TOPIRAMATE- topiramate tablet
Medsource Pharmaceuticals

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TOPIRAMATE TABLETS safely and effectively. See full prescribing information for TOPIRAMATE TABLETS.

TOPIRAMATE tablets, for oral Use.

Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

• Indications and Usage (1)	05/2017
• Dosage and Administration (2)	05/2017
• Dosage and Administration, Geriatric Patients (Ages 65 Years and Over)	Removed 05/2017
• Patients with Hepatic Disease	Removed 05/2017
• Warnings and Precautions (5.4, 5.6, 5.9, 5.10)	05/2017
• Warnings and Precautions Sudden Unexplained Death in Epilepsy (SUDEP)	Removed 05/2017
• Paresthesia	Removed 05/2017
• Adjustment of Dose in Renal Failure	Removed 05/2017
• Decreased Hepatic Function	Removed 05/2017
• Monitoring: Laboratory Tests	Removed 05/2017

INDICATIONS AND USAGE

Topiramate tablets USP is indicated for:
- Monotherapy epilepsy: Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures (1.1)
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS) (1.2)
- Prophylaxis of migraine in patients 12 years of age and older (1.3)

DOSAGE AND ADMINISTRATION

Topiramate tablets initial dose, titration, and recommended maintenance dose varies by indication and age group. See Full Prescribing Information for recommended dosage, and dosing considerations in patients with renal impairment, geriatric patients, and patients undergoing hemodialysis (2.1, 2.2, 2.3, 2.4, 2.5, 2.6)

DOSAGE FORMS AND STRENGTHS

Tablets: 25 mg, 50 mg, 100 mg, and 200 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS
- Acute myopia and secondary angle closure glaucoma: can lead to permanent visual loss; discontinue topiramate tablets as soon as possible (5.1)
- Visual field defects: Consider discontinuation of topiramate (5.2)
- Oligohidrosis and hyperthermia: Monitor decreased sweating and increased body temperature, especially in pediatric patients (5.3)
- Metabolic acidosis: Baseline and periodic measurement of serum bicarbonate is recommended. Consider dose reduction or discontinuation of topiramate if clinically appropriate (5.4)
- Suicidal behavior and ideation: Antiepileptic drugs increase the risk of suicidal behavior or ideation (5.5)
- Cognitive/neuropsychiatric: Use caution when operating machinery including automobiles. Depression and mood problems may occur in epilepsy populations (5.6)
- Fetal Toxicity: Use during pregnancy can cause cleft lip and/or palate (5.7)
- Withdrawal of AEDs: Withdrawal of topiramate should be done gradually (5.8)
- Hyperammonemia and encephalopathy: Measure ammonia if encephalopathic symptoms occur (5.9)
- Kidney stones: avoid use with other carbonic anhydrase inhibitors, drugs causing metabolic acidosis, or in patients on a ketogenic diet (5.10)
- Hypothermia has been reported with and without hyperammonemia during topiramate treatment with concomitant valproic acid use (5.11)

ADVERSE REACTIONS

Epilepsy: Most common (≥10% more frequent than placebo or low-dose topiramate tablets) adverse reactions in adult and pediatric patients were: paresthesia, anorexia, weight loss, speech disorders/related speech problems, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, abnormal vision and fever (6.1)
Migraine: Most common (≥5% more frequent than placebo) adverse reactions in adult and pediatric patients were: paresthesia, anorexia, weight loss, difficulty with memory, taste perversion, diarrhea, hypoesthesia, nausea, abdominal pain and upper respiratory tract infection (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd, at 1-866-604-3268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS
- Oral contraceptives: decreased contraceptive efficacy and increased breakthrough bleeding, especially at doses greater than 200 mg/day(7.3)
- Monitor lithium levels if lithium is used with high-dose topiramate tablets (7.4)

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy Epilepsy

Topiramate tablets USP are indicated as initial monotherapy in patients 2 years of age and older with partial onset or primary generalized tonic-clonic seizures.

