เอกสารกำกับยาภาษาอังกฤษ

PRODUCT NAME

TOPAMAX® (topiramate).

DOSAGE FORMS AND STRENGTHS

Film-coated tablet.

Sprinkle capsule.

Film-Coated Tablets

The tablets are debossed, engraved or embossed.

25 mg tablet

Round, white tablet imprinted with “TOP” on one side and “25” on the other. Each tablet contains 25 mg of topiramate.

50 mg tablet

Round, light yellow tablet imprinted with “TOP” on one side and “50” on the other. Each tablet contains 50 mg of topiramate.

100 mg tablet

Round, yellow tablet imprinted with “TOP” on one side and “100” on the other. Each tablet contains 100 mg of topiramate.

Sprinkle Capsules

25 mg capsule

Small, white to off-white spheres in a gelatin capsule consisting of a white body with a clear or natural cap, printed in black ink with “TOP” on the cap and “25 mg” on the body. Each capsule contains 25 mg of topiramate.

50 mg capsule

Small, white to off-white spheres in a gelatin capsule consisting of a white body with a clear or natural cap, printed in black ink with “TOP” on the cap and “50 mg” on the body. Each capsule contains 50 mg of topiramate.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

Epilepsy

TOPAMAX is indicated as monotherapy in patients with newly diagnosed epilepsy or for conversion to monotherapy in patients with epilepsy.

TOPAMAX is indicated as adjunctive therapy for adults and children aged 2 and above with partial onset seizures or generalized tonic-clonic seizures.

TOPAMAX is also indicated in adults and children as adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome.

Migraine

TOPAMAX is indicated in adults for the prophylaxis of migraine headache. The usefulness of TOPAMAX in the acute treatment of migraine headache has not been studied.

Dosage and Administration

It is not necessary to monitor topiramate plasma concentrations to optimize therapy with TOPAMAX. On rare occasions, 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 carbamazepine to adjunctive therapy with TOPAMAX may require adjustment of the dose of TOPAMAX.

Dosage

It is recommended that therapy be initiated at a low dose followed by titration to an effective dose.

Epilepsy – adjunctive therapy

- **Adults**

Therapy should begin at 25 to 50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25 to 50 [to 100] mg/day and taken in two divided doses. Dose titration should be guided by clinical outcome. Some patients may achieve efficacy with once-a-day dosing.

In clinical trials as adjunctive therapy, 200 mg was effective and was the lowest dosage studied. This is therefore considered the minimum effective dose. The usual daily dose is 200 to 400 mg in two divided doses. Individual patients have received doses as high as 1600 mg/day.

These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease (see *Warnings and Precautions – Renal impairment*).

- **Children aged 2 and above**

The recommended total daily dose of TOPAMAX as adjunctive therapy 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.

Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

Epilepsy – monotherapy

When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve monotherapy with topiramate, consideration should be given to the effects this may have on seizure control. Unless safety concerns require an abrupt withdrawal of the concomitant AED, a gradual discontinuation at the rate of approximately one-third of the concomitant AED dose every 2 weeks is recommended (see *Warnings and Precautions – Withdrawal of TOPAMAX*).

When enzyme inducing drugs are withdrawn, topiramate levels will increase. A decrease in TOPAMAX dosage may be required if clinically indicated.

- **Adults**

Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2-week intervals by increments of 25 or 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used. Dose and titration rate should be guided by clinical outcome.

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day and the maximum recommended daily dose is 500 mg. Some patients with refractory forms of epilepsy have tolerated topiramate monotherapy at doses of 1000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

- **Children aged 2 and above**

Treatment of children aged 2 years and above should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 0.5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used. Dose and dose titration rate should be guided by clinical outcome.

The recommended initial target dose range for topiramate monotherapy in children aged two years and above is 100 to 400 mg/day. Children with recently diagnosed partial onset seizures have received doses of up to 500 mg/day.

Migraine

- **Adults**

The recommended total daily dose of topiramate for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used.

Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. Dose and titration rate should be guided by clinical outcome (see *Pharmacodynamic Properties – Migraine clinical trials*).

Special populations

Renal impairment

Patients with moderate and severe renal impairment (CL_{CR} <70 mL/min) may require a dose reduction. Half of the usual starting and maintenance dose is recommended (see *Pharmacokinetic Properties – Special populations, Renal impairment*).

Since TOPAMAX is removed from plasma by hemodialysis, a supplemental dose of TOPAMAX equal to approximately one-half the daily dose should be administered on hemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the hemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used (see *Pharmacokinetic Properties – Special populations, Renal impairment*).

Hepatic impairment

Topiramate should be administered with caution in patients with hepatic impairment (see *Pharmacokinetic Properties – Special populations, Hepatic impairment*).

Administration

TOPAMAX is available in tablets and a capsule sprinkle formulation, for oral administration. It is recommended that TOPAMAX tablets not be broken. The sprinkle formulation is provided for those patients who cannot swallow tablets, e.g. pediatric and elderly patients.

TOPAMAX 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.

TOPAMAX can be taken without regard to meals.

Contraindications

Hypersensitivity to any component of this product.

Warnings and Precautions

Withdrawal of TOPAMAX

In patients with or without a history of seizures or epilepsy, AEDs including TOPAMAX should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased in weekly intervals by 50 to 100 mg in adults with epilepsy and by 25 to 50 mg in adults receiving TOPAMAX at doses up to 100 mg/day for migraine prophylaxis. In clinical trials of children, TOPAMAX was gradually withdrawn over a 2 to 8 week period. In situations where rapid withdrawal of TOPAMAX is medically required, appropriate monitoring is recommended.

Renal impairment

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with moderate or severe renal impairment may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function.

As with all patients, the titration schedule should be guided by clinical outcome (i.e., seizure control, avoidance of side effects) with the knowledge that subjects with known renal impairment may require a longer time to reach steady-state at each dose (see *Dosage and Administration – Special Populations, Renal impairment* and *Pharmacokinetic Properties – Special populations, Renal impairment*).

Hydration

Oligohidrosis (decreased sweating) and anhidrosis have been reported in association with the use of topiramate. Decreased sweating and hyperthermia (rise in body temperature) may occur especially in young children exposed to high ambient temperatures (see *Adverse Reactions*).

Adequate hydration while using topiramate is very important. Hydration can reduce the risk of nephrolithiasis (see *Warnings and Precautions – Nephrolithiasis*). Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse events (see *Adverse Reactions*).

Mood disturbances/depression

An increased incidence of mood disturbances and depression has been observed during topiramate treatment.

Suicide/suicidal ideation

AEDs, including TOPAMAX, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. A meta-analysis of randomized placebo-controlled trials of AEDs has shown an increased risk of suicidal ideation and behavior (0.43% on AEDs versus 0.24% on placebo). The mechanism of this risk is not known.

In double-blind clinical trials, suicide related events (suicidal ideation, suicide attempts, and suicide) occurred at a frequency of 0.5% in topiramate treated patients (46 out of 8652 patients

treated) compared to 0.2% treated with placebo (8 out of 4045 patients treated). One completed suicide was reported in a bipolar disorder double-blind trial in a patient on topiramate.

