reduced mitochondrial activity may have an increased risk of hyperammonemia. Measure ammonia if encephalopathic symptoms occur (5.9)
- Kidney stones: Use with other carbonic anhydrase inhibitors, other drugs causing metabolic acidosis, or in patients on a ketogenic diet should be avoided (5.10)
- Hypothermia has been reported with and without hyperammonemia during topiramate treatment with concomitant valproic acid use (5.11)

----------ADVERSE REACTIONS----------

The most common (≥5% more frequent than placebo or low-dose TOPAMAX® in monotherapy) adverse reactions in controlled, epilepsy clinical trials were paresthesia, anorexia, weight decrease, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, difficulty with memory, difficulty with concentration/attention, cognitive problem, confusion, mood problems, fever, infection, and flushing . The most common (≥5% more frequent than placebo) adverse reactions in controlled, migraine clinical trials were paresthesia and taste perversion (6) .

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *WWW.FDA.GOV/MEDWATCH.*

----------DRUG INTERACTIONS----------

Summary of antiepileptic drug (AED) interactions with TOPAMAX® (7.1)

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400 mg/day	13% decrease

[a] = Plasma concentration increased 25% in some patients, generally those on a twice a day dosing regimen of phenytoin.
[b] = Is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration.
NE = Not Evaluated

- Oral contraceptives: Decreased contraceptive efficacy and increased breakthrough bleeding should be considered, especially at doses greater than 200 mg/day (7.3)
- Metformin is contraindicated with metabolic acidosis, an effect of TOPAMAX® (7.4)
- Lithium levels should be monitored when co-administered with high-dose TOPAMAX® (7.5)
- Other carbonic anhydrase inhibitors: Monitor the patient for the appearance or worsening of metabolic acidosis (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- Renal impairment: In renally impaired patients (creatinine clearance less than 70 mL/min/1.73 m^2), one-half of the adult dose is recommended (2.4)
- Patients undergoing hemodialysis: Topiramate is cleared by hemodialysis. Dosage adjustment is necessary to avoid rapid drops in topiramate plasma concentration during hemodialysis (2.6)
- Pregnancy: Increased risk of cleft lip and/or palate. Pregnancy registry available (8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing mother (8.3)
- Geriatric use: Dosage adjustment may be necessary for elderly with impaired renal function (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Monotherapy Epilepsy
1.2 Adjunctive Therapy Epilepsy
1.3 Migraine
2 DOSAGE AND ADMINISTRATION
2.1 Epilepsy
2.2 Migraine
2.3 Administration of TOPAMAX® Sprinkle Capsules
2.4 Patients with Renal Impairment
2.5 Geriatric Patients (Ages 65 Years and Over)
2.6 Patients Undergoing Hemodialysis
2.7 Patients with Hepatic Disease
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Acute Myopia and Secondary Angle Closure Glaucoma
5.2 Oligohidrosis and Hyperthermia
5.3 Metabolic Acidosis
5.4 Suicidal Behavior and Ideation
5.5 Cognitive/Neuropsychiatric Adverse Reactions
5.6 Fetal Toxicity
5.7 Withdrawal of Antiepileptic Drugs (AEDs)
5.8 Sudden Unexplained Death in Epilepsy (SUDEP)
5.9 Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use)
5.10 Kidney Stones
5.11 Hypothermia with Concomitant Valproic Acid (VPA) Use
5.12 Paresthesia
5.13 Adjustment of Dose in Renal Failure
5.14 Decreased Hepatic Function
5.15 Monitoring: Laboratory Tests
6 ADVERSE REACTIONS
6.1 Monotherapy Epilepsy
6.2 Adjunctive Therapy Epilepsy
6.3 Incidence in Epilepsy Controlled Clinical Trials – Adjunctive Therapy – Partial Onset Seizures, Primary Generalized Tonic-Clonic Seizures, and Lennox-Gastaut Syndrome
6.4 Other Adverse Reactions Observed During Double-Blind Epilepsy Adjunctive Therapy Trials
6.5 Incidence in Study 119 – Add-On Therapy– Adults with Partial Onset Seizures
6.6 Other Adverse Reactions Observed During All Epilepsy Clinical Trials
6.7 Migraine
6.8 Other Adverse Reactions Observed During Migraine Clinical Trials
6.9 Postmarketing and Other Experience
7 DRUG INTERACTIONS
7.1 Antiepileptic Drugs
7.2 CNS Depressants
7.3 Oral Contraceptives
7.4 Metformin
7.5 Lithium
7.6 Other Carbonic Anhydrase Inhibitors
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Race and Gender Effects
8.7 Renal Impairment
8.8 Patients Undergoing Hemodialysis
8.9 Women of Childbearing Potential
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NON-CLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility
14 CLINICAL STUDIES
14.1 Monotherapy Epilepsy Controlled Trial
14.2 Adjunctive Therapy Epilepsy Controlled Trials
14.3 Migraine Prophylaxis

16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Eye Disorders
17.2 Oligohydrosis and Hyperthermia
17.3 Metabolic Acidosis
17.4 Suicidal Behavior and Ideation
17.5 Interference with Cognitive and Motor Performance
17.6 Fetal Toxicity
17.7 Hyperammonemia and Encephalopathy
17.8 Kidney Stones

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy Epilepsy

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as initial monotherapy in patients 2 years of age and older with partial onset or primary generalized tonic-clonic seizures. Safety and effectiveness in patients who were converted to monotherapy from a previous regimen of other anticonvulsant drugs have not been established in controlled trials *[see Clinical Studies (14.1)]*.

1.2 Adjunctive Therapy Epilepsy

TOPAMAX® Tablets and TOPAMAX® Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2 to 16 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome *[see Clinical Studies (14.2)]*.

1.3 Migraine

TOPAMAX® Tablets and TOPAMAX® Sprinkle Capsules are indicated for adults for the prophylaxis of migraine headache *[see Clinical Studies (14.3)]*. The usefulness of TOPAMAX® in the acute treatment of migraine headache has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Epilepsy

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® (topiramate) therapy.

On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®.

Because of the bitter taste, tablets should not be broken.

TOPAMAX® can be taken without regard to meals.

Monotherapy Use

Adults and Pediatric Patients 10 Years and Older

The recommended dose for TOPAMAX® monotherapy in adults and pediatric patients 10 years of age and older is 400 mg/day in two divided doses. Approximately 58% of patients randomized to 400 mg/day achieved this maximal dose in the monotherapy controlled trial; the mean dose achieved in the trial was 275 mg/day. The dose should be achieved by titration according to the following schedule (Table 1):

Table 1: Monotherapy Titration Schedule for Adults and Pediatric Patients 10 years and older

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

Children Ages 2 to <10 Years

Dosing of topiramate as initial monotherapy in children 2 to < 10 years of age with partial onset or primary generalized tonic-clonic seizures was based on a pharmacometric bridging approach *[see Clinical Studies (14.1)]*.

Dosing in patients 2 to <10 years is based on weight. During the titration period, the initial dose of TOPAMAX® should be 25 mg/day administered nightly for the first week. Based upon tolerability, the dosage can be increased to 50 mg/day (25 mg twice daily) in the second week. Dosage can be increased by 25-50 mg/day each subsequent week as tolerated. Titration to the minimum maintenance dose should be attempted over 5-7 weeks of the total titration period. Based upon tolerability and seizure control, additional titration to a higher dose (up to the maximum maintenance dose) can be attempted at 25-50 mg/day weekly increments. The total daily dose should not exceed the maximum maintenance dose for each range of body weight (Table 2).

Table 2: Monotherapy Target Total Daily Maintenance Dosing for Patients 2 to <10 Years

Weight (kg)	Total Daily Dose (mg/day)* Minimum Maintenance Dose	Total Daily Dose (mg/day)* Maximum Maintenance Dose
Up to 11	150	250
12 - 22	200	300
23 - 31	200	350
32 - 38	250	350
Greater than 38	250	400

* Administered in two equally divided doses

Adjunctive Therapy Use

Adults 17 Years of Age and Over - Partial Onset Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome

The recommended total daily dose of TOPAMAX® as adjunctive therapy in adults with partial onset seizures is 200 to 400 mg/day in two divided doses, and 400 mg/day in two divided doses as adjunctive treatment in adults with primary generalized tonic-clonic seizures. It is recommended that therapy be initiated at 25 to 50 mg/day followed by titration to an effective dose in increments of 25 to 50 mg/day every week. Titrating in increments of 25 mg/day every week may delay the time to reach an effective dose. Doses above 400 mg/day (600, 800 or 1,000 mg/day) have not been shown to improve responses in dose-response studies in adults with partial onset seizures. Daily doses above 1,600 mg have not been studied.

In the study of primary generalized tonic-clonic seizures, the initial titration rate was slower than in previous studies; the assigned dose was reached at the end of 8 weeks *[see Clinical Studies (14.1)]*.

Pediatric Patients Ages 2 - 16 Years – Partial Onset Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome

The recommended total daily dose of TOPAMAX® as adjunctive therapy for pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg/day (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome.

In the study of primary generalized tonic-clonic seizures, the initial titration rate was slower than in previous studies; the assigned dose of 6 mg/kg/day was reached at the end of 8 weeks *[see Clinical Studies (14.1)]*.

2.2 Migraine

The recommended total daily dose of TOPAMAX® as treatment for adults for prophylaxis of migraine headache is 100 mg/day administered in two divided doses (Table 3). The recommended titration rate for topiramate for migraine prophylaxis to 100 mg/day is:

Table 3: Migraine Prophylaxis Titration Schedule for Adults

	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

Dose and titration rate should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.

TOPAMAX® can be taken without regard to meals.

2.3 Administration of TOPAMAX® Sprinkle Capsules

TOPAMAX® (topiramate capsules) Sprinkle Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

2.4 Patients with Renal Impairment

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73 m^2), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

2.5 Geriatric Patients (Ages 65 Years and Over)

Dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate <70 mL/min/1.73 m^2) is evident *[see Clinical Pharmacology (12.3)]*.

2.6 Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate

plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

2.7 Patients with Hepatic Disease

In hepatically impaired patients, topiramate plasma concentrations may be increased. The mechanism is not well understood.

3 DOSAGE FORMS AND STRENGTHS

TOPAMAX® (topiramate) Tablets are available as debossed, coated, round tablets in the following strengths and colors:

25 mg cream (debossed “OMN” on one side; "25" on the other)

50 mg light-yellow (debossed “OMN” on one side; "50" on the other)

100 mg yellow (debossed “OMN” on one side; "100" on the other)

200 mg salmon (debossed “OMN” on one side; "200" on the other)

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain small, white to off-white spheres. The gelatin capsules are white and clear.

They are marked as follows:

15 mg capsule with “TOP” and “15 mg” on the side

25 mg capsule with “TOP” and “25 mg” on the side

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Myopia and Secondary Angle Closure Glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX® (topiramate). Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary

effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating TOPAMAX® therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible, according to the judgment of the treating 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.

5.2 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 pediatric patients. 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.