1.2 Adjunctive Therapy Epilepsy

Topiramate tablets are indicated as adjunctive therapy for adults and pediatric patients 2 to 16 years of age with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

1.3 Migraine

Topiramate tablets are indicated for patients 12 years of age and older for the prophylaxis of migraine headache.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing in Monotherapy Epilepsy

Adults and Pediatric Patients 10 Years and Older

The recommended dose for topiramate monotherapy in adults and pediatric patients 10 years of age and older is 400 mg/day in two divided doses. The dose should be achieved by titration according to the following schedule (Table 1):

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

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

Children Ages 2 to 9 Years

Dosing in patients 2 to 9 years of age is based on weight. During the titration period, the initial dose of topiramate should be 25 mg/day administered nightly for the first week. Based upon tolerability, the dosage can be increased to 50 mg/day (25 mg twice daily) in the second week. Dosage can be increased by 25–50 mg/day each subsequent week as tolerated. Titration to the minimum maintenance dose should be attempted over 5–7 weeks of the total titration period. Based upon tolerability and seizure control, additional titration to a higher dose (up to the maximum maintenance dose) can be attempted at 25–50 mg/day weekly increments. The total daily dose should not exceed the maximum maintenance dose for each range of body weight (Table 2).

Table 2: Monotherapy Target Total Daily Maintenance Dosing for Patients 2 to 9 Years of Age

Weight(kg)	Total Daily Dose(mg/day)* Minimum Maintenance Dose	Total Daily Dose(mg/day)* Maximum Maintenance Dose
Upto 11	150	250
12–22	200	300
23–31	200	350
32–38	250	350
Greater than38	250	400

*Administered in two equally divided doses

2.2 Dosing in Adjunctive Therapy Epilepsy

Adults (17 Years of Age and Over)

The recommended total daily dose of topiramate tablets as adjunctive therapy in adults with partial onset seizures or Lennox-Gastaut Syndrome is 200 to 400 mg/day in two divided doses, and 400 mg/day in two divided doses as adjunctive treatment in adults with primary generalized tonic-clonic seizures. Topiramate tablets should be initiated at 25 to 50 mg/day followed by titration to an effective dose in increments of 25 to 50 mg/day every week. Titrating in increments of 25 mg/day every week may delay the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in dose-response studies in adults with partial onset seizures.

Pediatric Patients Ages 2 – 16 Years

The recommended total daily dose of topiramate tablets as adjunctive therapy for pediatric patients 2 to 16 years of age with partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg/day (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome.

2.3 Dosing in Migraine Prophylaxis

The recommended total daily dose of topiramate tablets as treatment for patients 12 years of age and older for prophylaxis of migraine headache is 100 mg/day administered in two divided doses (Table 3). The recommended titration rate for topiramate tablets for migraine prophylaxis is as follows:

Table 3: Migraine Prophylaxis Titration Schedule for Patients 12 Years of Age and Older

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

2.4 Administration Information

Topiramate tablets can be taken without regard to meals.

Topiramate tablets

Because of the bitter taste, tablets should not be broken

2.5 Dosing in Patients with Renal Impairment

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73 m^2), one-half of the usual adult dose is recommended. *[see Use in Specific Populations (8.5, 8.6), Clinical Pharmacology (12.3)]* .

2.6 Dosing in Patients Undergoing Hemodialysis

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 *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]* .

3 DOSAGE FORMS AND STRENGTHS

Topiramate tablets USP are available in the following strengths and colors:

25 mg, White colored, circular, biconvex film-coated tablets, debossed with "122" on one side and "C" on the other side

50 mg, Light orange colored, circular, biconvex, film-coated tablets, debossed with "123" on one side and "C" on the other side.

100 mg, Orange colored, circular, biconvex, film-coated tablets, debossed with "124" on one side and "Cipla" on the other side.

200 mg, Pink colored, capsule shaped, biconvex, film-coated tablets, debossed with "125" on one side and "Cipla" on other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Acute Myopia and Secondary Angle Closure Glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate tablets. 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 topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of topiramate tablets as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of topiramate tablets, may be helpful.

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

5.2 Visual Field Defects

Visual field defects (independent of elevated intraocular pressure) have been reported in clinical trials and in post marketing experience in patients receiving topiramate. 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.

5.3 Oligohidrosis and Hyperthermia

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

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

5.4 Metabolic Acidosis

Topiramate can cause hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis). This metabolic acidosis is caused by renal bicarbonate loss due to carbonic anhydrase inhibition by topiramate. Topiramate-induced metabolic acidosis can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet, or specific drugs) may be additive to the bicarbonate lowering effects of topiramate.

Metabolic acidosis was commonly observed in adult and pediatric patients treated with topiramate in clinical trials. The incidence of decreased serum bicarbonate in pediatric trials, for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures was as high as 67% for topiramate (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value < 17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was up to 11%, compared to < 2% for placebo.

Manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates, which may decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in long-term, placebo-controlled trials. Long-term, open-label treatment of pediatric patients 1 to 24 months old with intractable partial epilepsy, for up to 1 year, showed reductions from baseline in length, weight, and head circumference compared to age and sex-matched normative data, although these patients with epilepsy are likely to have different growth rates than normal 1 to 24 month old pediatrics. Reductions in length and weight were correlated to the degree of acidosis *[see Use in Specific Populations (8.4)]* . Topiramate treatment that causes metabolic acidosis during pregnancy can possibly produce adverse effects on the fetus and might also cause metabolic acidosis in the neonate from possible transfer of topiramate to the fetus *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1)]* .

Measurement of Serum Bicarbonate in Epilepsy and Migraine Patients

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

5.5 Suicidal Behavior and Ideation

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

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

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

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

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

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

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

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

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

related to the illness being treated.

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

5.6 Cognitive/Neuropsychiatric Adverse Reactions

Topiramate can cause cognitive/neuropsychiatric adverse reactions. The most frequent of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g., depression or mood problems); and 3) Somnolence or fatigue

Adult Patients

Cognitive-Related Dysfunction

Rapid titration rate and higher initial dose were associated with higher incidences of cognitive-related dysfunction.

In adult epilepsy add-on controlled trials, which used rapid titration (100-200 mg/day weekly increments), and target topiramate doses of 200 mg-1000 mg/day, 56% of patients in the 800 mg/day and 1000 mg/day dose groups experienced cognitive-related dysfunction compared to approximately 42% of patients in the 200-400 mg/day groups and 14% for placebo. In this rapid titration regimen, these dose-related adverse reactions began in the titration or in the maintenance phase, and in some patients these events began during titration and persisted into the maintenance phase.

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

In the 6-month migraine prophylaxis controlled trials, which used a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reactions was 19% for topiramate 50 mg/day, 22% for 100 mg/day (the recommended dose), 28% for 200 mg/day, and 10% for placebo. Cognitive adverse reactions most commonly developed during titration and sometimes persisted after completion of titration.

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (e.g., depression, mood) were dose-related for both the adjunctive epilepsy and migraine populations *[see Warnings and Precautions (5.5)]*.

Somnolence/Fatigue

Somnolence and fatigue were the adverse reactions most frequently reported during clinical trials of topiramate for adjunctive epilepsy. For the adjunctive epilepsy population, the incidence of fatigue, appeared dose related. For the monotherapy epilepsy population, the incidence of somnolence was dose-related. For the migraine population, the incidences of both fatigue and somnolence were dose-related and more common in the titration phase.

Pediatric Patients

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

In pediatric migraine patients, the incidence of cognitive/neuropsychiatric adverse reactions was increased in topiramate-treated patients compared to placebo.

The risk for cognitive/neuropsychiatric adverse reactions was dose-dependent, and was greatest at the highest dose (200 mg). This risk for cognitive/neuropsychiatric adverse reactions was also greater in younger patients (6 to 11 years of age) than in older patients (12 to 17 years of age). The most common cognitive/neuropsychiatric adverse reaction in these trials was difficulty with concentration/attention. Cognitive adverse reactions most commonly developed during titration and sometimes persisted for various durations after completion of titration.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to adolescents (12 to 17 years) to assess the effects of topiramate on cognitive function at baseline and at the end of the Study 12 *[see Clinical Studies (14.3)]* . Mean change from baseline in certain CANTAB tests suggests that topiramate treatment may result in psychomotor slowing and decreased verbal fluency.

5.7 Fetal Toxicity

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

Consider the benefits and the risks of topiramate tablets when administering this drug in women of childbearing potential, particularly when topiramate is considered for a condition not usually associated with permanent injury or death *[see Use in Specific Populations (8.9) and Patient Counseling Information(17)]* . Topiramate tablets should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1) and (8.9)]*.

5.8 Withdrawal of Antiepileptic Drugs

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

5.9 Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid

Topiramate treatment can cause hyperammonemia with or without encephalopathy *[see Adverse Reactions (6.2)]*. The risk for hyperammonemia with topiramate appears dose-related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid. Postmarketing cases of hyperammonemia with or without encephalopathy have been reported with topiramate and valproic acid in patients who previously tolerated either drug alone *[see Drug Interactions (7.1)]* .

Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy and/or vomiting. In most cases, hyperammonemic encephalopathy abated with discontinuation of treatment.

The incidence of hyperammonemia in pediatric patients 12 to 17 years of age in migraine prophylaxis trials was 26% in patients taking topiramate monotherapy at 100 mg/day, and 14% in patients taking topiramate at 50 mg/day, compared to 9% in patients taking placebo. There was also an increased incidence of markedly increased hyperammonemia at the 100 mg dose.

Dose-related hyperammonemia was also seen in pediatric patients 1 to 24 months of age treated with topiramate and concomitant valproic acid for partial onset epilepsy and this was not due to a pharmacokinetic interaction.

In some patients, hyperammonemia can be asymptomatic.

Monitoring for Hyperammonemia

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, topiramate treatment or an interaction of concomitant topiramate and valproic acid treatment may exacerbate existing defects or unmask deficiencies in susceptible persons.

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

5.10 Kidney Stones

Topiramate increases the risk of kidney stones. During adjunctive epilepsy trials, the risk for kidney stones in topiramate-treated adults was 1.5%, an incidence about 2 to 4 times greater than expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate-treated patients was higher in men. Kidney stones have also been reported in pediatric patients taking topiramate for epilepsy or migraine. During long-term (up to 1 year) topiramate treatment in an open-label extension study of 284 pediatric patients 1-24 months old with epilepsy, 7% developed kidney or bladder stones. Topiramate is not approved for treatment of epilepsy in pediatric patients less than 2 years old *[see Use in Specific Populations (8.4)]*.

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

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

5.11 Hypothermia with Concomitant Valproic Acid (VPA)

Hypothermia, defined as an unintentional drop in body core temperature to <35°C (95°F), has been reported in association with topiramate use with concomitant valproic acid (VPA) both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse reaction in patients using concomitant topiramate and valproate can occur after starting topiramate treatment or after increasing the daily dose of topiramate *[see Drug Interactions (7.1)]*. Consideration should be given to stopping topiramate or valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

6 ADVERSE REACTIONS

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

Acute Myopia and Secondary Angle Closure *[see Warnings and Precautions (5.1)]*

Visual Field Defects *[see Warnings and Precautions (5.2)]*

Oligohidrosis and Hyperthermia *[see Warnings and Precautions (5.3)]*

Metabolic Acidosis *[see Warnings and Precautions (5.4)]*

Suicidal Behavior and Ideation *[see Warnings and Precautions (5.5)]*

Cognitive/Neuropsychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*

Fetal Toxicity *[see Warnings and Precautions (5.7)* and *Use in Specific Populations (8.1)]*

Sudden Unexplained Death in Epilepsy (SUDEP) *[see Warnings and Precautions (5.9)]*

Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use) *[see Warnings and Precautions (5.10)]*

Kidney Stones *[see Warnings and Precautions (5.11)]*

Hypothermia with Concomitant Valproic Acid (VPA) Use *[see Warnings and Precautions (5.12)]*

Paresthesia *[see Warnings and Precautions (5.13)]*

The data described in the following sections were obtained using topiramate tablets.

6.1 Clinical Trials Experience

Monotherapy Epilepsy

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

Increased Risk for Bleeding

Topiramate tablets treatment is associated with an increased risk for bleeding. In a pooled

analysis of placebo-controlled studies of approved and unapproved indications, bleeding was more frequently reported as an adverse event for topiramate tablets than for placebo (4.5% versus 3.0% in adult patients, and 4.4% versus 2.3% in pediatric patients). In this analysis, the incidence of serious bleeding events for topiramate tablets and placebo was 0.3% versus 0.2% for adult patients, and 0.4% versus 0% for pediatric patients.

Adverse bleeding reactions reported with topiramate tablets ranged from mild epistaxis,

ecchymosis, and increased menstrual bleeding to life-threatening hemorrhages. In patients with serious bleeding events, conditions that increased the risk for bleeding were often present, or patients were often taking drugs that cause thrombocytopenia (other antiepileptic drugs) or affect platelet function or coagulation (e.g., aspirin, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, or warfarin or other anticoagulants).

Monotherapy Epilepsy

Adults ≥16 Years

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

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

Pediatric Patients 6 to <16 Years of Age

The adverse reactions in the controlled trial that occurred most commonly in pediatric patients in the 400 mg/day topiramate tablets group and at a rate higher (≥ 5%) than in the 50 mg/day group were fever, weight decrease, mood problems, cognitive problems, infection, flushing, and paresthesia (see Table 5). Table 5 also presents the incidence of adverse reactions occurring in at least 2% of adult and pediatric patients treated with 400 mg/day topiramate tablets and occurring with greater incidence than 50 mg/day topiramate tablets.