Patients therefore should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and, when appropriate, caregivers of patients) should be advised to seek immediate medical advice should signs of suicidal ideation or behaviour emerge.

Nephrolithiasis

Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain.

Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during topiramate treatment. In addition, patients taking other medication associated with nephrolithiasis may be at increased risk (see *Interactions – Other forms of interactions, Agents predisposing to nephrolithiasis*).

Hepatic impairment

In hepatically-impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased (see *Dosage and Administration – Special Populations, Hepatic impairment* and *Pharmacokinetic Properties – Special populations, Hepatic impairment*).

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. Treatment includes discontinuation of TOPAMAX, as rapidly as possible in the judgment of the treating physician, and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure.

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

Visual field defects

Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible after topiramate

discontinuation. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug.

Metabolic acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with topiramate treatment. This decrease in serum bicarbonate is due to the inhibitory effect of topiramate on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/L at doses of 100 mg/day or above in adults and at approximately 6 mg/kg/day in pediatric patients). Rarely, patients have experienced decreases to values below 10 mmol/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or certain drugs) may be additive to the bicarbonate lowering effects of topiramate.

Chronic metabolic acidosis in pediatric patients can reduce growth rates. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in pediatric or adult populations.

Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with topiramate therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

Hyperammonemia and encephalopathy

Hyperammonemia with or without encephalopathy has been reported with topiramate treatment (see *Adverse Reactions*). The risk for hyperammonemia with topiramate appears dose-related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid (see *Interactions*).

Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy. In most cases, hyperammonemic encephalopathy abated with discontinuation of treatment. In patients who develop unexplained lethargy, or changes in mental status associated with topiramate monotherapy or adjunctive therapy, it is recommended to consider hyperammonemic encephalopathy and measuring ammonia levels.

Nutritional supplementation

A dietary supplement or increased food intake may be considered if the patient is losing weight while on this medication.

Interactions

(For purposes of this section, a no effect dose is defined as a ≤ 15% change.)

Effects of other AEDs on TOPAMAX

Phenytoin and carbamazepine decrease the plasma concentration of TOPAMAX. The addition or withdrawal of phenytoin or carbamazepine to TOPAMAX therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of TOPAMAX and, therefore, does not warrant dosage adjustment of TOPAMAX. The results of these interactions are summarized below:

AED Coadministered	AED Concentration	TOPAMAX Concentration
Phenytoin	↔**	↓ (48%)
Carbamazepine (CBZ)	↔	↓ (40%)
Valproic acid	↔	↔
Lamotrigine	↔	↔
Phenobarbital	↔	NS
Primidone	↔	NS

↔ = No effect on plasma concentration (≤ 15% change)
** = Plasma concentrations increase in individual patients
↓ = Plasma concentrations decrease
NS = Not studied
AED = Antiepileptic drug

Effects of TOPAMAX on other AEDs

The addition of TOPAMAX to other AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of TOPAMAX to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform (CYP2C19). Consequently, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

A pharmacokinetic interaction study of patients with epilepsy indicated the addition of topiramate to lamotrigine had no effect on steady state plasma concentration of lamotrigine at topiramate doses of 100 to 400 mg/day. In addition, there was no change in steady state plasma concentration of topiramate during or after removal of lamotrigine treatment (mean dose of 327 mg/day).

Other drug interactions

Digoxin

In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased 12% due to concomitant administration of TOPAMAX. The clinical relevance of this observation has not been established. When TOPAMAX is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

Central nervous system (CNS) depressants

Concomitant administration of TOPAMAX and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. It is recommended that TOPAMAX not be used concomitantly with alcohol or other CNS depressant drugs.

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.

Lithium

In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure (26% for AUC) following topiramate doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with topiramate.

Risperidone

Drug-drug interaction studies conducted under single and multiple dose conditions in healthy volunteers and patients with bipolar disorder yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively). Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no clinically significant changes in the systemic exposure of the risperidone total active moiety or of topiramate, therefore this interaction is not likely to be of clinical significance.

Hydrochlorothiazide (HCTZ)

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg every 24h) and topiramate (96 mg every 12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max}

increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean C_{max} and mean $AUC_{0\text{-}12h}$ increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When TOPAMAX is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

Pioglitazone

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

Glyburide

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glyburide AUC_{24} during topiramate administration. Systemic exposure of the active metabolites, 4-*trans*-hydroxy-glyburide (M1) and 3-*cis*-hydroxyglyburide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide. When topiramate is added to glyburide therapy or glyburide is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Other forms of interactions

Agents predisposing to nephrolithiasis

TOPAMAX, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using TOPAMAX, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation.

Valproic acid

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug (see *Warnings and Precautions and Adverse Reactions*). This adverse reaction is not due to a pharmacokinetic interaction.

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

Additional pharmacokinetic drug interaction studies

Clinical studies have been conducted to assess the potential pharmacokinetic drug interaction between topiramate and other agents. The changes in C_{max} or AUC as a result of the interactions are summarized below. The second column (concomitant drug concentration) describes what happens to the concentration of the concomitant drug 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.

Summary of Results from Additional Clinical Pharmacokinetic Drug Interaction Studies

	Concomitant Drug	
Concomitant Drug	**Concentration [a]**	**Topiramate Concentration [a]**
Amitriptyline	↔ 20% increase in C_{max} and AUC of nortriptyline metabolite	NS
Dihydroergotamine (Oral and Subcutaneous)	↔	↔
Haloperidol	↔ 31% increase in AUC of the reduced metabolite	NS
Propranolol	↔ 17% increase in C_{max} for 4-OH propranolol (TPM 50mg q12h)	9% and 16% increase in C_{max}, 9% and 17% increase in AUC (40mg and 80mg propranolol q12h, respectively)
Sumatriptan (Oral and Subcutaneous)	↔	NS
Pizotifen	↔	↔

Diltiazem	25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔ for DEM*	20% increase in AUC
Venlafaxine	↔	↔
Flunarizine	16% increase in AUC (TPM 50 mg q12h)[b]	↔

[a] = % values are the changes in treatment mean C_{max} or AUC with respect to monotherapy
↔ = No effect on C_{max} and AUC (≤ 15% change) of the parent compound
NS = Not studied
*DEA = Des acetyl diltiazem, DEM = N-demethyl diltiazem
[b] = Flunarizine AUC increased 14% in subjects taking flunarizine alone. Increase in exposure may be attributed to accumulation during achievement of steady state.

Pregnancy and Breast-feeding

Pregnancy

Studies in animals have shown reproductive toxicity (see *Non-Clinical Information – Reproductive and Developmental Toxicology*). In rats, topiramate crosses the placental barrier.

There are no adequate and well-controlled studies using TOPAMAX in pregnant women.

TOPAMAX can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk of congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen.

In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of AEDs in combination therapy.