5.3 Metabolic Acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with TOPAMAX® treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea,

ketogenic diet, or specific drugs) may be additive to the bicarbonate lowering effects of topiramate.

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mEq/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence of persistent treatment-emergent decreases in serum bicarbonate in adults in the epilepsy controlled clinical trial for monotherapy was 15% for 50 mg/day and 25% for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in the adjunctive therapy trials was 3% for 400 mg/day, and 0% for placebo and in the monotherapy trial was 1% for 50 mg/day and 7% for 400 mg/day. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

In pediatric patients (2 to 16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures was 67% for TOPAMAX® (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for TOPAMAX® and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

Although not approved for use in patients under 2 years of age with partial onset seizures, a controlled trial that examined this population revealed that topiramate produced a metabolic acidosis that is notably greater in magnitude than that observed in controlled trials in older children and adults. The mean treatment difference (25 mg/kg/day topiramate-placebo) was -5.9 mEq/L for bicarbonate. The incidence of metabolic acidosis (defined by a serum bicarbonate <20 mEq/L) was 0% for placebo, 30% for 5 mg/kg/day, 50% for 15 mg/kg/day, and 45% for 25 mg/kg/day. The incidence of markedly abnormal changes (i.e., < 17 mEq/L and > 5 mEq/L decrease from baseline of $\geq$ 20 mEq/L) was 0 % for placebo, 4% for 5 mg/kg/day, 5 % for 15 mg/kg/day, and 5 % for 25 mg/kg/day *[see Use in Special Populations (8.4)]*.

In pediatric patients (6 to 15 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in the epilepsy controlled clinical trial for monotherapy was 9 % for 50 mg/day and 25 % for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in this

trial was 1 % for 50 mg/day and 6 % for 400 mg/day. In adult patients (≥ 16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in the epilepsy controlled clinical trial for monotherapy was 14 % for 50 mg/day and 25 % for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in this trial for adults was 1 % for 50 mg/day and 6 % for 400 mg/day.

The incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44% for 200 mg/day, 39% for 100 mg/day, 23% for 50 mg/day, and 7% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for 200 mg/day, 9% for 100 mg/day, 2% for 50 mg/day, and <1% for placebo.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in long-term, placebo-controlled trials. Long-term, open-label treatment of infants/toddlers, with intractable partial epilepsy, for up to 1 year, showed reductions from baseline in Z SCORES for length, weight, and head circumference compared to age and sex-matched normative data, although these patients with epilepsy are likely to have different growth rates than normal infants. Reductions in Z SCORES for length and weight were correlated to the degree of acidosis *[see Use in Specific Populations (8.4)]*. Topiramate treatment that causes metabolic acidosis during pregnancy can possibly produce adverse effects on the fetus and might also cause metabolic acidosis in the neonate from possible transfer of topiramate to the fetus *[see Warnings and Precautions (5.6) Use in Specific Populations (8.1)]*.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be

considered.

5.4 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including TOPAMAX®, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 4 shows absolute and relative risk by indication for all evaluated AEDs.

Table 4: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing TOPAMAX® or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior or the emergence of suicidal thoughts, or behavior or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.5 Cognitive/Neuropsychiatric Adverse Reactions

Adverse reactions 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.

Adult Patients

Cognitive-Related Dysfunction

The majority of cognitive-related adverse reactions 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 reactions. Many of these reactions contributed to withdrawal from treatment *[see Adverse Reactions (6)]*.

In the 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 reactions was 42% for 200 mg/day, 41% for 400 mg/day, 52% for 600 mg/day, 56% for 800 and 1,000 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 reactions in the titration phase had a dose-related recurrence of these reactions in the maintenance phase.

In the monotherapy epilepsy controlled trial, the proportion of patients who experienced one or more cognitive-related adverse reactions 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 reactions was 19% for TOPAMAX® 50 mg/day, 22% for 100 mg/day (the recommended dose), 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 reactions and this recurrence was typically in the titration phase. A relatively small proportion of topiramate-treated patients experienced more than one concurrent cognitive adverse reaction. The most common cognitive adverse reactions 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 reactions.

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (depression or mood) were dose-related for both the epilepsy and migraine populations [*see Warnings and Precautions (5.4)]*.

Somnolence/Fatigue

Somnolence and fatigue were the adverse reactions 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 1,000 mg/day, but the incidence of fatigue was dose-related and increased at dosages above 400 mg/day. For the monotherapy epilepsy population in the 50 mg/day and 400 mg/day groups, the incidence of somnolence was dose-related (9% for the 50 mg/day group and 15% for the 400 mg/day group) and the incidence of fatigue was comparable in both treatment groups (14% each). For the migraine population, fatigue and somnolence were dose-related and more common in the titration phase.

Additional nonspecific CNS events commonly observed with topiramate in the add-on epilepsy population included dizziness or ataxia.

Pediatric Patients

In double-blind adjunctive therapy and monotherapy epilepsy clinical studies, the incidences of cognitive/neuropsychiatric adverse reactions in pediatric patients were generally lower than observed in adults. These reactions included psychomotor slowing, difficulty with concentration/attention, speech disorders/related speech problems, and language problems. The most frequently reported neuropsychiatric reactions in pediatric patients during adjunctive therapy double-blind studies were somnolence and fatigue. The most frequently reported neuropsychiatric reactions in pediatric patients in the 50 mg/day and 400 mg/day groups during the monotherapy double-blind study were headache, dizziness, anorexia, and somnolence.

No patients discontinued treatment due to any adverse reactions in the adjunctive epilepsy double-blind trials. In the monotherapy epilepsy double-blind trial, 1 pediatric patient (2%) in the 50 mg/day group and 7 pediatric patients (12%) in the 400 mg/day group discontinued treatment due to any adverse reactions. The most common adverse reaction associated with discontinuation of therapy was difficulty with concentration/attention; all occurred in the 400 mg/day group.

5.6 Fetal Toxicity

TOPAMAX® can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring *[see Use in Specific Populations (8.1)]*.

Consider the benefits and the risks of TOPAMAX® when administering this drug in women of childbearing potential, particularly when TOPAMAX® is considered for a condition not usually associated with permanent injury or death *[see Use in Specific Populations (8.9) and Patient Counseling Information (17.8)]*. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1) and (8.9)]*.

5.7 Withdrawal of Antiepileptic Drugs (AEDs)

In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including TOPAMAX®, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency *[see Clinical Studies (14)]*. In situations where rapid withdrawal of TOPAMAX® is medically required, appropriate monitoring is recommended.

5.8 Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of topiramate tablets, 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2796 subject years of exposure). This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX® (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX® program, to 0.005 for patients with refractory epilepsy).

5.9 Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use)

Hyperammonemia/Encephalopathy Without Concomitant Valproic Acid (VPA)

Topiramate treatment has produced hyperammonemia (in some instances dose-related) in clinical investigational programs of adolescents (12-16 years) who were treated with topiramate monotherapy for migraine prophylaxis (incidence above the upper limit of normal, 22% for placebo, 26% for 50 mg/day, 41% for 100 mg/day) and in very young pediatric patients (1-24 months) who were treated with adjunctive topiramate for partial onset epilepsy (8% for placebo, 10% for 5 mg/kg/day, 0% for 15 mg/kg/day, 9% for 25 mg/kg/day). TOPAMAX® is not approved as monotherapy for migraine prophylaxis in adolescent patients or as adjunctive treatment of partial onset seizures in pediatric patients less than 2 years old. In some patients,

ammonia was markedly increased (≥50% above upper limit of normal). In adolescent patients, the incidence of markedly increased hyperammonemia was 6% for placebo, 6% for 50 mg, and 12% for 100 mg topiramate daily. The hyperammonemia associated with topiramate treatment occurred with and without encephalopathy in placebo-controlled trials and in an open-label, extension trial. Dose-related hyperammonemia was also observed in the extension trial in pediatric patients up to 2 years old. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting.

Hyperammonemia with and without encephalopathy has also been observed in post-marketing reports in patients who were taking topiramate without concomitant valproic acid (VPA).

Hyperammonemia/Encephalopathy With Concomitant Valproic Acid (VPA)

Concomitant administration of topiramate and valproic acid (VPA) has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone based upon post-marketing reports. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse reaction is not due to a pharmacokinetic interaction.

Although TOPAMAX® is not indicated for use in infants/toddlers (1-24 months), VPA clearly produced a dose-related increase in the incidence of treatment-emergent hyperammonemia (above the upper limit of normal, 0% for placebo, 12% for 5 mg/kg/day, 7% for 15 mg/kg/day, 17% for 25 mg/kg/day) in an investigational program. Markedly increased, dose-related hyperammonemia (0% for placebo and 5 mg/kg/day, 7% for 15 mg/kg/day, 8% for 25 mg/kg/day) also occurred in these infants/toddlers. Dose-related hyperammonemia was similarly observed in a long-term extension trial in these very young, pediatric patients *[see Use in Specific Populations (8.4)]*.

Hyperammonemia with and without encephalopathy has also been observed in post-marketing reports in patients taking topiramate with VPA.

The hyperammonemia associated with topiramate treatment appears to be more common when topiramate is used concomitantly with VPA.

Monitoring for Hyperammonemia

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an

increased risk for hyperammonemia with or without encephalopathy. Although not studied, topiramate treatment or an interaction of concomitant topiramate and valproic acid treatment may exacerbate existing defects or unmask deficiencies in susceptible persons.

In patients who develop unexplained lethargy, vomiting, or changes in mental status associated with any topiramate treatment, hyperammonemic encephalopathy should be considered and an ammonia level should be measured.

5.10 Kidney Stones

A total of 32/2086 (1.5%) of adults exposed to topiramate during its adjunctive epilepsy therapy development reported the occurrence of kidney stones, an incidence about 2 to 4 times greater than expected in a similar, untreated population. In the double-blind monotherapy epilepsy study, a total of 4/319 (1.3%) of adults exposed to topiramate reported the occurrence of kidney stones. As in the general population, the incidence of stone formation among topiramate-treated patients was higher in men. Kidney stones have also been reported in pediatric patients. During long-term (up to 1 year) topiramate treatment in an open-label extension study of 284 pediatric patients 1-24 months old with epilepsy, 7% developed kidney or bladder stones that were diagnosed clinically or by sonogram. TOPAMAX® is not approved for pediatric patients less than 2 years old *[see Use in Specific Populations (8.4)]*.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide, or dichlorphenamide) can promote stone formation by reducing urinary citrate excretion and by increasing urinary pH *[see Warnings and Precautions (5.4)]*. The concomitant use of TOPAMAX® with any other drug producing metabolic acidosis, or potentially in patients on a ketogenic diet, may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

5.11 Hypothermia with Concomitant Valproic Acid (VPA) Use

Hypothermia, defined as an unintentional drop in body core temperature to <35°C (95°F), has been reported in association with topiramate use with concomitant valproic acid (VPA) both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse reaction in patients using concomitant topiramate and valproate can occur after starting

topiramate treatment or after increasing the daily dose of topiramate *[see Drug Interactions (7.1)]*. Consideration should be given to stopping topiramate or valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

5.12 Paresthesia

Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®. Paresthesia was more frequently reported in the monotherapy epilepsy trials and migraine prophylaxis trials than in the adjunctive therapy epilepsy trials. In the majority of instances, paresthesia did not lead to treatment discontinuation.