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

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

	Age Group			
	Pediatric (6 to <16 Years)		Adult (Age ≥16 Years)	
	Topiramate Tablets Daily Dosage Group (mg/day)			
	50	400	50	400
Body System	(N=74)	(N=77)	(N=160)	(N=159)
Adverse Reaction	% *	% *	% *	% *
Body as a Whole - General Disorders				
Asthenia	0	3	4	6
Chest pain			1	2
Fever	1	12		
Leg pain			2	3
Central & Peripheral Nervous System Disorders				
Ataxia			3	4
Dizziness			13	14
Hypertonia			0	3
Hypoesthesia			4	5
Muscle contractions involuntary	0	3		
Paresthesia	3	12	21	40
Vertigo	0	3		
Gastro-Intestinal System Disorders				
Constipation			1	4
Diarrhea	8	9		
Gastritis			0	3
Gastroesophageal reflux			1	2
Dry mouth			1	3
Liver and Biliary System Disorders				
Gamma-GT increased			1	3
Metabolic and Nutritional Disorders				
Weight decrease	7	17	6	17
Platelet, Bleeding & Clotting Disorders				
Epistaxis	0	4		
Psychiatric Disorders				
Anorexia			4	14
Anxiety			4	6
Cognitive problems	1	6	1	4
Confusion	0	3		

Depression	0	3	7	9
Difficulty with concentration/attention	7	10	7	8
Difficulty with memory	1	3	6	11
Insomnia			8	9
Libido decreased			0	3
Mood problems	1	8	2	5
Personality disorder(behavior problems)	0	3		
Psychomotor slowing			3	5
Somnolence			10	15
Red Blood Cell Disorders				
Anemia	1	3		
Reproductive Disorders, Female[†]				
Intermenstrual Bleeding	0	3		
Vaginal Hemorrhage			0	3
Resistance Mechanism Disorders				
Infection	3	8	2	3
Infection viral	3	6	6	8
Respiratory System Disorders				
Bronchitis	1	5	3	4
Dyspnea			1	2
Rhinitis	5	6	2	4
Sinusitis	1	4		
Upper respiratory tract infection	16	18		
Skin and Appendages Disorders				
Acne			2	3
Alopecia	1	4	3	4
Pruritus			1	4
Rash	3	4	1	4
Special Senses Other, Disorders				
Taste perversion			3	5
Urinary System Disorders				
Cystitis			1	3
Dysuria			0	2
Micturition frequency	0	3	0	2
Renal calculus			0	3
Urinary incontinence	1	3		
Urinary tract infection			1	2
Vascular (Extracardiac) Disorders				
Flushing	0	5		

*Percentages calculated with the number of subjects in each group as denominator
†N with Female Reproductive Disorders – Incidence calculated relative to the number of females; Pediatric TPM 50 mg n=40; Pediatric TPM 400 mg n=33; Adult TPM 50 mg n=84; TPM 400 mg n=80

Adjunctive Therapy Epilepsy

The most commonly observed adverse reactions associated with the use of topiramate tablets at dosages of 200 to 400 mg/day (recommended dose range) in controlled trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at an incidence higher (≥ 5%) than in the placebo group were : somnolence, weight decrease, anorexia, dizziness, ataxia, speech disorders and related speech problems, language problems, psychomotor slowing, confusion, abnormal vision, difficulty with memory, paresthesia, diplopia, nervousness, and asthenia (see Table 6). Dose-related adverse reactions at dosages of 200 to 1,000 mg/day are shown in Table 8.

The most commonly observed adverse reactions associated with the use of topiramate tablets at dosages of 5 to 9 mg/kg/day in controlled trials in pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at an incidence higher (≥ 5%) than in the placebo group were : fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease (see Table 9). Table 9 also presents the incidence of adverse reactions occurring in at least 1% of pediatric patients treated with topiramate tablets and occurring with greater incidence than placebo.