Compared with a reference group not taking AEDs, registry data for TOPAMAX monotherapy showed a higher prevalence of low birth weight (<2500 grams). One pregnancy registry reported an increased frequency of infants who were small for gestational age (SGA; defined as birth weight below the 10th percentile corrected for their gestational age, stratified by sex) among those exposed to topiramate monotherapy *in utero*. The long-term consequences of the SGA findings could not be determined. A causal relationship for low birth weight and SGA has not been established.

TOPAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In treating and counseling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks and consider alternative therapeutic options. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Breast-feeding

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 excretion of topiramate into breast milk. Since many drugs are excreted in human milk,

a decision should be made whether to discontinue breast-feeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Effects on Ability to Drive and Use Machines

TOPAMAX acts on the central nervous system and may produce drowsiness, dizziness or other related symptoms. It may also cause visual disturbances and/or blurred vision. These adverse events could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the drug is established.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of topiramate based on the comprehensive assessment of the available adverse event information. A causal relationship with topiramate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

The safety of TOPAMAX was evaluated from a clinical trial database consisting of 4111 patients (3182 on TOPAMAX and 929 on placebo) who participated in 20 double-blind trials and 2847 patients who participated in 34 open-label trials, respectively, for the treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, newly or recently diagnosed epilepsy or migraine. The information presented in this section was derived from pooled data.

The majority of all adverse reactions were mild to moderate in severity.

Double-blind, placebo-controlled data, adjunctive epilepsy trials – adult patients

Adverse reactions reported in ≥1% of TOPAMAX -treated adult patients in double-blind, placebo-controlled adjunctive epilepsy trials are shown in Table 1. Adverse reactions that had an incidence >5% in the recommended dose range (200 to 400 mg/day) in adults in double-blind, placebo-controlled adjunctive epilepsy studies in descending order of frequency included somnolence, dizziness, fatigue, irritability, weight decreased, bradyphrenia, paresthesias, diplopia, coordination abnormal, nausea, nystgamus, lethargy, anorexia, dysarthria, vision blurred, decreased appetite, memory impairment and diarrhea.

Table 1: Adverse Reactions Reported by ≥1% of TOPAMAX-Treated Adult Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX 200-400 mg/day (N=354) %	TOPAMAX 600-1000 mg/day (N=437) %	PLACEBO (N=382) %
Metabolism and Nutrition Disorders			
Anorexia	5.4	6.2	1.8
Decreased appetite	5.1	8.7	3.7

Psychiatric Disorders			
Bradyphrenia	8.2	19.5	3.1
Expressive language disorder	4.5	9.4	1.6
Confusional state	3.1	5.0	0.8
Depression	3.1	11.7	3.4
Insomnia	3.1	6.4	4.5
Aggression	2.8	3.2	1.8
Agitation	1.7	2.3	1.3
Anger	1.7	2.1	0.5
Anxiety	1.7	6.6	2.9
Disorientation	1.7	3.2	1.0
Mood altered	1.7	4.6	1.0
Nervous System Disorders			
Somnolence	17.8	17.4	8.4
Dizziness	16.4	34.1	13.6
Paresthesia	8.2	17.2	3.7
Coordination abnormal	7.1	11.4	4.2
Nystagmus	6.2	11.7	6.8
Lethargy	5.6	8.0	2.1
Dysarthria	5.4	6.2	1.0
Memory impairment	5.1	10.8	1.8
Disturbance in attention	4.5	11.9	1.8
Tremor	4.0	9.4	5.0
Amnesia	3.4	5.3	1.0
Balance disorder	3.4	3.9	2.4
Hypoesthesia	3.1	5.9	1.0
Intention tremor	3.1	4.8	2.9
Dysgeusia	1.4	4.3	0.8
Mental impairment	1.4	5.0	1.3
Speech disorder	1.1	2.7	0.5
Eye Disorders			
Diplopia	7.3	12.1	5.0
Vision blurred	5.4	8.9	2.4
Visual disturbance	2.0	1.4	0.3
Gastrointestinal Disorders			
Nausea	6.8	15.1	8.4
Diarrhea	5.1	14.0	5.2
Abdominal pain upper	3.7	3.9	2.1
Constipation	3.7	3.2	1.8
Stomach discomfort	3.1	3.2	1.3
Dyspepsia	2.3	3.0	2.1
Dry mouth	1.7	3.7	0.3
Abdominal pain	1.1	2.7	0.8
Musculoskeletal and Connective Tissue Disorders			
Myalgia	2.0	2.5	1.3
Muscle spasms	1.7	2.1	0.8
Musculoskeletal chest pain	1.1	1.8	0.3
General Disorders and Administration Site Conditions			
Fatigue	13.0	30.7	11.8
Irritability	9.3	14.6	3.7
Asthenia	3.4	3.0	1.8
Gait disturbance	1.4	2.5	1.3
Investigations			
Weight decreased	9.0	11.9	4.2

The recommended dose for adjunctive epilepsy therapy in adults is 200-400 mg/day.

Double-blind, placebo-controlled data, adjunctive epilepsy trials – pediatric patients

Adverse reactions reported in >2% of TOPAMAX-treated pediatric patients (2 to 16 years of age) in double-blind, placebo-controlled adjunctive epilepsy trials are shown in Table 2. Adverse reactions that had an incidence >5% in the recommended dose range (5 to 9 mg/kg/day) in descending order of frequency included decreased appetite, fatigue, somnolence, lethargy, irritability, disturbance in attention, weight decreased, aggression, rash, abnormal behavior, anorexia, balance disorder, and constipation.

Table 2: Adverse Reactions Reported by ≥2% of TOPAMAX-Treated Pediatric Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX (N=104) %	PLACEBO (N=102) %
Metabolism and Nutrition Disorders		
Decreased appetite	19.2	12.7
Anorexia	5.8	1.0
Psychiatric Disorders		
Aggression	8.7	6.9
Abnormal behavior	5.8	3.9
Confusional state	2.9	2.0
Mood altered	2.9	2.0
Nervous System Disorders		
Somnolence	15.4	6.9
Lethargy	13.5	8.8
Disturbance in attention	10.6	2.0
Balance disorder	5.8	2.0
Dizziness	4.8	2.9
Memory impairment	3.8	1.0
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	4.8	1.0
Gastrointestinal Disorders		
Constipation	5.8	4.9
Skin and Subcutaneous Tissue Disorders		
Rash	6.7	5.9
General Disorders and Administration Site Conditions		
Fatigue	16.3	4.9
Irritability	11.5	8.8
Gait disturbance	4.8	2.0
Investigations		
Weight decreased	9.6	1.0

The recommended dose for adjunctive epilepsy therapy in children (2-16 years of age) is 5 to 9 mg/kg/day.

Double-blind, controlled data, monotherapy epilepsy trials – adult patients

Adverse reactions reported in ≥1% of TOPAMAX-treated adult patients in double-blind, controlled monotherapy epilepsy trials are shown in Table 3. Adverse reactions that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included paresthesia, weight decreased, fatigue, anorexia, depression, memory impairment, anxiety, diarrhea, asthenia, dysguesia, and hypoesthesia.