5.13 Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required in patients with reduced renal function *[see Dosage and Administration (2.4)]*.

5.14 Decreased Hepatic Function

In hepatically impaired patients, TOPAMAX® should be administered with caution as the clearance of topiramate may be decreased *[see Dosage and Administration (2.7)]*.

5.15 Monitoring: Laboratory Tests

Topiramate treatment was associated with changes in several clinical laboratory analytes in randomized, double-blind, placebo-controlled studies.

Topiramate treatment causes non-anion gap, hyperchloremic metabolic acidosis manifested by a decrease in serum bicarbonate and an increase in serum chloride. Measurement of baseline and periodic serum bicarbonate during TOPAMAX® treatment is recommended *[see Warnings and Precautions (5.3)]*.

Controlled trials of adjunctive topiramate treatment of adults for partial onset seizures showed an increased incidence of markedly decreased serum phosphorus (6% topiramate, 2% placebo), markedly increased serum alkaline phosphatase (3% topiramate, 1% placebo), and decreased serum potassium (0.4 % topiramate, 0.1 % placebo). The clinical significance of these abnormalities has not been clearly established.

Changes in several clinical laboratory values (i.e., increased creatinine, BUN, alkaline phosphatase, total protein, total eosin Phil count, and decreased potassium) have been observed in a clinical investigational program in very young (<2 years) pediatric patients who were treated with adjunctive topiramate for partial onset seizures [*see Use in Specific Populations (8.4)*].

Topiramate treatment produced a dose-related increased shift in serum creatinine from normal at baseline to an increased value at the end of 4 months treatment in adolescent patients (ages 12-16 years)who were treated for migraine prophylaxis in a double-blind, placebo-controlled study.

TOPAMAX® treatment with or without concomitant valproic acid (VPA) can cause hyperammonemia with or without encephalopathy *[see Warnings and Precautions (5.9)]*.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Acute Myopia and Secondary Angle Closure *[see Warnings and Precautions (5.1)]*
- Oligohidrosis and Hyperthermia *[see Warnings and Precautions (5.2)]*
- Metabolic Acidosis *[see Warnings and Precautions (5.3)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.4)]*
- Cognitive/Neuropsychiatric Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Fetal Toxicity *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.1)]*
- Withdrawal of Antiepileptic Drugs (AEDs) *[see Warnings and Precautions (5.7)]*
- Sudden Unexplained Death in Epilepsy (SUDEP) *[see Warnings and Precautions (5.8)]*
- Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use *[see Warnings and Precautions (5.9)]*
- Kidney Stones *[see Warnings and Precautions (5.10)]*
- Hypothermia with Concomitant Valproic Acid (VPA) Use *[see Warnings and Precautions (5.11)]*
- Paresthesia *[see Warnings and Precautions (5.12)]*

The data described in the following sections were obtained using TOPAMAX® (topiramate) Tablets.

6.1 Monotherapy Epilepsy

Adults ≥16 Years

The adverse reactions in the controlled trial that occurred most commonly in adults in the 400 mg/day TOPAMAX® group and at a rate higher (≥ 5 %) than in the 50 mg/day group were: paresthesia, weight decrease, anorexia, somnolence, and difficulty with memory (see Table 5).

Approximately 21% of the 159 adult patients in the 400 mg/day group who received topiramate as monotherapy in the controlled clinical trial discontinued therapy due to adverse reactions. The most common (≥ 2% more frequent than low-dose 50 mg/day TOPAMAX®) adverse reactions causing discontinuation in this trial were difficulty with memory, fatigue, asthenia, insomnia, somnolence, and paresthesia.

Pediatric Patients 6 to <16 Years of Age

The adverse reactions in the controlled trial that occurred most commonly in pediatric patients in the 400 mg/day TOPAMAX® group and at a rate higher (≥ 5%) than in the 50 mg/day group were fever, weight decrease, mood problems, cognitive problems, infection, flushing, and paresthesia (see Table 5).

Approximately 14 % of the 77 pediatric patients in the 400 mg/day group who received TOPAMAX® as monotherapy in the controlled clinical trial discontinued therapy due to adverse reactions. The most common (≥ 2% more frequent than low-dose 50 mg/day TOPAMAX®) adverse reactions resulting in discontinuation in this trial were difficulty with concentration/attention, fever, flushing, and confusion.

Table 5: Incidence of Treatment-Emergent Adverse Reactions in Monotherapy Epilepsy Where the Rate Was at Least 2% in Any TOPAMAX® Group and the Rate in the 400 mg/day TOPAMAX® Group Was Greater Than the Rate in the 50 mg/day TOPAMAX® Group for Adults (≥16 Years) and Pediatric (6 to <16 Years) Patients in Study TOPMAX-EPMN-106

	Age Group			
	Pediatric (6 to <16 Years)		Adult (Age ≥16 Years)	
	TOPAMAX® Daily Dosage Group (mg/day)			
	50	400	50	400
Body System	(N=74)	(N=77)		(N=159)
Adverse Reaction	%†	%†	%†	%†
Body as a Whole - General Disorders				
Asthenia	0	3	4	6
Chest pain			1	2

Table 5: Incidence of Treatment-Emergent Adverse Reactions in Monotherapy Epilepsy Where the Rate Was at Least 2% in Any TOPAMAX® Group and the Rate in the 400 mg/day TOPAMAX® Group Was Greater Than the Rate in the 50 mg/day TOPAMAX® Group for Adults (≥16 Years) and Pediatric (6 to <16 Years) Patients in Study TOPMAX-EPMN-106

	Age Group			
	Pediatric (6 to <16 Years)		Adult (Age ≥16 Years)	
	TOPAMAX® Daily Dosage Group (mg/day)			
	50	400	50	400
Body System	(N=74)	(N=77)		(N=159)
Adverse Reaction	%†	%†	%†	%†
Fever	1	12		
Leg pain			2	3
Central & Peripheral Nervous System Disorders				
Ataxia			3	4
Dizziness			13	14
Hypertonia			0	3
Hypoesthesia			4	5
Muscle contractions involuntary	0	3		
Paresthesia	3	12	21	40
Vertigo	0	3		
Gastro-Intestinal System Disorders				
Constipation			1	4
Diarrhea	8	9		
Gastritis			0	3
Gastroesophageal reflux			1	2
Dry mouth			1	3
Liver and Biliary System Disorders				
Gamma-GT increased			1	3
Metabolic and Nutritional Disorders				
Weight decrease	7	17	6	17
Platelet, Bleeding & Clotting Disorders				
Epistaxis	0	4		
Psychiatric Disorders				
Anorexia			4	14
Anxiety			4	6
Cognitive problems	1	6	1	4
Confusion	0	3		
Depression	0	3	7	9
Difficulty with concentration/attention	7	10	7	8
Difficulty with memory	1	3	6	11
Insomnia			8	9
Libido decreased			0	3
Mood problems	1	8	2	5
Personality disorder(behavior problems)	0	3		
Psychomotor slowing			3	5
Somnolence			10	15
Red Blood Cell Disorders				
Anemia	1	3		

Table 5: Incidence of Treatment-Emergent Adverse Reactions in Monotherapy Epilepsy Where the Rate Was at Least 2% in Any TOPAMAX® Group and the Rate in the 400 mg/day TOPAMAX® Group Was Greater Than the Rate in the 50 mg/day TOPAMAX® Group for Adults (≥16 Years) and Pediatric (6 to <16 Years) Patients in Study TOPMAX-EPMN-106

	Age Group			
	Pediatric (6 to <16 Years)		Adult (Age ≥16 Years)	
	TOPAMAX® Daily Dosage Group (mg/day)			
	50	400	50	400
Body System	(N=74)	(N=77)		(N=159)
Adverse Reaction	%†	%†	%†	%†
Reproductive Disorders, Female *				
Intermenstrual Bleeding	0	3		
Vaginal Hemorrhage			0	3
Resistance Mechanism Disorders				
Infection	3	8	2	3
Infection viral	3	6	6	8
Respiratory System Disorders				
Bronchitis	1	5	3	4
Dyspnea			1	2
Rhinitis	5	6	2	4
Sinusitis	1	4		
Upper respiratory tract infection	16	18		
Skin and Appendages Disorders				
Acne			2	3
Alopecia	1	4	3	4
Pruritus			1	4
Rash	3	4	1	4
Special Senses Other, Disorders				
Taste perversion			3	5
Urinary System Disorders				
Cystitis			1	3
Dysuria			0	2
Micturition frequency	0	3	0	2
Renal calculus			0	3
Urinary incontinence	1	3		
Urinary tract infection			1	2
Vascular (Extracardiac) Disorders				
Flushing	0	5		

* N with Female Reproductive Disorders – Incidence calculated relative to the number of females; Pediatric TPM 50 mg n=40; Pediatric TPM 400 mg n=33; Adult TPM 50 mg n=84; TPM 400 mg n=80

†Percentages calculated with the number of subjects in each group as denominator

6.2 Adjunctive Therapy Epilepsy

The most commonly observed adverse reactions associated with the use of TOPAMAX® at dosages of 200 to 400 mg/day in controlled trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater

frequency in TOPAMAX®-treated patients and did not appear to be dose-related were somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia and diplopia (see Table 6). The most common dose-related adverse reactions at dosages of 200 to 1,000 mg/day were fatigue, nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, anxiety, mood problems, and weight decrease (see Table 8).

Adverse reactions associated with the use of TOPAMAX® at dosages of 5 to 9 mg/kg/day in controlled trials in pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater frequency in TOPAMAX® treated patients were fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease (see Table 9).

In controlled clinical trials in adults, 11% of patients receiving TOPAMAX® 200 to 400 mg/day as adjunctive therapy discontinued due to adverse reactions. This rate appeared to increase at dosages above 400 mg/day. Adverse reactions associated with discontinuing therapy included somnolence, dizziness, anxiety, difficulty with concentration or attention, fatigue, and paresthesia and increased at dosages above 400 mg/day. None of the pediatric patients who received TOPAMAX® adjunctive therapy at 5 to 9 mg/kg/day in controlled clinical trials discontinued due to adverse reactions.

Approximately 28% of the 1757 adults with epilepsy who received TOPAMAX® at dosages of 200 to 1,600 mg/day in clinical studies discontinued treatment because of adverse reactions; an individual patient could have reported more than one adverse reaction. These adverse reactions were psychomotor slowing (4.0%), difficulty with memory (3.2%), fatigue (3.2%), confusion (3.1%), somnolence (3.2%), difficulty with concentration/attention (2.9%), anorexia (2.7%), depression (2.6%), dizziness (2.5%), weight decrease (2.5%), nervousness (2.3%), ataxia (2.1%), and paresthesia (2.0%). Approximately 11% of the 310 pediatric patients who received TOPAMAX® at dosages up to 30 mg/kg/day discontinued due to adverse reactions. Adverse reactions associated with discontinuing therapy included aggravated convulsions (2.3%), difficulty with concentration/attention (1.6%), language problems (1.3%), personality disorder (1.3%), and somnolence (1.3%).