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

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

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

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

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

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

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

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

		Topiramate Dosage (mg/day)	
Body System/	Placebo	200–400	600–1,000
Adverse Reaction [c]	(N=291)	(N=183)	(N=414)
Body as a Whole - General Disorders			
Fatigue	13	15	30
Asthenia	1	6	3
Back pain	4	5	3
Chest pain	3	4	2
Influenza-like symptoms	2	3	4
Leg pain	2	2	4
Hot flushes	1	2	1
Allergy	1	2	3
Edema	1	2	1
Body odor	0	1	0
Rigors	0	1	<1
Central & Peripheral Nervous System Disorders			
Dizziness	15	25	32
Ataxia	7	16	14
Speech disorders/Related speech problems	2	13	11

Paresthesia	4	11	19
Nystagmus	7	10	11
Tremor	6	9	9
Language problems	1	6	10
Coordination abnormal	2	4	4
Hypoesthesia	1	2	1
Gait abnormal	1	3	2
Muscle contractions involuntary	1	2	2
Stupor	0	2	1
Vertigo	1	1	2
Gastro-Intestinal System Disorders			
Nausea	8	10	12
Dyspepsia	6	7	6
Abdominal pain	4	6	7
Constipation	2	4	3
Gastroenteritis	1	2	1
Dry mouth	1	2	4
Gingivitis	<1	1	1
GI disorder	<1	1	0
Hearing and Vestibular Disorders			
Hearing decreased	1	2	1
Metabolic and Nutritional Disorders			
Weight decrease	3	9	13
Muscle-Skeletal System Disorders			
Myalgia	1	2	2
Skeletal pain	0	1	0
Platelet, Bleeding, & Clotting Disorders			
Epistaxis	1	2	1
Psychiatric Disorders			
Somnolence	12	29	28
Nervousness	6	16	19
Psychomotor slowing	2	13	21
Difficulty with memory	3	12	14
Anorexia	4	10	12
Confusion	5	11	14
Depression	5	5	13
Difficulty with concentration/attention	2	6	14
Mood problems	2	4	9
Agitation	2	3	3
Aggressive reaction	2	3	3
Emotional lability	1	3	3
Cognitive problems	1	3	3
Libido decreased	1	2	<1
Apathy	1	1	3
Depersonalization	1	1	2
Reproductive Disorders, Female			
Breast pain	2	4	0
Amenorrhea	1	2	2
Menorrhagia	0	2	1
Menstrual disorder	1	2	1
Reproductive Disorders, Male			
Prostatic disorder	<1	2	0
Resistance Mechanism Disorders			
Infection	1	2	1
Infection viral	1	2	<1
Moniliasis	<1	1	0
Respiratory **System Disorders**			
Pharyngitis	2	6	3
Rhinitis	6	7	6
Sinusitis	4	5	6
Dyspnea	1	1	2
Skin and Appendages Disorders			
Skin disorder	<1	2	1
Sweating increased	<1	1	<1
Rash erythematous	<1	1	<1
Special Sense Other, Disorders			
Taste perversion	0	2	4
Urinary System Disorders			
Hematuria	1	2	<1
Urinary tract infection	1	2	3
Micturition frequency	1	1	2
Urinary incontinence	<1	2	1
Urine abnormal	0	1	<1
Vision Disorders			
Vision abnormal	2	13	10
Diplopia	5	10	10
White Cell and RES Disorders			
Leukopenia	1	2	1

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

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

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

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

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

The most commonly observed adverse reactions associated with the use of topiramate tablets that were seen at an incidence higher (≥ 5%) than in the placebo group were : paresthesia, nervousness, somnolence, difficulty with concentration/attention, and fatigue (see Table 7). Because these topiramate tablets treatment difference incidence (Topiramate Tablets % -Placebo %) of many adverse reactions reported in this study were markedly lower than those reported in the previous epilepsy studies, they cannot be directly compared with data obtained in other studies

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

		Topiramate Tablets Dosage (mg/day)
Body System/	Placebo	200
Adverse Reaction [c]	(N=92)	(N=171)
Body as a Whole-General Disorders		
Fatigue	4	9
Chest pain	1	2
Cardiovascular Disorders, General		
Hypertension	0	2
Central & Peripheral Nervous System Disorders		
Paresthesia	2	9
Dizziness	4	7
Tremor	2	3
Hypoesthesia	0	2
Leg cramps	0	2
Language problems	0	2
Gastro-Intestinal System Disorders		
Abdominal pain	3	5
Constipation	0	4
Diarrhea	1	2

