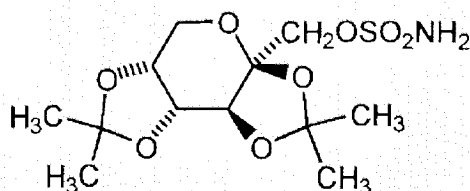


DESCRIPTION

Topiramate is a sulfamate-substituted monosaccharide that is intended for use as an antiepileptic drug. TOPAMAX[®] (topiramate capsules) Sprinkle Capsules are available as 15 mg, 25 mg and 50mg sprinkle capsules for oral administration as whole capsules or for opening and sprinkling 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 C₁₂H₂₁NO₈S 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:



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/1.73m²) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m²) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m²). 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 dose is recommended in patients with moderate or severe renal impairment.

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:

Clearance of topiramate was not affected by age (18-67 years), 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. Although the relationship between age and clearance among patients of pediatric age has not been systematically evaluated, it appears that the weight adjusted clearance of topiramate is 50% higher in pediatric patients than in adults.

CLINICAL STUDIES

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

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

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 an 8-12 week baseline phase. Patients who experienced at least 12 (or 8, for 8-week baseline studies) partial onset seizures, with or without secondarily generalization, during the baseline phase 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. 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. After titration, patients entered an 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 I.

Table 1: Topiramate Dose Summary During the Stabilization Periods of Each of Five Double-Blind, Placebo-Controlled, Add-On Trials

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	--

^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, 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. Responder rate (fraction of patients with at least a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 2.

Table 2: Median Percent Seizure Rate Reduction and Percent Responders in Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol Efficacy results		Target Topiramate Dosage (mg/day)					
		Placebo	200	400	600	800	1,000
YD	N	45	45	45	46		
	Median % Reduction	11.6	27.2 ^b	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	--

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

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 capsules) Sprinkle Capsules are indicated as adjunctive therapy for the treatment of adults with partial onset seizures.

CONTRAINDICATIONS

TOPAMAX[®] (topiramate capsules) Sprinkle Capsules are contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS

Withdrawal of AEDs

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

Cognitive/Neuropsychiatric Adverse Events

Adverse events most often associated with the use of TOPAMAX[®] were central nervous system-related. 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. 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 5).

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.

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 patients exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2-4 times that expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men.

An explanation for the association of TOPAMAX[®] and kidney stones may lie in the fact that topiramate is a weak 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 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 (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, 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.

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

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 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 with oral contraceptives using a combination product containing norethindrone and ethinyl estradiol, TOPAMAX[®] did not significantly affect the clearance of norethindrone. The mean oral clearance of ethinyl estradiol at 800 mg/day dose was increased by 47% (range: 13-107%). The mean total exposure to the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400, and 800 mg/day, respectively. Therefore, efficacy of oral contraceptives may be compromised by topiramate. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. The effect of oral contraceptives on the pharmacokinetics of topiramate is not known.

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.

Laboratory Tests: 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m² 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/m² basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m² 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/m² basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m² 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.

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. It is not known if topiramate is excreted in human 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 children have not been established. The pharmacokinetic profile of TOPAMAX[®] was studied in patients between the ages of 4 and 17 years. (see CLINICAL PHARMACOLOGY; Pediatric Pharmacokinetics).

Geriatric Use:

In clinical trials, 2% of patients were over 60. No age related difference in effectiveness or adverse effects were seen. There were no pharmacokinetic differences related to age alone, although the possibility of age-associated renal functional abnormalities should be considered.

Race and Gender Effects:

Evaluation of efficacy 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, 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, nystagmus, and paresthesia [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, cognitive problems not otherwise specified, weight decreased, and tremor [see Table 5].

In controlled clinical trials, 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.

Approximately 28% of the 1,715 individuals 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 (4.1%), difficulty with memory (3.3%), fatigue (3.3%), confusion (3.2%), somnolence (3.2%), difficulty with concentration/attention (2.9%), anorexia (2.9%), depression (2.6%), dizziness (2.6%), weight decrease (2.5%), nervousness (2.2%), ataxia (2.2%), paresthesia (2.0%), and language problems (2.0%).

Incidence in Controlled Clinical Trials - Add-On Therapy

Table 4 lists treatment-emergent adverse events that occurred in at least 1% of patients 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.