6.3 Incidence in Epilepsy Controlled Clinical Trials – Adjunctive Therapy – Partial Onset Seizures, Primary Generalized Tonic-Clonic Seizures, and Lennox-Gastaut Syndrome

Table 6 lists treatment-emergent adverse reactions that occurred in at least 1% of adults treated with 200 to 400 mg/day TOPAMAX® in controlled trials that were numerically more common at this dose than in the patients treated with placebo. In general, most patients who experienced adverse reactions during the first eight weeks of these trials no longer experienced them by their last visit. Table 9 lists treatment-emergent adverse reactions that occurred in at least 1% of pediatric patients treated with 5 to 9 mg/kg TOPAMAX® in controlled trials that were numerically more common than in patients treated with placebo.

The prescriber should be aware that these data were obtained when TOPAMAX® was added to concurrent antiepileptic drug therapy and cannot be used to predict the frequency of adverse reactions in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse reaction incidences in the population studied.

6.4 Other Adverse Reactions Observed During Double-Blind Epilepsy Adjunctive Therapy Trials

Other adverse reactions that occurred in more than 1% of adults treated with 200 to 400 mg of TOPAMAX® in placebo-controlled epilepsy trials but with equal or greater frequency in the placebo group were headache, injury, anxiety, rash, pain, convulsions aggravated, coughing, fever, diarrhea, vomiting, muscle weakness, insomnia, personality disorder, dysmenorrhea, upper respiratory tract infection, and eye pain.

Table 6: Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Add-On Epilepsy Trials in Adults[a,b] Where Incidence Was ≥ 1% in Any TOPAMAX® Group and Greater Than the Rate in Placebo-Treated Patients

		TOPAMAX® Dosage (mg/day)	
Body System/ Adverse Reaction[c]	Placebo (N=291)	200-400 (N=183)	600-1,000 (N=414)
Body as a Whole-General Disorders			
Fatigue	13	15	30
Asthenia	1	6	3
Back pain	4	5	3
Chest pain	3	4	2
Influenza-like symptoms	2	3	4
Leg pain	2	2	4
Hot flushes	1	2	1
Allergy	1	2	3
Edema	1	2	1
Body odor	0	1	0
Rigors	0	1	<1
Central & Peripheral Nervous System Disorders			
Dizziness	15	25	32
Ataxia	7	16	14
Speech disorders/Related speech problems	2	13	11
Paresthesia	4	11	19
Nystagmus	7	10	11
Tremor	6	9	9
Language problems	1	6	10
Coordination abnormal	2	4	4
Hypoesthesia	1	2	1
Gait abnormal	1	3	2
Muscle contractions involuntary	1	2	2
Stupor	0	2	1
Vertigo	1	1	2
Gastro-Intestinal System Disorders			
Nausea	8	10	12
Dyspepsia	6	7	6
Abdominal pain	4	6	7
Constipation	2	4	3
Gastroenteritis	1	2	1
Dry mouth	1	2	4
Gingivitis	<1	1	1
GI disorder	<1	1	0
Hearing and Vestibular Disorders			
Hearing decreased	1	2	1
Metabolic and Nutritional Disorders			
Weight decrease	3	9	13
Muscle-Skeletal System Disorders			
Myalgia	1	2	2
Skeletal pain	0	1	0
Platelet, Bleeding, & Clotting Disorders			
Epistaxis	1	2	1
Psychiatric Disorders			
Somnolence	12	29	28
Nervousness	6	16	19
Psychomotor slowing	2	13	21
Difficulty with memory	3	12	14

		TOPAMAX® Dosage (mg/day)	
Body System/ Adverse Reaction[c]	Placebo (N=291)	200-400 (N=183)	600-1,000 (N=414)
Anorexia	4	10	12
Confusion	5	11	14
Depression	5	5	13
Difficulty with concentration/attention	2	6	14
Mood problems	2	4	9
Agitation	2	3	3
Aggressive reaction	2	3	3
Emotional lability	1	3	3
Cognitive problems	1	3	3
Libido decreased	1	2	<1
Apathy	1	1	3
Depersonalization	1	1	2
Reproductive Disorders, Female			
Breast pain	2	4	0
Amenorrhea	1	2	2
Menorrhagia	0	2	1
Menstrual disorder	1	2	1
Reproductive Disorders, Male			
Prostatic disorder	<1	2	0
Resistance Mechanism Disorders			
Infection	1	2	1
Infection viral	1	2	<1
Moniliasis	<1	1	0
R**espiratory System Disorders**			
Pharyngitis	2	6	3
Rhinitis	6	7	6
Sinusitis	4	5	6
Dyspnea	1	1	2
Skin and Appendages Disorders			
Skin disorder	<1	2	1
Sweating increased	<1	1	<1
Rash erythematous	<1	1	<1
Special Sense Other, Disorders			
Taste perversion	0	2	4
Urinary System Disorders			
Hematuria	1	2	<1
Urinary tract infection	1	2	3
Micturition frequency	1	1	2
Urinary incontinence	<1	2	1
Urine abnormal	0	1	<1
Vision Disorders			
Vision abnormal	2	13	10
Diplopia	5	10	10
White Cell and RES Disorders			
Leukopenia	1	2	1

[a] Patients in these add-on/ adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

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

[c] Adverse reactions reported by at least 1% of patients in the TOPAMAX® 200-400 mg/day group and more common than in the placebo group are listed in this table.

6.5 Incidence in Study 119 – Add-On Therapy– Adults with Partial Onset Seizures

Study 119 was a randomized, double-blind, add-on/adjunctive, placebo-controlled, parallel group study with 3 treatment arms: 1) placebo; 2) TOPAMAX® 200 mg/day with a 25 mg/day starting dose, increased by 25 mg/day each week for 8 weeks until the 200 mg/day maintenance dose was reached; and 3) TOPAMAX® 200 mg/day with a 50 mg/day starting dose, increased by 50 mg/day each week for 4 weeks until the 200 mg/day maintenance dose was reached. All patients were maintained on concomitant carbamazepine with or without another concomitant antiepileptic drug.

The incidence of adverse reactions (Table 7) did not differ significantly between the 2 TOPAMAX® regimens. Because the frequencies of adverse reactions reported in this study were markedly lower than those reported in the previous epilepsy studies, they cannot be directly compared with data obtained in other studies.

Table 7: Incidence of Treatment-Emergent Adverse Reactions in Study 119[a,b] Where Incidence Was ≥ 2% in the TOPAMAX® Group and Greater Than the Rate in Placebo-Treated Patients

		TOPAMAX® Dosage (mg/day)
Body System/ Adverse Reaction[c]	Placebo (N=92)	200 (N=171)
Body as a Whole-General Disorders		
Fatigue	4	9
Chest pain	1	2
Cardiovascular Disorders, General		
Hypertension	0	2
Central & Peripheral Nervous System Disorders		
Paresthesia	2	9
Dizziness	4	7
Tremor	2	3
Hypoesthesia	0	2
Leg cramps	0	2
Language problems	0	2
Gastro-Intestinal System Disorders		
Abdominal pain	3	5
Constipation	0	4
Diarrhea	1	2
Dyspepsia	0	2
Dry mouth	0	2
Hearing and Vestibular Disorders		
Tinnitus	0	2
Metabolic and Nutritional Disorders		
Weight decrease	4	8
Psychiatric Disorders		

Somnolence	9	15
Anorexia	7	9
Nervousness	2	9
Difficulty with concentration/attention	0	5
Insomnia	3	4
Difficulty with memory	1	2
Aggressive reaction	0	2
Respiratory System Disorders		
Rhinitis	0	4
Urinary System Disorders		
Cystitis	0	2
Vision Disorders		
Diplopia	0	2
Vision abnormal	0	2

[a] Patients in these add-on/adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.
[b] Values represent the percentage of patients reporting a given adverse reaction. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category.
[c] Adverse reactions reported by at least 2% of patients in the TOPAMAX® 200 mg/day group and more common than in the placebo group are listed in this table.

Table 8: Incidence (%) of Dose-Related Adverse Reactions From Placebo-Controlled, Add-On Trials in Adults With Partial Onset Seizures[a]

	TOPAMAX® Dosage (mg/day)			
Adverse Reaction	Placebo (N = 216)	200 (N = 45)	400 (N = 68)	600 - 1,000 (N = 414)
Fatigue	13	11	12	30
Nervousness	7	13	18	19
Difficulty with concentration/attention	1	7	9	14
Confusion	4	9	10	14
Depression	6	9	7	13
Anorexia	4	4	6	12
Language problems	<1	2	9	10
Anxiety	6	2	3	10
Mood problems	2	0	6	9
Weight decrease	3	4	9	13

[a] Dose-response studies were not conducted for other adult indications or for pediatric indications.

Table 9: Incidence (%) of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Add-On Epilepsy Trials in Pediatric Patients (Ages 2 -16 Years)[a,b] (Reactions That Occurred in at Least 1% of TOPAMAX®-Treated Patients and Occurred More Frequently in TOPAMAX®-Treated Than Placebo-Treated Patients)

Body System/ Adverse Reaction	Placebo (N=101)	TOPAMAX® (N=98)
Body as a Whole - General Disorders		
Fatigue	5	16
Injury	13	14
Allergic reaction	1	2
Back pain	0	1
Pallor	0	1
Cardiovascular Disorders, General		
Hypertension	0	1
Central & Peripheral Nervous System Disorders		
Gait abnormal	5	8
Ataxia	2	6
Hyperkinesia	4	5
Dizziness	2	4
Speech disorders/Related speech problems	2	4
Hyporeflexia	0	2
Convulsions grand mal	0	1
Fecal incontinence	0	1
Paresthesia	0	1
Gastro-Intestinal System Disorders		
Nausea	5	6
Saliva increased	4	6
Constipation	4	5
Gastroenteritis	2	3
Dysphagia	0	1
Flatulence	0	1
Gastroesophageal reflux	0	1
Glossitis	0	1
Gum hyperplasia	0	1
Heart Rate and Rhythm Disorders		
Bradycardia	0	1
Metabolic and Nutritional Disorders		
Weight decrease	1	9
Thirst	1	2
Hypoglycemia	0	1
Weight increase	0	1
Platelet, Bleeding, & Clotting Disorders		
Purpura	4	8
Epistaxis	1	4
Hematoma	0	1
Prothrombin increased	0	1
Thrombocytopenia	0	1
Psychiatric Disorders		
Somnolence	16	26
Anorexia	15	24
Nervousness	7	14

Body System/ Adverse Reaction	Placebo (N=101)	TOPAMAX® (N=98)
Personality disorder (behavior problems)	9	11
Difficulty with concentration/attention	2	10
Aggressive reaction	4	9
Insomnia	7	8
Difficulty with memory	0	5
Confusion	3	4
Psychomotor slowing	2	3
Appetite increased	0	1
Neurosis	0	1
Reproductive Disorders, Female		
Leukorrhea		2
Resistance Mechanism Disorders		
Infection viral	3	7
Respiratory System Disorders		
Pneumonia	1	5
Respiratory disorder	0	1
Skin and Appendages Disorders		
Skin disorder	2	3
Alopecia	1	2
Dermatitis	0	2
Hypertrichosis	1	2
Rash erythematous	0	2
Eczema	0	1
Seborrhea	0	1
Skin discoloration	0	1
Urinary System Disorders		
Urinary incontinence	2	4
Nocturia	0	1
Vision Disorders		
Eye abnormality	1	2
Vision abnormal	1	2
Diplopia	0	1
Lacrimation abnormal	0	1
Myopia	0	1
White Cell and RES Disorders		
Leukopenia	0	2

[a] Patients in these add-on/adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

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

6.6 Other Adverse Reactions Observed During All Epilepsy Clinical Trials

TOPAMAX® has been administered to 2246 adults and 427 pediatric patients with epilepsy during all clinical studies, only some of which were placebo-controlled. During these studies, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse

reactions, similar types of reactions were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The frequencies presented represent the proportion of patients who experienced a reaction of the type cited on at least one occasion while receiving TOPAMAX®. Reported reactions are included except those already listed in the previous tables or text, those too general to be informative, and those not reasonably associated with the use of the drug.