Table 3: Adverse Reactions Reported by ≥1% of TOPAMAX-Treated Adult Patients in Double-Blind,

Controlled Monotherapy Epilepsy Trials		
System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=257) %	TOPAMAX 400 mg/day (N=153) %
Blood and Lymphatic System Disorders		
Anemia	0.8	2.0
Metabolism and Nutrition Disorders		
Anorexia	3.5	12.4
Decreased appetite	2.3	2.6
Psychiatric Disorders		
Depression	4.3	8.5
Anxiety	3.9	6.5
Bradyphrenia	2.3	4.6
Expressive language disorder	3.5	4.6
Depressed mood	0.8	2.6
Mood altered	0.4	2.0
Mood swings	1.6	2.0
Nervous System Disorders		
Paresthesia	18.7	40.5
Memory impairment	1.2	7.2
Dysgeusia	2.3	5.9
Hypoesthesia	4.3	5.2
Balance disorder	1.6	3.3
Dysarthria	1.6	2.6
Cognitive disorder	0.4	2.0
Lethargy	1.2	2.0
Mental impairment	0.8	2.0
Psychomotor skills impaired	0	2.0
Sedation	0	1.3
Visual field defect	0.4	1.3
Eye Disorders		
Dry eye	0	1.3
Ear and Labyrinth Disorders		
Ear pain	0	1.3
Tinnitus	1.6	1.3
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	1.2	2.0
Rhinorrhea	0	1.3
Gastrointestinal Disorders		
Diarrhea	5.4	6.5
Paresthesia oral	1.2	3.3
Dry mouth	0.4	2.6
Gastritis	0.8	2.6
Abdominal pain	1.2	2.0
Gastroesophageal reflux disease	0.4	2.0
Gingival bleeding	0	1.3
Skin and Subcutaneous Tissue Disorders		
Rash	0.4	3.9
Alopecia	1.6	3.3
Pruritus	0.4	3.3
Hypoesthesia facial	0.4	2.0
Pruritus generalized	0	1.3
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	2.7	3.3

Arthralgia	1.9	2.0
Muscle twitching	0.4	1.3
Renal and Urinary Disorders		
Nephrolithiasis	0	2.6
Dysuria	0.8	2.0
Pollakiuria	0.8	2.0
Reproductive System and Breast Disorders		
Erectile dysfunction	0.8	1.3
General Disorders and Administration Site Conditions		
Fatigue	15.2	14.4
Asthenia	3.5	5.9
Irritability	3.1	3.3
Investigations		
Weight decreased	7.0	17.0

The recommended dose for monotherapy therapy in adults is 400 mg/day.

Double-blind, controlled data, monotherapy epilepsy trials – pediatric patients

Adverse reactions reported in ≥2% of TOPAMAX-treated pediatric patients (10 to 16 years of age) in double-blind, controlled monotherapy epilepsy trials are shown in Table 4. Adverse reactions that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included weight decreased, paresthesia, diarrhea, disturbance in attention, pyrexia, and alopecia.

Table 4: Adverse Reactions Reported by ≥2% of TOPAMAX-Treated Pediatric Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials

System/Organ Class Adverse Reaction	**TOPAMAX 50 mg/day (N=77) %**	**TOPAMAX 400 mg/day (N=63) %**
Metabolism and Nutrition Disorders		
Decreased appetite	1.3	4.8
Psychiatric Disorders		
Bradyphrenia	0	4.8
Mood altered	1.3	4.8
Depression	0	3.2
Nervous System Disorders		
Paresthesia	3.9	15.9
Disturbance in attention	3.9	7.9
Ear and Labyrinth Disorders		
Vertigo	0	3.2
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	0	3.2
Gastrointestinal Disorders		
Diarrhea	3.9	9.5
Vomiting	3.9	4.8
Skin and Subcutaneous Tissue Disorders		
Alopecia	0	6.3
General Disorders and Administration Site Conditions		
Pyrexia	0	6.3
Asthenia	0	4.8
Investigations		
Weight decreased	7.8	20.6
Social Circumstances		

Learning disability	0	3.2

The recommended dose for monotherapy therapy in children 10 years and older is 400 mg/day.

Double-blind, placebo-controlled data, migraine prophylaxis trials – adult patients

Adverse reactions reported in ≥1% of TOPAMAX-treated adult patients in double-blind, placebo-controlled migraine prophylaxis trials are shown in Table 5. Adverse reactions that had an incidence >5% at the recommended dose (100 mg/day) in descending order of frequency included paresthesia, fatigue, nausea, diarrhea, weight decreased, dysguesia, anorexia, decreased appetite, insomnia, hypoesthesia, disturbance in attention, anxiety, somnolence, and expressive language disorder.

Table 5: Adverse Reactions Reported by ≥1% of TOPAMAX-Treated Adult Patients in Double-Blind, Placebo-Controlled Migraine Prophylaxis Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=227) %	TOPAMAX 100 mg/day (N=374) %	TOPAMAX 200 mg/day (N=501) %	PLACEBO (N=436) %
Metabolism and Nutrition Disorders				
Anorexia	3.5	7.5	7.2	3.0
Decreased appetite	5.7	7.0	6.8	3.0
Psychiatric Disorders				
Insomnia	4.8	7.0	5.6	3.9
Anxiety	4.0	5.3	5.0	1.8
Expressive language disorder	6.6	5.1	5.2	1.4
Depression	3.5	4.8	7.4	4.1
Depressed mood	0.4	2.9	2.0	0.9
Confusional state	0.4	1.6	2.0	1.1
Mood swings	1.8	1.3	1.0	0.2
Affect lability	0.4	1.1	0.2	0.2
Bradyphrenia	1.8	1.1	3.4	1.4
Nervous System Disorders				
Paresthesia	35.7	50.0	48.5	5.0
Dysgeusia	15.4	8.0	12.6	0.9
Hypoesthesia	5.3	6.7	7.4	1.4
Disturbance in attention	2.6	6.4	9.2	2.3
Somnolence	6.2	5.1	6.8	3.0
Memory impairment	4.0	4.5	6.2	1.6
Amnesia	3.5	2.9	5.2	0.5
Tremor	1.3	1.9	2.4	1.4
Balance disorder	0.4	1.3	0.4	0
Mental impairment	0.4	1.1	1.8	0.9
Eye Disorders				
Vision blurred	4.0	2.4	4.4	2.5
Ear and Labyrinth Disorders				
Tinnitus	0.4	1.3	1.6	0.7
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	1.3	2.7	1.6	1.4
Epistaxis	0.4	1.1	0.6	0.5
Gastrointestinal Disorders				
Nausea	9.3	13.6	14.6	8.3
Diarrhea	9.3	11.2	10.0	4.4
Dry mouth	1.8	3.2	5.0	2.5
Paresthesia oral	1.3	2.9	1.6	0.5

Constipation	1.8	2.1	1.8	1.4
Abdominal distension	0	1.3	0.2	0.2
Stomach discomfort	2.2	1.3	1.0	0.2
Gastroesophageal reflux disease	0.4	1.1	1.2	0.5
Musculoskeletal and Connective Tissue Disorders				
Muscle twitching	1.8	1.3	1.8	0.7
General Disorders and Administration Site Conditions				
Fatigue	15.0	15.2	19.2	11.2
Asthenia	0.9	2.1	2.6	0.5
Irritability	3.1	1.9	2.4	0.9
Thirst	1.3	1.6	1.0	0.5
Investigations				
Weight decreased	5.3	9.1	10.8	1.4

The recommended dose for migraine prophylaxis is 100 mg/day.

