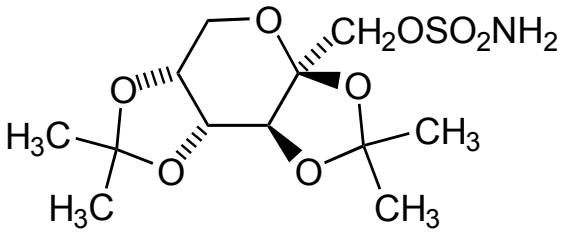
NDA 20-505 S-010, S-017, S-019
NDA 20-844 S-006, S-014, S-016
Approved Labeling Text dated 12/16/03

TOPAMAX®
(topiramate)
Tablets
TOPAMAX®
(topiramate capsules)
Sprinkle Capsules

DESCRIPTION

Topiramate is a sulfamate-substituted monosaccharide that is intended for use as an antiepileptic drug. 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 339.37. Topiramate is designated chemically as 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate and has the following structural formula:



TOPAMAX® (topiramate) 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 (100 and 200 mg tablets) and polysorbate 80.

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

CLINICAL PHARMACOLOGY

Mechanism of Action:

The precise mechanism by which topiramate exerts its antiseizure effect is unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's antiepileptic efficacy. 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 kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

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.

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 13-17% bound to human plasma proteins over the concentration range of 1-250 µg/mL.

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 humans following oral administration.

Pharmacokinetic Interactions (see also Drug Interactions):

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized under **PRECAUTIONS (Table 3).**

Special Populations:

Renal Impairment:

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30-69 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 **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION**).

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 20-30 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**).

Hepatic Impairment:

In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood.

Age, Gender, and Race:

The pharmacokinetics of topiramate in elderly subjects (65-85 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 1-2 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 m2) is evident. It may be useful to monitor renal function in the elderly patient. (See **Special Populations: Renal Impairment, PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION**).

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

Pediatric Pharmacokinetics:

Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose.

Pediatric patients have a 50% higher clearance and consequently shorter elimination half-life than adults. Consequently, the plasma concentration for the same mg/kg dose may be lower in pediatric patients compared to adults. As in adults, hepatic enzyme-

inducing antiepileptic drugs decrease the steady state plasma concentrations of topiramate.

CLINICAL STUDIES

The results of controlled clinical trials established the efficacy of TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules as adjunctive therapy in adults and pediatric patients ages 2-16 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.

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

Controlled Trials in Patients With Partial Onset Seizures

Adults 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 a 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 1.

Pediatric Patients Ages 2 - 16 Years With Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for pediatric patients ages 2 - 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 per 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 per day was reached, unless intolerance prevented increases. After titration, patients entered an 8-week stabilization period.

Controlled Trials in 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 per 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 per day was reached, unless intolerance prevented increases. After titration, patients entered a 12-week stabilization period.

Controlled Trial in 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 four 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 per day for a week; the dose was then increased to 3 mg/kg per day for one week then to 6 mg/kg per 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 1: Topiramate Dose Summary During the Stabilization Periods of Each of Five Double-Blind, Placebo-Controlled, Add-On Trials in Adults with Partial Onset Seizures[b]

Protocol Stabilization Dose		Target Topiramate Dosage (mg/day)					
		Placebo[a]	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] 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.

[b] Dose response studies were not conducted for other indications or pediatric partial onset seizures.

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 2. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

Table 2: Efficacy Results in Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Efficacy Results	Placebo	Target Topiramate Dosage (mg/day) 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[e]	--	--	--
Y3	N	28	--	--	--	28	--	--
	Median % Reduction	-20.6	--	--	--	24.3[e]	--	--
	% Responders	0	--	--	--	43[e]	--	--
119	N	91	168	--	--	--	--	--
	Median % Reduction	20.0	44.2[e]	--	--	--	--	--
	% Responders	24	45[e]	--	--	--	--	--
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.

INDICATIONS AND USAGE

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2 - 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.

CONTRAINDICATIONS

TOPAMAX® is contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS

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 topiramate 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 to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or 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 a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 3% for 400 mg/day, and 0% for placebo. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

In pediatric patients (<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 the prophylaxis of migraine, 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.

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.

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®. 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 judgement 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.