Dyspepsia	0	2
Dry mouth	0	2
Hearing and Vestibular Disorders		
Tinnitus	0	2
Metabolic and Nutritional Disorders		
Weight decrease	4	8
Psychiatric Disorders		
Somnolence	9	15
Anorexia	7	9
Nervousness	2	9
Difficulty with concentration/attention	0	5
Insomnia	3	4
Difficulty with memory	1	2
Aggressive reaction	0	2
Respiratory System Disorders		
Rhinitis	0	4
Urinary System Disorders		
Cystitis	0	2
Vision Disorders		
Diplopia	0	2
Vision abnormal	0	2

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

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

[c] Adverse reactions reported by at least 2% of patients in the topiramate tablets 200 mg/day group and more common than in the placebo group are listed in this table.

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

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

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

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

Body System/	Placebo	Topiramate
Adverse Reaction	(N=101)	(N=98)
Body as a Whole - General Disorders		
Fatigue	5	16
Injury	13	14
Allergic reaction	1	2
Back pain	0	1
Pallor	0	1
Cardiovascular Disorders, General		
Hypertension	0	1
Central & Peripheral Nervous System Disorders		
Gait abnormal	5	8
Ataxia	2	6
Hyperkinesia	4	5
Dizziness	2	4
Speech disorders/Related speech problems	2	4
Hyporeflexia	0	2
Convulsions grand mal	0	1
Fecal incontinence	0	1
Paresthesia	0	1
Gastro-Intestinal System Disorders		
Nausea	5	6
Saliva increased	4	6
Constipation	4	5
Gastroenteritis	2	3
Dysphagia	0	1
Flatulence	0	1
Gastroesophageal reflux	0	1
Glossitis	0	1
Gum hyperplasia	0	1
Heart Rate and Rhythm Disorders		
Bradycardia	0	1
Metabolic and Nutritional Disorders		
Weight decrease	1	9
Thirst	1	2
Hypoglycemia	0	1
Weight increase	0	1
Platelet, Bleeding, & Clotting Disorders		
Purpura	4	8
Epistaxis	1	4
Hematoma	0	1
Prothrombin increased	0	1
Thrombocytopenia	0	1
Psychiatric Disorders		
Somnolence	16	26
Anorexia	15	24
Nervousness	7	14
Personality disorder (behavior problems)	9	11
Difficulty with concentration/attention	2	10
Aggressive reaction	4	9
Insomnia	7	8
Difficulty with memory	0	5
Confusion	3	4
Psychomotor slowing	2	3
Appetite increased	0	1
Neurosis	0	1
Reproductive Disorders, Female		
Leukorrhea	0	2
Resistance Mechanism Disorders		
Infection viral	3	7
Respiratory System Disorders		
Pneumonia	1	5
Respiratory disorder	0	1
Skin and Appendages Disorders		
Skin disorder	2	3
Alopecia	1	2
Dermatitis	0	2
Hypertrichosis	1	2
Rash erythematous	0	2
Eczema	0	1
Seborrhea	0	1
Skin discoloration	0	1

Urinary System Disorders		
Urinary incontinence	2	4
Nocturia	0	1
Vision Disorders		
Eye abnormality	1	2
Vision abnormal	1	2
Diplopia	0	1
Lacrimation abnormal	0	1
Myopia	0	1
White Cell and RES Disorders		
Leukopenia	0	2

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

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

Other Adverse Reactions Observed During All Epilepsy Clinical Trials

Topiramate tablets has been administered to 2246 adults and 427 pediatric patients with epilepsy during all clinical studies, only some of which were placebo-controlled. During these studies, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reactions, similar types of reactions were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The frequencies presented represent the proportion of patients who experienced a reaction of the type cited on at least one occasion while receiving topiramate tablets. Reported reactions are included except those already listed in the previous tables or text, those too general to be informative, and those not reasonably associated with the use of the drug.

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

Autonomic Nervous System Disorders: *Infrequent:* vasodilation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.2 Postmarketing Experience

In addition to the adverse experiences reported during clinical testing of topiramate tablets, the following adverse experiences have been reported worldwide in patients receiving topiramate tablets post-approval.

These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, maculopathy, pancreatitis, and pemphigus.

7 DRUG INTERACTIONS

7.1 Antiepileptic Drugs

Concomitant administration of phenytoin or carbamazepine with topiramate resulted in a clinically significant decrease in plasma concentrations of topiramate when compared to topiramate given alone. A dosage adjustment may be needed [see Dosage and Administration (2.1), Clinical Pharmacology (12.3).]