Reactions are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* occurring in at least 1/100 patients; *infrequent* occurring in 1/100 to 1/1000 patients; *rare* occurring in fewer than 1/1000 patients.

Autonomic Nervous System Disorders: *Infrequent:* vasodilation.

Body as a Whole: *Frequent:* syncope. *Infrequent*: abdomen enlarged. *Rare:* alcohol intolerance.

Cardiovascular Disorders, General: *Infrequent:* hypotension, postural hypotension, angina pectoris.

Central & Peripheral Nervous System Disorders: *Infrequent*: neuropathy, apraxia, hyperesthesia, dyskinesia, dysphonia, scotoma, ptosis, dystonia, visual field defect, encephalopathy, EEG abnormal. *Rare:* upper motor neuron lesion, cerebellar syndrome, tongue paralysis.

Gastrointestinal System Disorders: *Infrequent:* hemorrhoids, stomatitis, melena, gastritis, esophagitis. *Rare:* tongue edema.

Heart Rate and Rhythm Disorders: *Infrequent:* AV block.

Liver and Biliary System Disorders: *Infrequent:* SGPT increased, SGOT increased.

Metabolic and Nutritional Disorders: *Infrequent:* dehydration, hypocalcemia, hyperlipemia, hyperglycemia, xerophthalmia, diabetes mellitus. *Rare:* hypernatremia, hyponatremia, hypocholesterolemia, creatinine increased.

Musculoskeletal System Disorders: *Frequent:* arthralgia. *Infrequent:* arthrosis.

Neoplasms: *Infrequent:* thrombocythemia. *Rare:* polycythemia.

Platelet, Bleeding, and Clotting Disorders: *Infrequent:* gingival bleeding, pulmonary embolism.

Psychiatric Disorders: *Frequent:* impotence, hallucination, psychosis, suicide attempt.

Infrequent: euphoria, paranoid reaction, delusion, paranoia, delirium, abnormal dreaming. *Rare:* libido increased, manic reaction.

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.

6.7 Migraine

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

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

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

		TOPAMAX® Dosage(mg/day)		
Body System/ Adverse Reaction	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
Hypoesthesia	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	<1	2	<1	<1
Psychiatric Disorders				
Anorexia	6	9	15	14
Somnolence	5	8	7	10
Difficulty with memory	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

		TOPAMAX® Dosage(mg/day)		
Body System/ Adverse Reaction	Placebo (N=445)	50 (N=235)	100 (N=386)	200 (N=514)
Libido decreased	1	1	1	2
Aggravated depression	1	1	2	2
Agitation	1	2	2	1
Cognitive problems	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
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 reaction. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category.

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

Of the 1135 patients exposed to TOPAMAX® in the placebo-controlled studies, 25% discontinued due to adverse reactions, compared to 10% of the 445 placebo patients. The adverse reactions associated with discontinuing therapy in the TOPAMAX® -treated patients included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%).

Patients treated with TOPAMAX® 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, TOPAMAX® 50, 100, and 200 mg groups, respectively.

Table 11 shows adverse reactions that were dose-dependent. Several central nervous system adverse reactions, including some that represented cognitive dysfunction, were dose-related. The most common dose-related adverse reactions 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 Reactions From Placebo-Controlled, Migraine Trials[a]

		TOPAMAX® Dosage (mg/day)		
Adverse Reaction	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	2	7	7	11
Diarrhea	4	9	11	11
Difficulty with concentration/ attention	2	3	6	10
Somnolence	5	8	7	10
Hypoesthesia	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 of adverse reactions in the 200 mg/day group was ≥ 2% than the incidence in both the placebo group and the 50 mg/day group.

6.8 Other Adverse Reactions Observed During Migraine Clinical Trials

TOPAMAX®, for the treatment of prophylaxis of migraine headache, has been administered to 1367 patients in all clinical studies (includes double-blind and open-label extension). During these studies, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reactions, similar types of reactions were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology.

The following additional adverse reactions that were not described earlier were reported by greater than 1% of the 1367 TOPAMAX®-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.

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.

6.9 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 TOPAMAX® 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, maculopathy, pancreatitis, and pemphigus.

7 DRUG INTERACTIONS

In vitro studies indicate that topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5 isozymes. *In vitro* studies indicate that topiramate is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4. Drug interactions with some antiepileptic drugs, CNS depressants and oral contraceptives are described here. For

other drug interactions, please refer to *Clinical Pharmacology (12.5)*.

7.1 Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. Concomitant administration of phenytoin or carbamazepine with topiramate decreased plasma concentrations of topiramate by 48% and 40%, respectively when compared to TOPAMAX® given alone *[see Clinical Pharmacology (12.5)]*.

Concomitant administration of valproic acid and TOPAMAX® has been associated with hyperammonemia with and without encephalopathy. Concomitant administration of TOPAMAX® with valproic acid has also been associated with hypothermia (with and without hyperammonemia) in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported *[see Warnings and Precautions (5.9) (5.11) or Clinical Pharmacology (12.5)]*.

7.2 CNS Depressants

Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse reactions, TOPAMAX® should be used with extreme caution if used in combination with alcohol and other CNS depressants.

7.3 Oral Contraceptives

Exposure to ethinyl estradiol was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when TOPAMAX® was given as adjunctive therapy in patients taking valproic acid. However, norethindrone exposure was not significantly affected. In another pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX®, given in the absence of other medications at doses of 50 to 200 mg/day, was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding [*see Clinical Pharmacology (12.5)]*.

7.4 Metformin

Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated [*see Clinical Pharmacology (12.5)]*.

7.5 Lithium

In patients, lithium levels were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure of lithium (27% for C_{max} and 26% for AUC) following topiramate doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with high-dose TOPAMAX® *[see Clinical Pharmacology (12.5)]*.

7.6 Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if TOPAMAX® is given concomitantly with another carbonic anhydrase inhibitor, the patient should be monitored for the appearance or worsening of metabolic acidosis *[see Clinical Pharmacology (12.5)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. *[see Warnings and Precautions (5.6)]*

TOPAMAX® (topiramate) can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.9)]*.

Pregnancy Registry

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334. Information about the North American Drug Pregnancy Registry can be found at

http://www.massgeneral.org/aed/.

Human Data

Data from the NAAED Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was 1.2% compared to a prevalence of 0.39% - 0.46% in infants exposed to other AEDs, and a prevalence of 0.12% in infants of mothers without epilepsy or treatment with other AEDs. For comparison, the Centers for Disease Control and Prevention (CDC) reviewed available data on oral clefts in the United States and found a similar background rate of 0.17%. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 9.6 (95% Confidence Interval = CI 3.6 – 25.7) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts of 3.2% among infants exposed to topiramate monotherapy. The observed rate of oral clefts was 16 times higher than the background rate in the UK, which is approximately 0.2%.

TOPAMAX® treatment can cause metabolic acidosis *[see Warnings and Precautions (5.3)]*. The effect of topiramate-induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) can cause decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus' ability to tolerate labor. Pregnant patients should be monitored for metabolic acidosis and treated as in the nonpregnant state *[see Warnings and Precautions (5.3)]*. Newborns of mothers treated with TOPAMAX® should be monitored for metabolic acidosis because of transfer of topiramate to the fetus and possible occurrence of transient metabolic acidosis following birth.

Animal Data

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in multiple animal species at clinically relevant doses. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD) 400 mg/day on a mg/m^2 basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m^2 basis) or greater

during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m^2 basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m^2 basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m^2 basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above.

When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m^2 basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m^2 basis) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30, or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m^2 basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m^2 basis) and higher.

8.2 Labor and Delivery

Although the effect of TOPAMAX® on labor and delivery in humans has not been established, the development of topiramate-induced metabolic acidosis in the mother and/or in the fetus might affect the fetus' ability to tolerate labor *[see Use in Specific Populations (8.1)]*.

8.3 Nursing Mothers

Limited data on 5 breastfeeding infants exposed to topiramate showed infant plasma topiramate levels equal to 10-20% of the maternal plasma level. The effects of this exposure on infants are unknown. Caution should be exercised when administered to a nursing woman.

8.4 Pediatric Use

Adjunctive Treatment for Partial Onset Epilepsy in Infants and Toddlers (1 to 24 months)

Safety and effectiveness in patients below the age of 2 years have not been established for the

adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. In a single randomized, double-blind, placebo-controlled investigational trial, the efficacy, safety, and tolerability of topiramate oral liquid and sprinkle formulations as an adjunct to concurrent antiepileptic drug therapy in infants 1 to 24 months of age with refractory partial onset seizures were assessed. After 20 days of double-blind treatment, topiramate (at fixed doses of 5, 15, and 25 mg/kg/day) did not demonstrate efficacy compared with placebo in controlling seizures.

In general, the adverse reaction profile in this population was similar to that of older pediatric patients, although results from the above controlled study and an open-label, long-term extension study in these infants/toddlers (1 to 24 months old) suggested some adverse reactions/toxicities(not previously observed in older pediatric patients and adults; i.e., growth/length retardation, certain clinical laboratory abnormalities, and other adverse reactions/toxicities that occurred with a greater frequency and/or greater severity than had been recognized previously from studies in older pediatric patients or adults for various indications.