Oligohidrosis and Hyperthermia

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

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

Withdrawal of AEDs

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

Cognitive/Neuropsychiatric Adverse Events

Adults

Adverse events most often associated with the use of TOPAMAX® were central nervous system related. In adults, the most significant of these can be classified into two general categories: 1) psychomotor slowing, difficulty with concentration, and

speech or language problems, in particular, word-finding difficulties and 2) somnolence or fatigue. Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression).

Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common in adults. Although in some cases these events were mild to moderate, they at times led to withdrawal from treatment. The incidence of psychomotor slowing is only marginally dose-related, but both language problems and difficulty with concentration or attention clearly increased in frequency with increasing dosage in the five double-blind trials [see **ADVERSE REACTIONS, Table 6**].

Somnolence and fatigue were the most frequently reported adverse events during clinical trials with TOPAMAX®. These events were generally mild to moderate and occurred early in therapy. While the incidence of somnolence does not appear to be dose-related, that of fatigue increases at dosages above 400 mg/day.

Pediatric Patients

In double-blind clinical studies, the incidences of cognitive/neuropsychiatric adverse events in pediatric patients were generally lower than previously observed in adults. These events included psychomotor slowing, difficulty with concentration/attention, speech disorders/related speech problems and language problems. The most frequently reported neuropsychiatric events in this population were somnolence and fatigue. No patients discontinued treatment due to adverse events in double-blind trials.

Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of TOPAMAX® (topiramate) Tablets, 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 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).

PRECAUTIONS

General:

Kidney Stones

A total of 32/2,086 (1.5%) of adults exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2-4 times greater than expected in a similar, untreated population. 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.

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., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors 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.

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®.

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**).

Decreased Hepatic Function

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

Information for Patients

Patients taking TOPAMAX® should be told to seek immediate medical attention if they experience blurred vision or periorbital pain.

Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather.

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation [see **PRECAUTIONS: General**, for support regarding hydration as a preventative measure].

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Additional food intake may be considered if the patient is losing weight while on this medication.

Please refer to the end of the product labeling for important information on how to take TOPAMAX® (topiramate capsules) Sprinkle Capsules.

Laboratory Tests:

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. (see **WARNINGS**).

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 the following table:

In Table 3, 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 coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 3: 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

[a] = Plasma concentration increased 25% in some patients, generally those on a b.i.d. 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.

Other Drug Interactions

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.

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 events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

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 200-800 mg/day, there was no significant dose dependent change in EE exposure for doses of 50-200 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.

Others: Concomitant use of TOPAMAX®, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided.

Drug/Laboratory Test Interactions: There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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).

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*.

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).

Pregnancy: Pregnancy Category C.

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. 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.

There are no studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established.

Labor and Delivery:

In studies of rats where dams were allowed to deliver pups naturally, no drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg/day.

The effect of TOPAMAX® on labor and delivery in humans is unknown.

Nursing Mothers:

Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive secretion of topiramate into breast milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to TOPAMAX® is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing.

Pediatric Use:

Safety and effectiveness in patients below the age of 2 years have not been established. Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia (rickets) and may 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 (see **WARNINGS**).

Geriatric Use:

In clinical trials, 3% of patients were over 60. No age related difference 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 patients with impaired renal function (creatinine clearance rate ≤70 mL/min/1.73 m^2) due to reduced clearance of topiramate. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Race and Gender Effects:

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

ADVERSE REACTIONS

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

The most commonly observed adverse events associated with the use of topiramate 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 topiramate-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 4]. The most common dose-related adverse events 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 6].

Adverse events associated with the use of topiramate 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 topiramate-treated patients were: fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease [see Table 7].

In controlled clinical trials in adults, 11% of patients receiving topiramate 200 to 400 mg/day as adjunctive therapy discontinued due to adverse events. This rate appeared

to increase at dosages above 400 mg/day. Adverse events 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 topiramate adjunctive therapy at 5 to 9 mg/kg/day in controlled clinical trials discontinued due to adverse events.

Approximately 28% of the 1,757 adults with epilepsy who received topiramate at dosages of 200 to 1,600 mg/day in clinical studies discontinued treatment because of adverse events; an individual patient could have reported more than one adverse event. These adverse events 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 topiramate at dosages up to 30 mg/kg/day discontinued due to adverse events. Adverse events 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%).