Other clinical trial data – adult patients

Adverse reactions reported in double-blind controlled clinical trials in <1% of TOPAMAX-treated adult patients or at any rate in open-label clinical trials of TOPAMAX-treated adult patients are shown in Table 6.

Table 6. Adverse Reactions Reported in Double-Blind Controlled Clinical Trials in <1% of TOPAMAX-Treated Adult Patients or at Any Rate in Open-Label Clinical Trials of TOPAMAX-Treated Adult Patients

Blood and Lymphatic System Disorders
Leukopenia, lymphadenopathy, thrombocytopenia
Immune System Disorders
Hypersensitivity
Metabolism and Nutrition Disorders
Acidosis hyperchloremic, hypokalemia, increased appetite, metabolic acidosis, polydipsia
Psychiatric Disorders
Abnormal behavior, anorgasmia, apathy, crying, distractibility, disturbance in sexual arousal, dysphemia, early morning awakening, elevated mood, euphoric mood, flat affect, hallucination, hallucination-auditory, hallucination-visual, hypomania, initial insomnia, lack of spontaneous speech, libido decreased, listless, loss of libido, mania, middle insomnia, orgasmic sensation decreased, panic attack, panic disorder, panic reaction, paranoia, perseveration, reading disorder, restlessness, sleep disorder, suicidal ideation, suicide attempt, tearfulness, thinking abnormal
Nervous System Disorders
Ageusia, akinesia, anosmia, aphasia, apraxia, aura, burning sensation, cerebellar syndrome, circadian rhythm sleep disorder, clumsiness, complex partial seizure, convulsion, depressed level of consciousness, dizziness postural, drooling, dysesthesia, dysgraphia, dyskinesia, dysphasia, dystonia, essential tremor, formication, grand mal convulsion, hyperesthesia, hypersomnia, hypogeusia, hypokinesia, hyposmia, neuropathy peripheral, parosmia, poor quality sleep, presyncope, repetitive speech, sensory disturbance, sensory loss, stupor, syncope, unresponsive to stimuli
Eye Disorders
Accommodation disorder, altered visual depth perception, amblyopia, blepharospasm, blindness transient, blindness unilateral, glaucoma, lacrimation increased, mydriasis, night blindness, photopsia, presbyopia, scintillating scotoma, scotoma, visual acuity reduced

Ear and Labyrinth Disorders
Deafness, deafness neurosensory, deafness unilateral, ear discomfort, hearing impaired

Cardiac Disorders
Bradycardia, sinus bradycardia, palpitations

Vascular Disorders
Flushing, hot flush, orthostatic hypotension, Raynaud's phenomenon

Respiratory, Thoracic, and Mediastinal Disorders
Dysphonia, dyspnea exertional, nasal congestion, paranasal sinus hypersecretion

Gastrointestinal Disorders
Abdominal discomfort, abdominal pain lower, abdominal tenderness, breath odor, epigastric discomfort, flatulence, glossodynia, hypoesthesia oral, oral pain, pancreatitis, salivary hypersecretion

Skin and Subcutaneous Tissue Disorders
Anhidrosis, dermatitis allergic, erythema, rash macular, skin discoloration, skin odor abnormal, swelling face, urticaria, urticaria localized

Musculoskeletal and Connective Tissue Disorders
Flank pain, muscle fatigue, muscular weakness, musculoskeletal stiffness

Renal and Urinary Disorders
Calculus ureteric, calculus urinary, hematuria, incontinence, micturition urgency, renal colic, renal pain, urinary incontinence

Reproductive System and Breast Disorders
Sexual dysfunction

General Disorders
Calcinosis, face edema, feeling abnormal, feeling drunk, feeling jittery, malaise, peripheral coldness, sluggishness

Investigations
Blood bicarbonate decreased, crystal urine present, tandem gait test abnormal, white blood cell count decreased

Other clinical trial data – pediatric patients

Adverse reactions reported in double-blind controlled clinical trials in <2% of TOPAMAX-treated pediatric patients or at any rate in open-label clinical trials of TOPAMAX-treated pediatric patients are shown in Table 7.

Table 7. Adverse Reactions Reported in Double-Blind Controlled Clinical Trials in <2% of TOPAMAX-Treated Pediatric Patients or at Any Rate in Open-Label Clinical Trials of TOPAMAX-Treated Pediatric Patients

Blood and Lymphatic System Disorders
Eosinophilia, leukopenia, lymphadenopathy, thrombocytopenia

Immune System Disorders
Hypersensitivity

Metabolism and Nutrition Disorders
Acidosis hyperchloremic, hypokalemia, increased appetite

Psychiatric Disorders

Anger, apathy, crying, distractibility, expressive language disorder, initial insomnia, insomnia, middle insomnia, mood swings, perseveration, sleep disorder, suicidal ideation, suicide attempt

Nervous System Disorders
Circadian rhythm sleep disorder, convulsion, dysarthria, dysgeusia, grand mal convulsion, hypoesthesia, mental impairment, nystagmus, parosmia, poor quality sleep, psychomotor hyperactivity, psychomotor skills impaired, syncope, tremor

Eye Disorders
Diplopia, lacrimation increased, vision blurred

Ear and Labyrinth Disorders
Ear pain

Cardiac Disorders
Palpitations, sinus bradycardia

Vascular Disorders
Orthostatic hypotension

Respiratory, Thoracic, and Mediastinal Disorders
Nasal congestion, paranasal sinus hypersecretion, rhinorrhea

Gastrointestinal Disorders
Abdominal discomfort, abdominal pain, dry mouth, flatulence, gastritis, gastroesophageal reflux disease, gingival bleeding, glossodynia, pancreatitis, paresthesia oral, stomach discomfort

Musculoskeletal and Connective Tissue Disorders
Arthralgia, musculoskeletal stiffness, myalgia

Renal and Urinary Disorders
Incontinence, micturition urgency, pollakiuria

General Disorders
Feeling abnormal, hyperthermia, malaise, sluggishness

Postmarketing data

Adverse events first identified as adverse reactions during postmarketing experience with TOPAMAX are included in Table 8. In table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports

In Table 8, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 8: Adverse Reactions Identified During Postmarketing Experience with TOPAMAX by Frequency Category Estimated from Spontaneous Reporting Rates	
Infections and Infestations	
Very rare	Nasopharyngitis
Blood and Lymphatic System Disorders	
Very rare	Neutropenia
Immune System Disorders	
Very rare	Allergic edema
Metabolism and Nutrition Disorders	
Very rare	Hyperammonemia
Very rare	Hyperammonemic encephalopathy
Psychiatric Disorders	
Very rare	Feeling of despair
Eye Disorders	
Very rare	Abnormal sensation in eye
Very rare	Angle closure glaucoma
Very rare	Conjunctival edema
Very rare	Eye movement disorder
Very rare	Eyelid edema
Very rare	Maculopathy
Very rare	Myopia
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Cough
Skin and Subcutaneous Tissue Disorders	
Very rare	Erythema multiforme
Very rare	Periorbital edema
Very rare	Stevens-Johnson syndrome
Very rare	Toxic epidermal necrolysis
Musculoskeletal and Connective Tissue Disorders	
Very rare	Joint swelling
Very rare	Limb discomfort
Renal and Urinary Disorders	
Very rare	Renal tubular acidosis
General Disorders and Administration Site Reactions	
Very rare	Generalized edema
Very rare	Influenza like illness
Investigations	
Very rare	Weight increased

Overdose

Symptoms and signs

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, 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 polydrug overdoses involving topiramate.

Topiramate overdose can result in severe metabolic acidosis (see *Warnings and Precautions – Metabolic acidosis*).

The highest topiramate overdose reported was calculated to be between 96 and 110 g and resulted in coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.

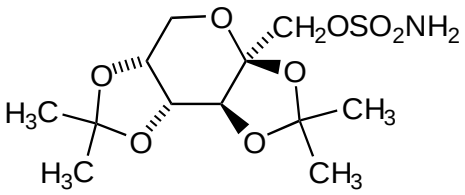
Treatment

In acute topiramate 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 has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

PHARMACOLOGICAL PROPERTIES

Topiramate is designated chemically as 2,3:4,5-bis-*O*-(1-methylethylidene)-ß-D-fructopyranose sulfamate.

The empirical formula is $C_{12}H_{21}NO_8S$. The molecular weight is 339.36. The structural formula is:



Topiramate is a white crystalline powder having 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.

Pharmacodynamic Properties

Pharmacotherapeutic group: other antiepileptics, ATC code: N03AX11.

Topiramate is classified as a sulfamate-substituted monosaccharide. The precise mechanism by which topiramate exerts its antiseizure and migraine prophylaxis effects are unknown. Electrophysiological and biochemical studies on cultured neurons have identified three properties that may contribute to the antiepileptic efficacy of topiramate.

Action potentials elicited repetitively by a sustained depolarization of the neurons were blocked by topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel blocking action. Topiramate increased the frequency at which γ-aminobutyrate (GABA) activated $GABA_A$ receptors, and enhanced the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter.

This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate $GABA_A$ receptors.

Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of $GABA_A$ receptor. Topiramate antagonized the ability of kainate to activate the kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of excitatory amino acid (glutamate) receptor, but had no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. These effects of topiramate were concentration-dependent over a range of 1 mcM to 200 mcM, with minimum activity observed at 1 mcM to 10 mcM.

In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This pharmacologic effect is much weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major component of topiramate's antiepileptic activity.

In animal studies, topiramate exhibits anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests and is 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. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole.

Studies in mice receiving concomitant administration of topiramate and carbamazepine or phenobarbital showed synergistic anticonvulsant activity, while combination with phenytoin showed additive anticonvulsant activity. In well-controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and its clinical efficacy. No evidence of tolerance has been demonstrated in man.

Epilepsy clinical trials

The results of controlled clinical trials established the efficacy of TOPAMAX Tablets and TOPAMAX Sprinkle Capsules as monotherapy for adults and children (ages 6 and older) with epilepsy, adjunctive therapy in adults and pediatric patients ages 2 to 16 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

Monotherapy

The effectiveness of topiramate as monotherapy in adults and children 6 years of age and older with newly diagnosed epilepsy was established in 4 randomized, double-blind, parallel-group trials. Study EPMN-106 was conducted in 487 patients (6 to 83 years of age) who had a new diagnosis of epilepsy (partial onset or generalized) or a diagnosis of recurrent epilepsy while not taking AEDs. Patients were randomized to receive topiramate 50 mg/day or topiramate 400 mg/day. Patients remained in the double-blind phase until they experienced a first partial onset or generalized tonic-clonic seizure, until termination of the double-blind phase 6 months after randomization of the last subject, or until withdrawal for protocol-specified reasons. The primary efficacy assessment was based on the comparison between topiramate dose groups with respect

to time to first partial onset or generalized tonic-clonic seizure during the double-blind phase. Comparison of the Kaplan-Meier survival curves of time to first seizure favored topiramate 400 mg/day over topiramate 50 mg/day (p=0.0002, log rank test). The separation between the groups in favor of the higher dose group occurred early in the titration phase and was statistically significant as early as 2 weeks post randomization (p = 0.046), when, by following the weekly titration schedule, the subjects in the higher dose group had achieved a maximum topiramate dose of 100 mg/day. The higher dose group was also superior to the lower dose group with respect to the proportion of subjects who remained seizure-free, based on the Kaplan-Meier estimates, for a minimum of 6 months of therapy (82.9% vs. 71.4%; p = 0.005), and for a minimum of 1 year of therapy (75.7% vs. 58.8%; p = 0.001). The ratio of hazard rates for time to first seizure was 0.516 (95% confidence interval, 0.364 to 0.733). The treatment effects with respect to time to first seizure were consistent across various subject subgroups defined by age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use.

In study YI, a single center study, patients ages 15-63 with refractory partial onset seizures (n=48) were converted from their existing treatment to TOPAMAX 100 mg/day or 1000 mg/day as monotherapy. The high dose group was statistically superior to the low dose group for efficacy variables. 54% of high dose patients achieved monotherapy compared with 17% in the low dose group with the difference between the doses being statistically significant (p=0.005). The mean time to exit was significantly greater in the high dose group (p=0.002). The investigator and subject global evaluations of clinical response statistically favored the high dose group (≤0.002).

In study EPMN-104, adult and pediatric patients (ages 6-85) with recently diagnosed epilepsy (n=252) were randomized into the low dose (25 or 50 mg/day) or the high dose group (200 or 500 mg/day) based on their body weight. Overall, 54% of high dose patients and 39% of low dose patients were reported to be seizure free during the double-blind phase (p=0.022). The high dose group was also superior to the low dose group with respect to seizure frequency distribution (p=0.008) and the difference in time to first seizure across three plasma topiramate concentration strata (p=0.015).

In study EPMN-105, patients aged 6-84 with newly diagnosed epilepsy (n=613) were randomized to receive either 100 or 200 mg/day of TOPAMAX or standard antiepileptic treatment (carbamazepine or valproate). TOPAMAX was at least as efficacious as carbamazepine or valproate in reducing seizures in these patients; the 95% confidence intervals for the difference between the two treatment groups were narrow and included zero, indicating that there were no statistically significant between-group difference. The two treatment groups were also comparable with respect to all clinical utility and efficacy endpoints including time to exit, proportion of seizure-free subjects and time to first seizure.