These very young pediatric patients appeared to experience an increased risk for infections (any topiramate dose 12%, placebo 0%) and of respiratory disorders (any topiramate dose 40%, placebo 16%). The following adverse reactions were observed in at least 3% of patients on topiramate and were 3% to 7% more frequent than in patients on placebo: viral infection, bronchitis, pharyngitis, rhinitis, otitis media, upper respiratory infection, cough, and bronchospasm. A generally similar profile was observed in older children *[see Adverse Reactions (6)]*.

Topiramate resulted in an increased incidence of patients with increased creatinine (any topiramate dose 5%, placebo 0%), BUN (any topiramate dose 3%, placebo 0%), and protein (any topiramate dose 34%, placebo 6%), and an increased incidence of decreased potassium (any topiramate dose 7%, placebo 0%). This increased frequency of abnormal values was not dose-related. Creatinine was the only analyte showing a noteworthy increased incidence (topiramate 25 mg/kg/day 5%, placebo 0%) of a markedly abnormal increase *[see Warnings and Precautions (5.15)]*. The significance of these findings is uncertain.

Topiramate treatment also produced a dose-related increase in the percentage of patients who had a shift from normal at baseline to high/increased (above the normal reference range) in total eosinophil count at the end of treatment. The incidence of these abnormal shifts was 6 % for placebo, 10% for 5 mg/kg/day, 9% for 15 mg/kg/day, 14% for 25 mg/kg/day, and 11% for any topiramate dose *[see Warnings and Precautions (5.15)]*. There was a mean dose-related increase

in alkaline phosphatase. The significance of these findings is uncertain.

Topiramate produced a dose-related increased incidence of treatment-emergent hyperammonemia *[see Warnings and Precautions (5.9)]*.

Treatment with topiramate for up to 1 year was associated with reductions in Z SCORES for length, weight, and head circumference *[see Warnings and Precautions (5.3) and Adverse Reactions (6)]*.

In open-label, uncontrolled experience, increasing impairment of adaptive behavior was documented in behavioral testing over time in this population. There was a suggestion that this effect was dose-related. However, because of the absence of an appropriate control group, it is not known if this decrement in function was treatment-related or reflects the patient's underlying disease (e.g., patients who received higher doses may have more severe underlying disease) *[see Warnings and Precautions (5.5)]*.

In this open-label, uncontrolled study, the mortality was 37 deaths/1000 patient years. It is not possible to know whether this mortality rate is related to topiramate treatment, because the background mortality rate for a similar, significantly refractory, young pediatric population (1-24 months) with partial epilepsy is not known.

Monotherapy Treatment in Partial Onset Epilepsy in Patients <2 Years Old

Safety and effectiveness in patients below the age of 2 years have not been established for the monotherapy treatment of epilepsy.

Migraine Prophylaxis in Pediatrics

Safety and effectiveness in pediatric patients have not been established for the prophylaxis treatment of migraine headache.

Topiramate treatment produced a dose-related increased shift in serum creatinine from normal at baseline to an increased value at the end of 4 months treatment in adolescent patients (ages 12-16 years) who were treated for migraine prophylaxis in a double-blind, placebo-controlled study. The incidence of these abnormal shifts was 4% for placebo, 4% for 50 mg, and 18%for 100 mg *[see Warnings and Precautions (5.15)]*.

Juvenile Animal Studies

When topiramate (30, 90, or 300 mg/kg/day) was administered orally to rats during the juvenile period of development (postnatal days 12 to 50), bone growth plate thickness was reduced in

males at the highest dose, which is approximately 5-8 times the maximum recommended pediatric dose (9 mg/kg/day) on a body surface area (mg/m^2) basis.

8.5 Geriatric Use

In clinical trials, 3% of patients were over 60. No age-related differences in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with impaired renal function (creatinine clearance rate <70 mL/min/1.73 m^2) due to reduced clearance of topiramate *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.5)]*.

8.6 Race and Gender Effects

Evaluation of effectiveness and safety in clinical trials has shown no race- or gender-related effects.

8.7 Renal Impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30 to 69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). One-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.4)]*.

8.8 Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than in a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of TOPAMAX® may be required.

The actual adjustment should take into account the duration of dialysis period, the clearance rate of the dialysis system being used, and the effective renal clearance of topiramate in the patient being dialyzed *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.4)]*.

8.9 Women of Childbearing Potential

Data from pregnancy registries indicate that infants exposed to TOPAMAX® *in utero* have an increased risk for cleft lip and/or cleft palate (oral clefts) *[see Warnings and Precautions (5.6)*

and Use in Specific Populations (8.1)]. Consider the benefits and the risks of TOPAMAX® when prescribing this drug to women of childbearing potential, particularly when TOPAMAX® is considered for a condition not usually associated with permanent injury or death. Because of the risk of oral clefts to the fetus, which occur in the first trimester of pregnancy before many women know they are pregnant, all women of childbearing potential should be apprised of the potential hazard to the fetus from exposure to TOPAMAX®. If the decision is made to use TOPAMAX®, women who are not planning a pregnancy should use effective contraception *[see Drug Interactions (7.3)]*. Women who are planning a pregnancy should be counseled regarding the relative risks and benefits of TOPAMAX® use during pregnancy, and alternative therapeutic options should be considered for these patients *[see Patient Counseling Information (17.6)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TOPAMAX® (topiramate) is not a controlled substance.

9.2 Abuse

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

9.3 Dependence

TOPAMAX® has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 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 and Precautions (5.3)]*.

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

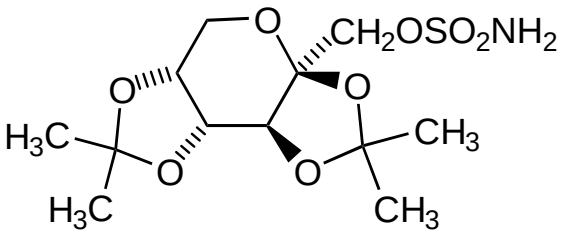
In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb

topiramate *in vitro*. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body.

11 DESCRIPTION

Topiramate is a sulfamate-substituted monosaccharide. TOPAMAX® (topiramate) Tablets are available as 25 mg, 50 mg, 100 mg, and 200 mg round tablets for oral administration. TOPAMAX® (topiramate capsules) Sprinkle Capsules are available as 15 mg and 25 mg sprinkle capsules for oral administration as whole capsules or opened and sprinkled onto soft food.

Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.36. Topiramate is designated chemically as 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate and has the following structural formula:



TOPAMAX® Tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

TOPAMAX® Sprinkle Capsules contain topiramate-coated beads in a hard gelatin capsule. The inactive ingredients are sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, sorbitan monolaurate, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms by which topiramate exerts its anticonvulsant and migraine prophylaxis effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and migraine prophylaxis. Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant

concentrations, blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

12.2 Pharmacodynamics

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole. Topiramate is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia.

12.3 Pharmacokinetics

The sprinkle formulation is bioequivalent to the immediate-release tablet formulation and, therefore, may be substituted as a therapeutic equivalent.

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady-state is thus reached in about 4 days in patients with normal renal function. Topiramate is 15% to 41% bound to human plasma proteins over the blood concentration range of 0.5 to 250 µg/mL. The fraction bound decreased as blood concentration increased.

Carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 µg/mL (a concentration 5 to 10 times higher than considered therapeutic for valproate) decreased the protein binding of topiramate from 23% to 13%. Topiramate does not influence the binding of sodium valproate.

Metabolism and Excretion

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via

hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in adults following oral administration.

Special Populations

Renal Impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30 to 69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment *[see Dosage and Administration (2.4) and (2.5) and Warnings and Precautions (5.13)]*.

Hemodialysis

Topiramate is cleared by hemodialysis. Using a high-efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20 to 30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may be required *[see Dosage and Administration (2.6)]*.

Hepatic Impairment

In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood *[see Dosage and Administration (2.7)]*.

Age, Gender, and Race

The pharmacokinetics of topiramate in elderly subjects (65 to 85 years of age, N=16) were evaluated in a controlled clinical study. The elderly subject population had reduced renal function (creatinine clearance [-20%]) compared to young adults. Following a single oral 100 mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1 to 2 hours. Reflecting the primary renal elimination of topiramate, topiramate

plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced. As recommended for all patients, dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate ≤70 mL/min/1.73 m^2) is evident. It may be useful to monitor renal function in the elderly patient *[see Dosage and Administration (2.4) and Warnings and Precautions (5.13)]*.

Clearance of topiramate in adults was not affected by gender or race.

Pediatric Pharmacokinetics

Pharmacokinetics of topiramate were evaluated in patients aged 2 to <16 years. Patients received either no or a combination of other antiepileptic drugs. A population pharmacokinetic model was developed on the basis of pharmacokinetic data from relevant topiramate clinical studies. This dataset contained data from 1217 subjects including 258 pediatric patients aged 2 to <16 years (95 pediatric patients <10 years of age).

Pediatric patients on adjunctive treatment exhibited a higher oral clearance (L/h) of topiramate compared to patients on monotherapy, presumably because of increased clearance from concomitant enzyme-inducing antiepileptic drugs. In comparison, topiramate clearance per kg is greater in pediatric patients than in adults and in young pediatric patients (down to 2 years) than in older pediatric patients. Consequently, the plasma drug concentration for the same mg/kg/day dose would be lower in pediatric patients compared to adults and also in younger pediatric patients compared to older pediatric patients. Clearance was independent of dose.

As in adults, hepatic enzyme-inducing antiepileptic drugs decrease the steady state plasma concentrations of topiramate.

Drug-Drug Interactions

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on mean plasma AUCs are summarized in Table 12.

In Table 12, the second column (AED concentration) describes what happens to the

concentration of the AED listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the co-administration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 12: Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400 mg/day	13% decrease

[a] = Plasma concentration increased 25% in some patients, generally those on a twice a day dosing regimen of phenytoin.
[b] = Is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration.
AED = Antiepileptic drug.
NE = Not Evaluated.
TPM = Topiramate

In addition to the pharmacokinetic interaction described in the above table, concomitant administration of valproic acid and TOPAMAX® has been associated with hyperammonemia with and without encephalopathy and hypothermia *[see Warnings and Precautions (5.9) (5.11) and Drug Interactions (7.1)]*.

CNS Depressants

Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of TOPAMAX® to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse reactions, TOPAMAX® should be used with extreme caution if used in combination with alcohol and other CNS depressants *[see Drug Interactions (7.2)]*.

Oral Contraceptives

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX®, given in the absence of other medications at doses of 50 to 200 mg/day, was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically

significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX® (50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose-dependent decrease in EE exposure for doses between 200 and 800 mg/day, there was no significant dose-dependent change in EE exposure for doses of 50 to 200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding *[see Drug Interactions (7.3)]*.

Digoxin

In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

Hydrochlorothiazide

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of hydrochlorothiazide (HCTZ) (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin

Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated.

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin (500 mg every 12 hr) and topiramate in plasma when metformin was given alone and when metformin and topiramate (100 mg every 12 hr) were given simultaneously. The results of this study indicated that the mean metformin C_{max} and $AUC_{0\text{-}12h}$ increased by 17% and 25%, respectively, when topiramate was added. Topiramate did not affect

metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is not known. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear *[see Drug Interactions (7.4)]*.