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^{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 ^c	TOPAMAX [®] Dosage (mg/day)		
	Placebo (N=174)	Z00-400 (N=113)	600-1,000 (N=247)
Body as a Whole-General Disorders			
Asthenia	1.1	8.0	4.5
Back Pain	4.0	6.2	2.0
Chest Pain	2.3	4.4	2.0
Influenza-like Symptoms	2.9	3.5	3.2
Leg Pain	2.3	3.5	2.4
Hot Flushes	1.7	2.7	0.8
Body Odor	0.0	1.8	0.0
Edema	1.1	1.8	1.2
Rigors	0.0	1.8	0.4
Central & Peripheral Nervous System Disorders			
Dizziness	14.4	28.3	32.4
Ataxia	6.9	21.2	17.0
Speech Disorders/Related Speech Problems	2.9	16.8	13.8
Nystagmus	11.5	15.0	15.0
Paresthesia	3.4	15.0	14.6
Tremor	6.3	10.6	13.8
Language Problems	0.6	6.2	11.7
Coordination Abnormal	1.7	5.3	3.6
Hypoaesthesia	1.1	2.7	0.8
Gastrointestinal System Disorders			
Nausea	6.3	11.5	13.8
Dyspepsia	5.2	8.0	5.7
Abdominal Pain	2.9	5.3	7.3
Constipation	0.6	5.3	3.2
Dry Mouth	1.1	2.7	3.2
Gingivitis	0.0	1.8	0.4
Hearing and Vestibular Disorders			
Hearing Decreased	1.1	1.8	1.6
Metabolic and Nutritional Disorders			
Weight Decrease	2.3	7.1	12.6
Musculoskeletal System Disorders			
Myalgia	1.1	1.8	1.2
Platelet, Bleeding and Clotting Disorders			
Epistaxis	1.1	1.8	0.8

(Continued)

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials^{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 ^c	TOPAMAX [®] Dosage (mg/day)		
	Placebo (N=174)	200-400 (N=113)	600,1,000 (N=247)
Psychiatric Disorders			
Somnolence	10.3	30.1	25.9
Psychomotor Slowing	2.3	16.8	25.1
Nervousness	7.5	15.9	20.6
Difficulty with Memory	2.9	12.4	12.6
Confusion	5.2	9.7	15.0
Depression	6.3	8.0	13.4
Difficulty with Concentration/Attention	1.1	8.0	15.4
Anorexia	4.0	5.3	11.3
Agitation	1.7	4.4	4.0
Mood Problems	1.7	3.5	10.1
Aggressive Reaction	0.6	2.7	4.0
Apathy	0.0	1.8	4.5
Depersonalization	0.6	1.8	1.6
Emotional Lability	1.1	1.8	2.4
Reproductive Disorders, Female			
Breast Pain, Female	(N=39)	(N=24)	(N=42)
Dysmenorrhea	0.0	8.3	0.0
Menstrual Disorder	2.6	8.3	0.0
	0.0	4.2	0.0
Respiratory System Disorders			
Upper Respiratory Infection	11.5	12.4	12.1
Pharyngitis	2.9	7.1	2.8
Sinusitis	4.0	4.4	4.0
Dyspnea	1.1	1.8	3.2
Skin and Appendages Disorders			
Rash	4.0	4.4	3.2
Pruritus	1.1	1.8	3.2
Sweating Increased	0.0	1.8	0.4
Urinary System Disorders			
Hematuria	0.6	1.8	0.8
Vision Disorders			
Diplopia	6.3	14.2	14.6
Vision Abnormal	2.9	14.2	10.5
Eye pain	1.1	1.8	2.0
White Cell and Res Disorders			
Leukopenia	0.6	2.7	1.6

^a Patients in these add-on trials were receiving 1 to 2 concomitant anti-epileptic 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[®] ZOO-400 mg/day group and more common than in the placebo group are listed in this table.

**Table 5: Incidence (%) of Dose-Related Adverse Events
From Five Placebo-Controlled, Add-On Trials**

Adverse Event	TOPAMAX [®] Dosage (mg/day)			
	Placebo (N=174)	200 (N= 45)	400 (N= 6X)	600-1,000 (N=247)
Fatigue	14.4	11.1	11.8	30.8
Nervousness	7.5	13.3	17.6	20.6
Difficulty with Concentration/Attention	1.1	6.7	8.8	15.4
Confusion	5.2	8.9	10.3	15.0
Depression	6.3	8.9	7.4	13.4
Anorexia	4.0	4.4	5.9	11.3
Language problems	0.6	2.2	8.8	11.7
Anxiety	5.2	2.2	2.9	9.3
Mood problems	1.7	0.0	5.9	10.1
Cognitive problems NOS	0.6	0.0	0.0	4.0
Weight decrease	2.3	4.4	8.8	12.6
Tremor	6.3	13.3	8.8	13.8

Other Adverse Events Observed

Other events that occurred in more than 1% of patients treated with 200 to 400 mg of topiramate in placebo-controlled trials but with equal or greater frequency in the placebo group were: fatigue, headache, injury, anxiety, rash, pain, convulsions aggravated, coughing, gastroenteritis, rhinitis, back pain, hot flushes, bronchitis, abnormal gait, involuntary muscle contractions, and epistaxis.

Other Adverse Events Observed During All Clinical Trials

Topiramate, initiated as adjunctive therapy, has been administered to 1,715 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 1,715 topiramate-treated 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, 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: *Frequent:* fatigue, fever, malaise. *Infrequent:* syncope, halitosis, abdomen enlarged. *Rare:* alcohol intolerance, substernal chest pain, sudden death.