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

Table 4 lists treatment-emergent adverse events that occurred in at least 1% of adults treated with 200 to 400 mg/day topiramate 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 events during the first eight weeks of these trials no longer experienced them by their last visit. Table 7 lists treatment-emergent adverse events that occurred in at least 1% of pediatric patients treated with 5 to 9 mg/kg topiramate 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 events 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 event incidences in the population studied.

Table 4: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials in Adults[a,b] Where Rate Was > 1% in Any Topiramate Group and Greater Than the Rate in Placebo-Treated Patients

	TOPAMAX® Dosage (mg/day)		
Body System/ Adverse Event[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
Hypoaesthesia	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
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

(Continued)

Table 4: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials in Adults[a,b] Where Rate Was > 1% in Any Topiramate Group and Greater Than the Rate in Placebo-Treated Patients (Continued)

	TOPAMAX® Dosage (mg/day)		
Body System/ Adverse Event[c]	Placebo (N=291)	200-400 (N=183)	600-1,000 (N=414)
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
Respiratory 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 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 event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.
[c] Adverse events 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.

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

Study 119 was a randomized, double-blind, placebo-controlled, parallel group study with 3 treatment arms: 1) placebo; 2) topiramate 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) topiramate 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 events did not differ significantly between the 2 topiramate regimens. The cited frequencies of adverse events cannot be directly compared with data obtained in other studies using different patients with different titration rates and taking different combinations of concomitant medications.

Table 5: Incidence of Treatment-Emergent Adverse Events in Study 119[a,b] Where Rate Was ≥ 2% in the Topiramate Group and Greater Than the Rate in Placebo-Treated Patients

	TOPAMAX® Dosage (mg/day)	
Body System/ Adverse Event[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
Hypoasthesia	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 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 event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

[c] Adverse events 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 6: Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Add-On Trials in Adults with Partial Onset Seizures[a]

		TOPAMAX® Dosage (mg/day)		
Adverse Event	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 7: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials in Pediatric Patients Ages 2 -16 Years[a,b] (Events that Occurred in at Least 1% of Topiramate-Treated Patients and Occurred More Frequently in Topiramate-Treated Than Placebo-Treated Patients)

Body System/ Adverse Event	Placebo (N=101)	Topiramate (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
Personality Disorder (Behavior Problems)	9	11
Difficulty with Concentration/Attention	2	10
Aggressive Reaction	4	9
Insomnia	7	8
Difficulty with Memory NOS	0	5
Confusion	3	4
Psychomotor Slowing	2	3
Appetite Increased	0	1
Neurosis	0	1

(Continued)

Table 7: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials in Pediatric Patients Ages 2 -16 Years[a,b] (Events that Occurred in at Least 1% of Topiramate-Treated Patients and Occurred More Frequently in Topiramate-Treated Than Placebo-Treated Patients) (Continued)

Body System/ Adverse Event	Placebo (N=101)	Topiramate (N=98)
Reproductive Disorders, Female		
Leukorrhoea	0	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
Seborrhoea	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 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 event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Other Adverse Events Observed

Other events that occurred in more than 1% of adults treated with 200 to 400 mg of topiramate in placebo-controlled 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.

Other Adverse Events Observed During All Clinical Trials

Topiramate, initiated as adjunctive therapy, has been administered to 1927 adults and 313 pediatric patients with epilepsy during all clinical studies. During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The

frequencies presented represent the proportion of patients who experienced an event of the type cited on at least one occasion while receiving topiramate. Reported events are included except those already listed in the previous table or text, those too general to be informative, and those not reasonably associated with the use of the drug.

Events 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: *Infrequent:* syncope, abdomen enlarged. *Rare:* alcohol intolerance.

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

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

Gastrointestinal System Disorders: *Frequent:* diarrhea, vomiting. *Infrequent:* hemorrhoids, stomatitis, melena, gastritis, tongue edema, esophagitis.

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

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

Metabolic and Nutritional Disorders: *Frequent:* dehydration. *Infrequent:* hypokalemia, alkaline phosphatase increased, hypocalcemia, hyperlipemia, acidosis, hyperglycemia, xerophthalmia. *Rare:* hyperchloremia, diabetes mellitus, hypernatremia, hyponatremia, hypocholesterolemia, hypophosphatemia, creatinine increased.

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

Myo-, Endo-, Pericardial & Valve Disorders: *Infrequent:* angina pectoris.