Pioglitazone

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the $AUC_{\tau,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known. When TOPAMAX® is added to pioglitazone therapy or pioglitazone is added to TOPAMAX® therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glyburide

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 22% decrease in C_{max} and a 25% reduction in AUC_{24} for glyburide during topiramate administration. Systemic exposure (AUC) of the active metabolites, 4-*trans*-hydroxy-glyburide (M1) and 3-*cis*-hydroxyglyburide (M2), was also reduced by 13% and 15%, and C_{max} was reduced by 18% and 25%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide.

Lithium

In patients, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure of lithium (27% for C_{max} and 26% for AUC) following topiramate doses up to 600 mg/day. Lithium levels should be monitored when co-administered with high-dose TOPAMAX® *[see Drug Interactions (7.5)]*.

Haloperidol

The pharmacokinetics of a single dose of haloperidol (5 mg) were not affected following multiple dosing of topiramate (100 mg every 12 hr) in 13 healthy adults (6 males, 7 females).

Amitriptyline

There was a 12% increase in AUC and C_{max} for amitriptyline (25 mg per day) in 18 normal subjects (9 males, 9 females) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels.

Sumatriptan

Multiple dosing of topiramate (100 mg every 12 hrs) in 24 healthy volunteers (14 males, 10 females) did not affect the pharmacokinetics of single-dose sumatriptan either orally (100 mg) or subcutaneously (6 mg).

Risperidone

When administered concomitantly with topiramate at escalating doses of 100, 250, and 400 mg/day, there was a reduction in risperidone systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses of topiramate). No alterations of 9-hydroxyrisperidone levels were observed. Co-administration of topiramate 400 mg/day with risperidone resulted in a 14% increase in C_{max} and a 12% increase in AUC_{12} of topiramate. There were no clinically significant changes in the systemic exposure of risperidone plus 9-hydroxyrisperidone or of topiramate; therefore, this interaction is not likely to be of clinical significance.

Propranolol

Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 males, 17 females) did not affect the pharmacokinetics of propranolol following daily 160 mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27 males, 12 females) had no effect on the exposure to topiramate, at a dose of 200 mg/day of topiramate.

Dihydroergotamine

Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 males, 12 females) did not affect the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergotamine. Similarly, a 1 mg subcutaneous dose of dihydroergotamine did not affect the pharmacokinetics of a 200 mg/day dose of topiramate in the same study.

Diltiazem

Co-administration of diltiazem (240 mg Cardizem CD®) with topiramate (150 mg/day) resulted in a 10% decrease in C_{max} and a 25% decrease in diltiazem AUC, a 27% decrease in C_{max} and an

18% decrease in des-acetyl diltiazem AUC, and no effect on N-desmethyl diltiazem. Co-administration of topiramate with diltiazem resulted in a 16% increase in C_{max} and a 19% increase in AUC_{12} of topiramate.

Venlafaxine

Multiple dosing of topiramate (150 mg/day) in healthy volunteers did not affect the pharmacokinetics of venlafaxine or O-desmethyl venlafaxine. Multiple dosing of venlafaxine (150 mg Effexor XR®) did not affect the pharmacokinetics of topiramate.

Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if TOPAMAX® is given concomitantly with another carbonic anhydrase inhibitor, the patient should be monitored for the appearance or worsening of metabolic acidosis [*see Drug Interactions (7.6)*].

Drug/Laboratory Tests Interactions

There are no known interactions of topiramate with commonly used laboratory tests.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady-state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5 to 2 times steady-state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a mg/m^2 basis).

Mutagenesis

Topiramate did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Topiramate was not mutagenic in the Ames test or the *in vitro* mouse lymphoma

assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro*; and it did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo*.

Impairment of Fertility

No adverse effects on male or female fertility were observed in rats at doses up to 100 mg/kg (2.5 times the RHD on a mg/m^2 basis).

14 CLINICAL STUDIES

The studies described in the following sections were conducted using TOPAMAX® (topiramate) Tablets.

14.1 Monotherapy Epilepsy Controlled Trial

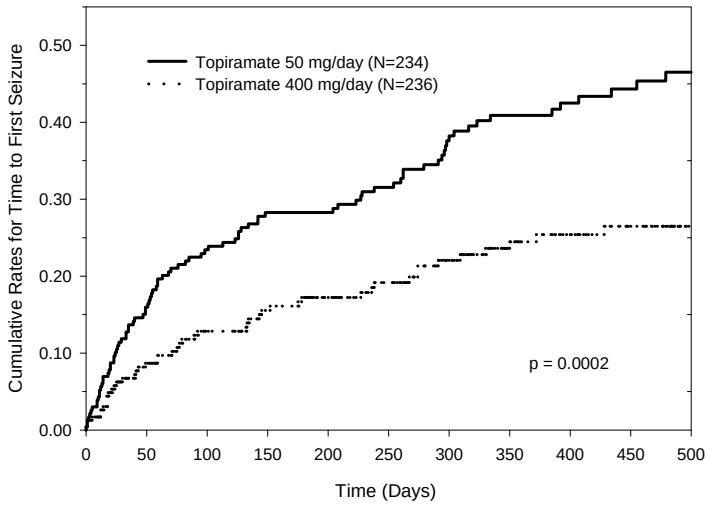
Patients with Partial Onset or Primary Generalized Tonic-Clonic Seizures

Adults and Pediatric Patients 10 Years of Age and Older

The effectiveness of topiramate as initial monotherapy in adults and children 10 years of age and older with partial onset or primary generalized tonic-clonic seizures was established in a multicenter, randomized, double-blind, parallel-group trial.

The trial was conducted in 487 patients diagnosed with epilepsy (6 to 83 years of age) who had 1 or 2 well-documented seizures during the 3-month retrospective baseline phase who then entered the study and received topiramate 25 mg/day for 7 days in an open-label fashion. Forty-nine percent of subjects had no prior AED treatment and 17% had a diagnosis of epilepsy for greater than 24 months. Any AED therapy used for temporary or emergency purposes was discontinued prior to randomization. In the double-blind phase, 470 patients were randomized to titrate up to 50 mg/day or 400 mg/day. If the target dose could not be achieved, patients were maintained on the maximum tolerated dose. Fifty-eight percent of patients achieved the maximal dose of 400 mg/day for >2 weeks, and patients who did not tolerate 150 mg/day were discontinued. The primary efficacy assessment was a between-group comparison of time to first seizure during the double-blind phase. Comparison of the Kaplan-Meier survival curves of time to first seizure favored the topiramate 400 mg/day group over the topiramate 50 mg/day group (p=0.0002, log rank test; Figure 1). The treatment effects with respect to time to first seizure were consistent across various patient subgroups defined by age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use.

Figure 1: Kaplan-Meier Estimates of Cumulative Rates for Time to First Seizure



Children 2 to <10 Years of Age

The conclusion that topiramate is effective as initial monotherapy in children 2 to < 10 years of age with partial onset or primary generalized tonic-clonic seizures was based on a pharmacometric bridging approach using data from the controlled epilepsy trials described in labeling. This approach consisted of first showing a similar exposure response relationship between pediatric patients down to 2 years of age and adults when topiramate was given as adjunctive therapy. Similarity of exposure-response was also demonstrated in pediatric patients ages 6 to <16 years and adults when topiramate was given as initial monotherapy. Specific dosing in children 2 to <10 years of age was derived from simulations utilizing plasma exposure ranges observed in pediatric and adult patients treated with topiramate initial monotherapy *[see Dosage and Administration (2.1)]*.

14.2 Adjunctive Therapy Epilepsy Controlled Trials

Adult Patients With Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for adults with partial onset seizures was established in six multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo and four comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalized seizures.

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® tablets or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during baseline phase lasting between 4 and 12 weeks.

Patients who experienced a prespecified minimum number of partial onset seizures, with or without secondary generalization, during the baseline phase (12 seizures for 12-week baseline, 8 for 8-week baseline or 3 for 4-week baseline) were randomly assigned to placebo or a specified dose of TOPAMAX® tablets in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. In five of the six studies, patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. In the sixth study (119), the 25 or 50 mg/day initial doses of topiramate were followed by respective weekly increments of 25 or 50 mg/day until the target dose of 200 mg/day was reached. After titration, patients entered a 4, 8 or 12-week stabilization period. The numbers of patients randomized to each dose and the actual mean and median doses in the stabilization period are shown in Table 13.

Pediatric Patients Ages 2 to 16 Years with Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for pediatric patients ages 2 to 16 years with partial onset seizures was established in a multicenter, randomized, double-blind, placebo-controlled trial, comparing topiramate and placebo in patients with a history of partial onset seizures, with or without secondarily generalized seizures.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® tablets or placebo. In this study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least six partial onset seizures, with or without secondarily generalized seizures, during the baseline phase were randomly assigned to placebo or TOPAMAX® tablets in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 25 or 50 mg/day; the dose was then increased by 25 mg to 150 mg/day increments every other week until the assigned dosage of 125, 175, 225, or 400 mg/day based on patients' weight to approximate a dosage of 6 mg/kg/day was reached, unless intolerance prevented increases. After titration, patients entered an 8-week stabilization period.

Patients With Primary Generalized Tonic-Clonic Seizures

The effectiveness of topiramate as an adjunctive treatment for primary generalized tonic-clonic seizures in patients 2 years old and older was established in a multicenter, randomized, double-blind, placebo-controlled trial, comparing a single dosage of topiramate and placebo.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. Patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least three primary generalized tonic-clonic seizures during the baseline phase were randomly assigned to placebo or TOPAMAX® in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 50 mg/day for four weeks; the dose was then increased by 50 mg to 150 mg/day increments every other week until the assigned dose of 175, 225, or 400 mg/day based on patients' body weight to approximate a dosage of 6 mg/kg/day was reached, unless intolerance prevented increases. After titration, patients entered a 12-week stabilization period.

Patients With Lennox-Gastaut Syndrome

The effectiveness of topiramate as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome was established in a multicenter, randomized, double-blind, placebo-controlled trial comparing a single dosage of topiramate with placebo in patients 2 years of age and older.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. Patients who were experiencing at least 60 seizures per month before study entry were stabilized on optimum dosages of their concomitant AEDs during a 4-week baseline phase. Following baseline, patients were randomly assigned to placebo or TOPAMAX® in addition to their other AEDs. Active drug was titrated beginning at 1 mg/kg/day for a week; the dose was then increased to 3 mg/kg/day for one week, then to 6 mg/kg/day. After titration, patients entered an 8-week stabilization period. The primary measures of effectiveness were the percent reduction in drop attacks and a parental global rating of seizure severity.