Patients (n=207; 32 were aged ≤ 16 years) who completed the double-blind phase of study YI and EPMN-104 were enrolled in long term extension studies with the majority of patients receiving TOPAMAX for 2 to 5 years. In these studies, sustained efficacy was demonstrated with long-term administration of TOPAMAX as monotherapy. There was no significant change

in dosage during the extension period and no indication that effectiveness of TOPAMAX monotherapy diminished with continued exposure.

Adjunctive therapy

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 AEDs in addition to TOPAMAX Tablets or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during baseline phase lasting between 4 and 12 weeks. Patients who experienced a prespecified minimum number of partial onset seizures, with or without secondary generalization, during the baseline phase (12 seizures for 12-week baseline, 8 for 8-week baseline, or 3 for 4-week baseline) were randomly assigned to placebo or a specified dose of TOPAMAX Tablets in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. In five of the six studies, patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. In the sixth study (119), the 25 or 50 mg/day initial doses of topiramate were followed by respective weekly increments of 25 or 50 mg/day until the target dose of 200 mg/day was reached. After titration, patients entered a 4, 8, or 12-week stabilization period. The numbers of patients randomized to each dose, and the actual mean and median doses in the stabilization period are shown in Tables 1 and 2.

Pediatric patients ages 2 to 16 years with partial onset seizures

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

Patients in this study were permitted a maximum of two 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 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 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.

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

Table 9: Efficacy Results in Double-Blind, Placebo-Controlled, Add-On Epilepsy Trials

		Target Topiramate Dosage (mg/day)					
Protocol Efficacy Results	Placebo	200	400	600	800	1000	≈6 mg/kg/day*
Partial Onset Seizures							
Studies in Adults							
YD N	45	45	45	46	--	--	--
Median % Reduction	11.6	27.2[a]	47.5[b]	44.7[c]	--	--	--
% Responders	18	24	44[d]	46[d]	--	--	--
YE N	47	--	--	48	48	47	--
Median % Reduction	1.7	--	--	40.8[c]	41.0[c]	36.0[c]	--
% Responders	9	--	--	40[c]	41[c]	36[d]	--
Y1 N	24	--	23	--	--	--	--
Median % Reduction	1.1	--	40.7[e]	--	--	--	--
% Responders	8	--	35[d]	--	--	--	--
Y2 N	30	--	--	30	--	--	--
Median % Reduction	-12.2	--	--	46.4[f]	--	--	--
% Responders	10	--	--	47[c]	--	--	--
Y3 N	28	--	--	--	28	--	--
Median % Reduction	-20.6	--	--	--	24.3[c]	--	--
% Responders	0	--	--	--	43[c]	--	--
119 N	91	168	--	--	--	--	--
Median % Reduction	20.0	44.2[c]	--	--	--	--	--
% Responders	24	45[c]	--	--	--	--	--
Studies in Pediatric Patients							
YP N	45	--	--	--	--	--	41
Median % Reduction	10.5	--	--	--	--	--	33.1[d]
% Responders	20	--	--	--	--	--	39
Primary Generalized Tonic-Clonic[h]							
YTC N	40	--	--	--	--	--	39
Median % Reduction	9.0	--	--	--	--	--	56.7[d]
% Responders	20	--	--	--	--	--	56[c]
Lennox-Gastaut Syndrome[i]							
YL N	49	--	--	--	--	--	46
Median % Reduction	-5.1	--	--	--	--	--	14.8[d]
% Responders	14	--	--	--	--	--	28[g]
Improvement in Seizure Severity[j]	28	--	--	--	--	--	52[d]

Comparisons with placebo: [a] p=0.080; [b] p≤0.010; [c] p≤0.001; [d] p≤0.050; [e] p=0.065; [f] p≤0.005;[g] p=0.071;

[h] Median % reduction and % responders are reported for PGTC Seizures;

[i] Median % reduction and % responders for drop attacks, i.e., tonic or atonic seizures;

[j] Percent of subjects who were minimally, much, or very much improved from baseline

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

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

Migraine clinical trials

The clinical development program to evaluate the efficacy of TOPAMAX in prophylaxis of migraine included two multicenter, randomized, double-blind placebo-controlled, parallel group pivotal trials conducted in North America (MIGR-001 and MIGR-002). The primary efficacy endpoint was the reduction in migraine headache frequency, as measured by the change in 4-week migraine rate from the baseline phase to the double-blind treatment phase in each TOPAMAX treatment group compared to placebo in the intent to treat (ITT) population.

The pooled results of the two pivotal trials evaluating TOPAMAX doses of 50 (N=233), 100 (N=244) and 200 mg/day (N=228) found a median percent reduction in average monthly migraine period rate of 35%, 51% and 49% respectively, compared to 21% for the placebo group (N=229). The 100 and 200 mg/day of TOPAMAX were statistically better then placebo. Notably, 27% of patients administered TOPAMAX 100 mg/day achieved at least a 75% reduction in migraine frequency, whilst 52% achieved at least a 50% reduction.

An additional supportive study, MIGR-003, demonstrated that TOPAMAX 100 mg/day was comparable in terms of efficacy to propranolol 160 mg/day. There was no statistically significant difference between the two groups in the primary efficacy endpoint.

Pharmacokinetic Properties

The tablet and sprinkle formulations are bioequivalent.

The pharmacokinetic profile of topiramate compared to other AEDs shows a long plasma half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding, and lack of clinically relevant active metabolites.

Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.

Absorption

Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of 1.5 mcg/mL was achieved within 2 to 3 hours (T_{max}). Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of ^{14}C-topiramate was at least 81%. There was no clinically significant effect of food on the bioavailability of topiramate.

Distribution

Generally, 13 to 17% of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 mcg/mL has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 L/kg for a single dose range of 100 to 1200 mg. An effect of gender on the volume of distribution was detected, with values for females circa 50% of

those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

Metabolism

Topiramate is not extensively metabolized (~20%) in healthy volunteers. It is metabolized up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolizing enzymes. Six metabolites, formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterized and identified from plasma, urine and feces of humans. Each metabolite represents less than 3% of the total radioactivity excreted following administration of ^{14}C-topiramate. Two metabolites, which retained most of the structure of topiramate, were tested and found to have little or no anticonvulsant activity.

Elimination

In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney (at least 81% of the dose). Approximately 66% of a dose of ^{14}C-topiramate was excreted unchanged in the urine within four days. Following twice a day dosing with 50 mg and 100 mg of topiramate the mean renal clearance was approximately 18 mL/min and 17 mL/min, respectively. There is evidence of renal tubular reabsorption of topiramate. This is supported by studies in rats where topiramate was co-administered with probenecid, and a significant increase in renal clearance of topiramate was observed. Overall, plasma clearance is approximately 20 to 30 mL/min in humans following oral administration.