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

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

Psychiatric Disorders: *Frequent:* impotence, hallucination, euphoria, psychosis, suicide attempt. *Infrequent:* paranoid reaction, delusion, paranoia, delirium, abnormal dreaming, neurosis, *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: *Frequent:* acne. *Infrequent:* urticaria, photosensitivity reaction, abnormal hair texture. *Rare:* chloasma.

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

Urinary System Disorders: *Frequent:* dysuria, renal calculus. *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.

Postmarketing and Other Experience

In addition to the adverse experiences reported during clinical testing of TOPAMAX®, the following adverse experiences have been reported worldwide in patients receiving topiramate post-approval. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, pancreatitis, pemphigus, and renal tubular acidosis.

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

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

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

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

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.

DOSAGE AND ADMINISTRATION

TOPAMAX® has been shown to be effective in adults and pediatric patients ages 2-16 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patient 2 years of age and older with seizures associated with Lennox-Gastaut syndrome. In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. 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.

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

Adults (17 Years of Age and Over)

The recommended total daily dose of TOPAMAX® as adjunctive therapy in adults with partial seizures is 200-400 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 25-50 mg/day followed by titration to an effective dose in increments of 25-50 mg/week. Titrating in increments of 25 mg/week may delay the time to reach an effective dose. 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, Controlled Trials in Patients With Primary Generalized Tonic-Clonic Seizures**).

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

The recommended total daily dose of TOPAMAX® (topiramate) as adjunctive therapy for patients with partial 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 (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, Controlled Trials in Patients With Primary Generalized Tonic-Clonic Seizures**).

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.

Patients with Renal Impairment:

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

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 **DOSAGE AND ADMINISTRATION**: **Patients with Renal Impairment** and **CLINICAL PHARMACOLOGY: Special Populations: Age, Gender, and Race**).

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.

Patients with Hepatic Disease:

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

HOW SUPPLIED

TOPAMAX® (topiramate) Tablets is available as debossed, coated, round tablets in the following strengths and colors:
25 mg white (coded "TOP" on one side; "25" on the other) 50 mg light-yellow (coded "TOPAMAX" on one side; "50" on the other)

100 mg yellow (coded "TOPAMAX" on one side; "100" on the other)
200 mg salmon (coded "TOPAMAX" on one side; "200" on the other)

They are supplied as follows:
25 mg tablets – bottles of 60 count with desiccant (NDC 0045-0639-65)
50 mg tablets – bottles of 60 count with desiccant (NDC 0045-0640-65)

100 mg tablets – bottles of 60 count with desiccant (NDC 0045-0641-65)
200 mg tablets – bottles of 60 count with desiccant (NDC 0045-0642-65)

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

The capsules are supplied as follows:
15 mg capsules – bottles of 60 (NDC 0045-0647-65)
25 mg capsules – bottles of 60 (NDC 0045-0645-65)

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

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

TOPAMAX® (topiramate) and TOPAMAX® (topiramate capsules) are trademarks of Ortho-McNeil Pharmaceutical.

HOW TO TAKE TOPAMAX® (topiramate capsules) SPRINKLE CAPSULES

A Guide for Patients and Their Caregivers

Your doctor has given you a prescription for TOPAMAX® (topiramate capsules) Sprinkle Capsules. Here are your instructions for taking this medication. Please read these instructions prior to use.

To Take With Food
You may sprinkle the contents of TOPAMAX® Sprinkle Capsules on a small amount (teaspoon) of soft food, such as applesauce, custard, ice cream, oatmeal, pudding, or yogurt.

Hold the capsule upright so that you can read the word "TOP".

Carefully twist off the clear portion of the capsule. You may find it best to do this over the small portion of the food onto which you will be pouring the sprinkles.

Sprinkle <u>all</u> of the capsule's contents onto a spoonful of soft food, taking care to see that the entire prescribed dosage is sprinkled onto the food.

Be sure the patient swallows the entire spoonful of the sprinkle/food mixture immediately. Chewing should be avoided. It may be helpful to have the patient drink fluids immediately in order to make sure all of the mixture is swallowed. IMPORTANT: Never store any sprinkle/food mixture for use at a later time.

To Take Without Food
TOPAMAX® Sprinkle Capsules may also be swallowed as whole capsules

For more information about TOPAMAX® Sprinkle Capsules, ask your doctor or pharmacist.

OMP Division
ORTHO-McNEIL PHARMACEUTICAL, INC.
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 Revision Date December 2003 XXXXXXX