Table 13: Topiramate Dose Summary During the Stabilization Periods of Each of Six Double-Blind, Placebo-Controlled, Add-On Trials in Adults with Partial Onset Seizures[a]

			Target Topiramate Dosage (mg/day)				
Protocol	**Stabilization Dose**	**Placebo[b]**	**200**	**400**	**600**	**800**	**1,000**
YD	N	42	42	40	41	--	--
	Mean Dose	5.9	200	390	556	--	--
	Median Dose	6.0	200	400	600	--	--
YE	N	44	--	--	40	45	40
	Mean Dose	9.7	--	--	544	739	796
	Median Dose	10.0	--	--	600	800	1,000
Y1	N	23	--	19	--	--	--
	Mean Dose	3.8	--	395	--	--	--
	Median Dose	4.0	--	400	--	--	--
Y2	N	30	--	--	28	--	--
	Mean Dose	5.7	--	--	522	--	--
	Median Dose	6.0	--	--	600	--	--
Y3	N	28	--	--	--	25	--
	Mean Dose	7.9	--	--	--	568	--
	Median Dose	8.0	--	--	--	600	--
119	N	90	157	--	--	--	--
	Mean Dose	8	200	--	--	--	--
	Median Dose	8	200	--	--	--	--

[a] Dose-response studies were not conducted for other indications or pediatric partial onset seizures.
[b] Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocols YD and Y2, 6 tablets/day; Protocol Y3 and 119, 8 tablets/day; Protocol YE, 10 tablets/day.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reductions in seizure rates and the responder rates (fraction of patients with at least a 50% reduction) by treatment group for each study are shown below in Table 14. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

Table 14: Efficacy Results in Double-Blind, Placebo-Controlled, Add-On Epilepsy Trials

		Target Topiramate Dosage (mg/day)					
Protocol Efficacy Results	**Placebo**	**200**	**400**	**600**	**800**	**1,000**	**≈6 mg/kg/day***
Partial Onset Seizures							
Studies in Adults							
YD N	45	45	45	46	--	--	--
Median % Reduction	11.6	27.2[a]	47.5[b]	44.7[c]	--	--	--
% Responders	18	24	44[d]	46[d]	--	--	--
YE N	47	--	--	48	48	47	--
Median % Reduction	1.7	--	--	40.8[c]	41.0[c]	36.0[c]	--
% Responders	9	--	--	40[c]	41[c]	36[d]	--
Y1 N	24	--	23	--	--	--	--
Median % Reduction	1.1	--	40.7[e]	--	--	--	--
% Responders	8	--	35[d]	--	--	--	--
Y2 N	30	--	--	30	--	--	--
Median % Reduction	-12.2	--	--	46.4[f]	--	--	--
% Responders	10	--	--	47[c]	--	--	--
Y3 N	28	--	--	--	28	--	--
Median % Reduction	-20.6	--	--	--	24.3[c]	--	--
% Responders	0	--	--	--	43[c]	--	--
119 N	91	168	--	--	--	--	--
Median % Reduction	20.0	44.2[c]	--	--	--	--	--
% Responders	24	45[c]	--	--	--	--	--
Studies in Pediatric Patients							
YP N	45	--	--	--	--	--	41
Median % Reduction	10.5	--	--	--	--	--	33.1[d]
% Responders	20	--	--	--	--	--	39
Primary Generalized Tonic-Clonic[h]							
YTC N	40	--	--	--	--	--	39
Median % Reduction	9.0	--	--	--	--	--	56.7[d]
% Responders	20	--	--	--	--	--	56[c]
Lennox-Gastaut Syndrome[i]							
YL N	49	--	--	--	--	--	46
Median % Reduction	-5.1	--	--	--	--	--	14.8[d]
% Responders	14	--	--	--	--	--	28[g]
Improvement in Seizure Severity[j]	28	--	--	--	--	--	52[d]

Comparisons with placebo: [a] p=0.080; [b] p≤0.010; [c] p≤0.001; [d] p≤0.050; [e] p=0.065; [f] p≤0.005;[g] p=0.071;
[h] Median % reduction and % responders are reported for PGTC Seizures;
[i] Median % reduction and % responders for drop attacks, i.e., tonic or atonic seizures;
[j] Percent of subjects who were minimally, much, or very much improved from baseline

* For Protocols YP and YTC, protocol-specified target dosages (<9.3 mg/kg/day) were assigned based on subject's weight to approximate a dosage of 6 mg/kg per day; these dosages corresponded to mg/day dosages of 125, 175, 225, and 400 mg/day.

Subset analyses of the antiepileptic efficacy of TOPAMAX® tablets in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

In clinical trials for epilepsy, daily dosages were decreased in weekly intervals by 50 to

100 mg/day in adults and over a 2- to 8-week period in children; transition was permitted to a new antiepileptic regimen when clinically indicated.

14.3 Migraine Prophylaxis

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).

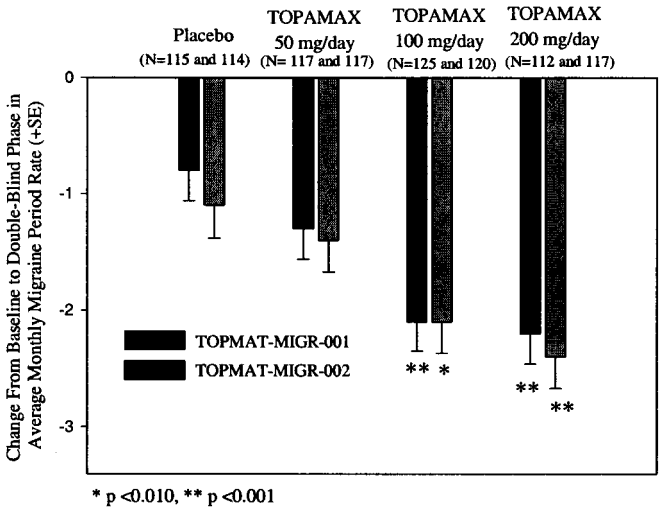
In the second study, a total of 468 patients (406 females, 62 males), ranging in age from 12 to 65 years, were randomized and provided efficacy data. Two hundred fifty-five patients completed the entire 26-week double-blind phase. The median average daily dosages were 46.5 mg/day, 85.6 mg/day, and 150.2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

For patients withdrawing from TOPAMAX®, daily dosages were decreased in weekly intervals by 25 to 50 mg/day.

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



16 HOW SUPPLIED/STORAGE AND HANDLING

TOPAMAX® Tablets

TOPAMAX® (topiramate) Tablets are available as debossed, coated, round tablets in the following strengths and colors:

25 mg cream tablet (debossed “OMN” on one side; "25" on the other) and are available in bottles of 60 count with desiccant (NDC 50458-639-65)

50 mg light yellow tablet (debossed “OMN” on one side; "50" on the other) and are available in bottles of 60 count with desiccant (NDC 50458-640-65)

100 mg yellow tablet (debossed “OMN” on one side; "100" on the other) and are available in bottles of 60 count with desiccant (NDC 50458-641-65)

200 mg salmon tablet (debossed “OMN” on one side; "200" on the other) and are available in bottles of 60 count with desiccant (NDC 50458-642-65)

TOPAMAX® Sprinkle Capsules

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain small, white to off-white spheres. The gelatin capsules are white and clear and are marked as follows:

15 mg capsule with “TOP” and “15 mg” on the side and are available in bottles of 60 (NDC 50458-647-65)

25 mg capsule with “TOP” and “25 mg” on the side and are available in bottles of 60 (NDC 50458-645-65)

Storage and Handling

TOPAMAX® Tablets should be stored in tightly-closed containers at controlled room temperature (59° to 86°F, 15° to 30°C). Protect from moisture.

TOPAMAX® Sprinkle Capsules should be stored in tightly-closed containers at or below 25°C (77°F). Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Patients and their caregivers should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to taking TOPAMAX®. Patients should be instructed to take TOPAMAX® only as prescribed. See FDA-approved Medication Guide.

17.1 Eye Disorders

Patients taking TOPAMAX® should be told to seek immediate medical attention if they experience blurred vision, visual disturbances, or periorbital pain *[see Warnings and Precautions (5.1)]*.

17.2 Oligohydrosis and Hyperthermia

Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather *[see Warnings and Precautions (5.2)]*.

17.3 Metabolic Acidosis

Patients should be warned about the potential significant risk for metabolic acidosis that may be asymptomatic and may be associated with adverse effects on kidneys (e.g., kidney stones, nephrocalcinosis), bones (e.g., osteoporosis, osteomalacia, and/or rickets in children), and growth (e.g., growth delay/retardation) in pediatric patients, and on the fetus *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

17.4 Suicidal Behavior and Ideation

Patients, their caregivers, and families should be counseled that AEDs, including Topamax, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior or the emergence of suicidal thoughts, or behavior or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers *[see Warnings and Precautions (5.4)]*.

17.5 Interference with Cognitive and Motor Performance

Patients should be warned about the potential for somnolence, dizziness, confusion, difficulty concentrating, or visual effects and should be advised not to drive or operate machinery until they have gained sufficient experience on TOPAMAX® to gauge whether it adversely affects their mental performance, motor performance, and/or vision *[see Warnings and Precautions (5.5)]*.

Even when taking TOPAMAX® or other anticonvulsants, some patients with epilepsy will continue to have unpredictable seizures. Therefore, all patients taking TOPAMAX® for epilepsy should be told to exercise appropriate caution when engaging in any activities where loss of consciousness could result in serious danger to themselves or those around them (including

swimming, driving a car, climbing in high places, etc.). Some patients with refractory epilepsy will need to avoid such activities altogether. Physicians should discuss the appropriate level of caution with their patients, before patients with epilepsy engage in such activities.

17.6 Fetal Toxicity

Inform pregnant women and women of childbearing potential that use of TOPAMAX® during pregnancy can cause fetal harm, including an increased risk for cleft lip and/or cleft palate (oral clefts), which occur early in pregnancy before many women know they are pregnant. There may also be risks to the fetus from chronic metabolic acidosis with use of TOPAMAX® during pregnancy *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.1), (8.9)]*. When appropriate, prescribers should counsel pregnant women and women of childbearing potential about alternative therapeutic options. This is particularly important when TOPAMAX® use is considered for a condition not usually associated with permanent injury or death.

Prescribers should advise women of childbearing potential who are not planning a pregnancy to use effective contraception while using TOPAMAX®, keeping in mind that there is a potential for decreased contraceptive efficacy when using estrogen-containing birth control with topiramate *[see Drug Interactions (7.3)]*.

Encourage pregnant women using TOPAMAX®, to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free-number, 1-888-233-2334. Information about the North American Drug Pregnancy Registry can be found at *http://www.massgeneral.org/aed/ [see Use in Specific Populations (8.1)]*.

17.7 Hyperammonemia and Encephalopathy

Patients should be warned about the possible development of hyperammonemia with or without encephalopathy. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. This hyperammonemia and encephalopathy can develop with TOPAMAX® treatment alone or with TOPAMAX® treatment with concomitant valproic acid (VPA).

Patients should be instructed to contact their physician if they develop unexplained lethargy, vomiting, or changes in mental status *[see Warnings and Precautions (5.9)]*.

17.8 Kidney Stones

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of kidney stone formation *[see Warnings and Precautions (5.10)]*.

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