Topiramate exhibits low intersubject variability in plasma concentrations and, therefore, has predictable pharmacokinetics. The pharmacokinetics of topiramate are linear with plasma clearance remaining constant and area under the plasma concentration curve increasing in a dose-proportional manner over a 100 to 400 mg single oral dose range in healthy subjects. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations. The mean C_{max} following multiple, twice a day oral doses of 100 mg to healthy subjects was 6.76 mcg/mL. Following administration of multiple doses of 50 mg and 100 mg of topiramate twice a day, the mean plasma elimination half-life was approximately 21 hours.

Use with other AEDs

Concomitant multiple-dose administration of topiramate, 100 to 400 mg twice a day, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

Special populations

Pediatrics (up to 12 years of age)

The pharmacokinetics of topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing AEDs decrease the steady-state plasma concentrations.

Elderly

Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

Renal impairment

The plasma and renal clearance of topiramate decreased in patients with moderate and severe impaired renal function (CL_{CR} <70 mL/min). As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. In addition, patients with renal impairment will require a longer time to reach steady-state at each dose. In patients with moderate and severe renal impairment, half of the usual starting and maintenance dose is recommended (see *Dosage and Administration – Special populations, Renal impairment*).

Topiramate is effectively removed from plasma by hemodialysis. A prolonged period of hemodialysis may cause topiramate concentration to fall below levels that are required to maintain an antiseizure 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.

Hepatic impairment

Plasma clearance of topiramate decreased a mean of 26% in patients with moderate to severe hepatic impairment. Therefore, topiramate should be administered with caution in patients with hepatic impairment.

NON-CLINICAL INFORMATION

Acute and long-term exposure of mice, rats, dogs and rabbits to topiramate was well tolerated. Hyperplasia of the gastric epithelial cells was observed only in rodents and in rats was reversible after 9 weeks without treatment.

Carcinogenicity and Mutagenicity

Tumors of smooth muscle origin in the urinary bladder were seen only in mice (oral dosages up to 300 mg/kg for 21 months) and appear to be unique to the species. Since no human counterpart exists, they were not considered clinically relevant. No such findings occurred in the rat carcinogenicity study (oral dosages up to 120 mg/kg/day for 24 months). Other toxicologic and pathologic effects of topiramate observed in these studies may be related to the weak induction of drug metabolizing enzymes or weak carbonic anhydrase inhibition.

In a battery of *in vitro* and *in vivo* mutagenicity assays, topiramate did not show genotoxic potential.

Reproductive and Developmental Toxicology

In preclinical studies, topiramate has been shown to have teratogenic effects in the species studied (mice, rats and rabbits). In mice, fetal weights and skeletal ossification were reduced at 500 mg/kg/day in conjunction with maternal toxicity. Overall numbers of fetal malformations in mice were increased for all drug-treated groups (20, 100 and 500 mg/kg/day), but no significant differences or dosage-response relationships were observed for overall or specific malformations, suggesting that other factors such as maternal toxicity may be involved.

In rats, dosage-related maternal and embryo/fetal toxicity (reduced fetal weights and/or skeletal ossification) were observed down to 20 mg/kg/day with teratogenic effects (limb and digit defects) at 400 mg/kg/day and above. In rabbits, dosage-related maternal toxicity was noted down to 10 mg/kg/day with embryo/fetal toxicity (increased lethality) down to 35 mg/kg/day, and teratogenic effects (rib and vertebral malformations) at 120 mg/kg/day.

The teratogenic effects seen in rats and rabbits were similar to those seen with carbonic anhydrase inhibitors, which have not been associated with malformations in humans. Effects on growth were also indicated by lower weights at birth and during lactation for pups from female rats treated with 20 or 100 mg/kg/day during gestation and lactation. In rats, topiramate crosses the placental barrier.

In juvenile rats, daily oral administration of topiramate at doses up to 300 mg/kg/day during the period of development corresponding to infancy, childhood, and adolescence resulted in toxicities similar to those in adult animals (decreased food consumption with decreased body weight gain, centrolobullar hepatocellular hypertrophy and slight urothelial hyperplasia in the urinary bladder). There were no relevant effects on long bone (tibia) growth or bone (femur) mineral density, preweaning and reproductive development, neurological development (including assessments on memory and learning), mating and fertility or hysterotomy parameters.

Fertility

Despite maternal and paternal toxicity as low as 8 mg/kg/day, no effects on fertility were observed, in male or female rats with up to 100 mg/kg/day.

PHARMACEUTICAL INFORMATION

List of Excipients

Film-coated tablets

Tablet core

Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Pregelatinized starch

Sodium starch glycolate

Film-coating

Carnauba wax
OPADRY® white, yellow, pink, which contain the following:
Hypromellose
Polyethylene glycol
Polysorbate
Synthetic iron oxides *(yellow and pink coating only)*
Titanium dioxide

Sprinkle capsules

Sprinkle beads

Cellulose acetate
Povidone
Sugar spheres

Gelatin capsule

Gelatin
Sodium lauryl sulfate
Sorbitan monolaurate
Titanium dioxide (for the white, opaque body)

Incompatibilities

None known.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Film-coated tablets

Store at or below 30°C. Store in the original package.

Sprinkle capsules

Do not store above 25°C. Keep the container tightly closed in order to protect from moisture.

Do not store the drug/food mixture.

Keep out of the sight and reach of children.

Nature and Contents of Container

Film-coated tablets

Bottles containing 60 tablets with desiccant.

Blister packs of 60 tablets. Individual (alu/alu) blister strips are packed inside a folding box.

Sprinkle capsules

Bottles containing 20, 28, 50, 60 or 100 sprinkle capsules.

Instructions for Use and Handling

Not applicable.

Manufactured by

Film-coated tablets

Cilag AG, Schaffhausen, Switzerland

Sprinkle capsules

Janssen-Ortho LLC, Gurabo, Puerto Rico, USA

MARKETING AUTHORIZATION NUMBER AND DATE OF AUTHORIZATION

Product	Market Authorization Number	Date of Authorization
TOPAMAX® (25 MG)	1C 210/41 (N)	4 January 2000
TOPAMAX® (50 MG)	1C 211/41 (N)	4 January 2000
TOPAMAX® (100 MG)	1C 212/41 (N)	4 January 2000
TOPAMAX® SPRINKLE CAPSULES (25 MG)	1C 15003/60 (N)	3 January 2018
TOPAMAX® SPRINKLE CAPSULES (50 MG)	1C 15002/60 (N)	3 January 2018

VERSION NUMBER

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Warnings

1) This drug may cause somnolence. Should not drive or operate machinery and should not drink alcohol or alcohol-containing beverage while using this drug.

2) This drug may cause blood cell abnormality.

3) Must not use this drug in pregnant women since it may cause defective infant.

4) Should use this drug with caution in patients with liver, kidney disease.

5) This drug may cause acute myopia and secondary angle closure glaucoma.

6) If using this drug and the eye abnormalities occur, i.e. blurred vision or eye pain, stop using the drug immediately and consult the doctor.

7) Should drink sufficient water every day to prevent kidney stone.