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

Central & Peripheral Nervous System Disorders: *Frequent:* hypokinesia, vertigo, stupor, convulsions grand mal, hyperkinesia, hypertonia. *Infrequent:* leg cramps, hyporeflexia, neuropathy, migraine, apraxia, hyperaesthesia, dyskinesia, hyperreflexia, dysphonia, scotoma, ptosis, dystonia, visual field defect, coma, encephalopathy, fecal incontinence, upper motor neuron lesion. *Rare:* cerebellar syndrome, EEG abnormal, tongue paralysis.

Endocrine Disorders: *Infrequent:* goiter. *Rare:* thyroid disorder

Gastrointestinal System Disorders: *Frequent:* diarrhea, vomiting, flatulence, gastroenteritis. *Infrequent:* gum hyperplasia, hemorrhoids, tooth caries, stomatitis, dysphagia, melena, gastritis, saliva increased, hiccough, gastroesophageal reflux, tongue edema, esophagitis. *Rare:* eructation.

Hearing and Vestibular Disorders: *Frequent:* tinnitus. *Rare:* earache, hyperacusis.

Heart Rate and Rhythm Disorders: *Frequent:* palpitation. *Infrequent:* AV block, bradycardia, bundle branch block. *Rare:* arrhythmia, arrhythmia atrial, fibrillation atrial.

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

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

Musculoskeletal System Disorders: *Frequent:* arthralgia, muscle weakness. *Infrequent:* arthrosis, osteoporosis.

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

Neoplasms: *Infrequent:* basal cell carcinoma, thrombocytopenia. *Rare:* polycythemia

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

Psychiatric Disorders: *Frequent:* insomnia, personality disorder, impotence, hallucination, euphoria, psychosis, libido decreased, suicide attempt. *Infrequent:* paranoid reaction, appetite increased, delusion, paranoia, delirium, abnormal dreaming, neurosis. *Rare:* libido increased, manic reaction.

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

Reproductive Disorders, Female: *Frequent:* intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis, amenorrhea.

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

Respiratory System Disorders: *Frequent:* coughing, bronchitis. *Infrequent:* asthma, bronchospasm. *Rare:* laryngismus.

Skin and Appendages Disorders: *Frequent:* acne, alopecia. *Infrequent:* dermatitis, nail disorder, folliculitis, dry skin, urticaria, skin discoloration, eczema, photosensitivity reaction, erythematous rash, seborrhea, sweating decreased, abnormal hair texture. *Rare:* chloasma.

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

Urinary System Disorders: *Frequent:* urinary tract infection, micturition frequency, urinary incontinence, dysuria, renal calculus. *Infrequent:* urinary retention, face edema, renal pain, nocturia, albuminuria, polyuria, oliguria.

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

Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, abnormal lacrimation, strabismus, color blindness, myopia, mydriasis. *Rare:* cataract, corneal opacity, iritis.

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

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

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 not been shown to adsorb topiramate in vitro. Therefore, its use in overdose is not recommended. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdose reported, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

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, and 1000 mg/day) have not been shown to improve responses.

The recommended total daily dose of TOPAMAX[®] (topiramate capsules) as adjunctive therapy is 400 mg/day in two divided doses. A daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. It is recommended that therapy be initiated at 50 mg/day followed by titration to a[®] effective dose. Daily doses above 1,600 mg have not been studied.

The recommended titration rate for topiramate is:

	<u>AM DOSE</u>	<u>PM DOSE</u>
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX[®] therapy. On occasion, the addition of TOPAMAX[®] to phenytoin may require a[®] 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[®].

TOPAMAX[®] can be taken **without** regard to meals

Administration of the 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/1.73m²), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

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

They are marked as follows:

15 mg capsules with "TOP" and "15mg" on the side

25 mg capsules with "TOP" and "25mg" on the side.

50 mg capsules with "TOP" and "50 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)

50 mg capsules bottles of 60 (NDA 0045-0646-65)

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

TOPAMAX[®] (topiramate capsules) is a trademark of McNeil Pharmaceutical.

ORTHO-MCNEIL PHARMACEUTICAL, INC.

Raritan, New Jersey 08869

HOW TO TAKE TOPAMAX® (topiramate capsules) SPRINKLE CAPSULES

A Guide for Patients and Their Caregivers

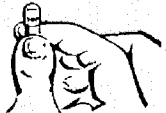
Your doctor has given you a prescription for TOPAMAX® (topiramate capsules) Sprinkle Capsules. Here are your instructions for taking this medication. Please read these instructions prior to use.



FPO - NOT FOR PRINT
FOR COMPIG ONLY

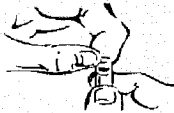
To Take With Food

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.



FPO - NOT FOR PRINT
FOR COMPIG ONLY

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



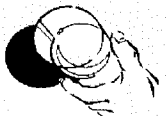
FPO - NOT FOR PRINT
FOR COMPIG ONLY

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.



FPO - NOT FOR PRINT
FOR COMPIG ONLY

Sprinkle all 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.



FPO - NOT FOR PRINT
FOR COMPIG ONLY

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.