Concomitant administration of valproic acid and topiramate has been associated with hypothermia and hyperammonemia with and without encephalopathy. Examine blood ammonia levels in patients in whom the onset of hypothermia has been reported [see Warnings and Precautions (5.9, 5.11), Clinical Pharmacology (12.3)

7.2 CNS Depressants

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

7.3 Oral Contraceptives

The possibility of decreased contraceptive efficacy and increased breakthrough bleeding may occur in patients taking combination oral contraceptive products with topiramate. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding *[see Clinical Pharmacology (12.3)]*.

7.4 Lithium

An increase in systemic exposure of lithium following topiramate doses of up to 600 mg/day can occur. Lithium levels should be monitored when co-administered with high-dose topiramate *[see Clinical Pharmacology (12.3)]*

7.5 Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide or acetazolamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, patients given topiramate concomitantly with another carbonic anhydrase inhibitor should be monitored particularly closely for the appearance or worsening of metabolic acidosis *[see Clinical Pharmacology (12.3)]* .

7.6 Hydrochlorothiazide (HCTZ)

Topiramate C_{max} and AUC increased when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate may require a decrease in the topiramate dose *[see Clinical Pharmacology (12.3)]* .

7.7 Pioglitazone

A decrease in the exposure of pioglitazone and its active metabolites were noted with the concurrent use of pioglitazone and topiramate in a clinical trial. The clinical relevance of these observations is unknown; however, when topiramate is added to pioglitazone therapy or pioglitazone is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state *[see Clinical Pharmacology (12.3)]* .

7.8 Amitriptyline

Some patients may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels *[see Clinical Pharmacology (12.3)]* .

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D ***[see Warnings and Precautions 5.7***]

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

Pregnancy Registry

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

Human Data

Data from pregnancy registries indicate an increased risk of oral clefts in infants exposed to

topiramate during the first trimester of pregnancy. In the NAAED pregnancy registry, the prevalence of oral clefts among topiramate-exposed infants (1.1%) was higher than the prevalence of infants exposed to a reference AED (0.36%) or the prevalence of infants in mothers without epilepsy and without exposure to AEDs (0.12%). It was also higher than the background prevalence in United States (0.17%) as estimated by the Centers for Disease Control and Prevention (CDC). The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 9.6 (95% Confidence Interval [CI] 4.0 – 23.0) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a prevalence of oral clefts among infants exposed to topiramate monotherapy (3.2%) that was 16 times higher than the background rate in the UK (0.2%).

Data from the NAAED pregnancy registry and a population-based birth registry cohort indicate that exposure to topiramate in utero is associated with an increased risk of small for gestational age (SGA) newborns (birth weight <10th percentile). In the NAAED pregnancy registry, 19.7% of topiramate-exposed newborns were SGA compared to 7.9% of newborns exposed to a reference AED and 5.4% of newborns of mothers without epilepsy and without AED exposure. In the Medical Birth Registry of Norway (MBRN), a population-based pregnancy registry, 25% of newborns in the topiramate monotherapy exposure group were SGA compared to 9 % in the comparison group unexposed to AEDs. The long term consequences of the SGA findings are not known.

Topiramate treatment can cause metabolic acidosis [see Warnings and Precautions (5.4)]. The effect of topiramate-induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) can cause decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus' ability to tolerate labor. Pregnant patients should be monitored for metabolic acidosis and treated as in the nonpregnant state [see Warnings and Precautions (5.4)]. Newborns of mothers treated with topiramate should be monitored for metabolic acidosis because of transfer of topiramate to the fetus and possible occurrence of transient metabolic acidosis following birth.

Animal Data

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

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m ^{2}basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m ^{2}basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

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

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

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Adjunctive Treatment for Partial Onset Epilepsy in Pediatric Patients 1 to 24 months

Safety and effectiveness in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. In a single randomized, double-blind, placebo-controlled investigational trial, the efficacy, safety, and tolerability of topiramate oral liquid and sprinkle formulations as an adjunct to concurrent antiepileptic drug therapy in pediatric patients 1 to 24 months of age with refractory partial onset seizures were assessed. After 20 days of double-blind treatment, topiramate (at fixed doses of 5, 15, and 25 mg/kg/day) did not demonstrate efficacy compared with placebo in controlling seizures.

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

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

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

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

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

Treatment with topiramate for up to 1 year was associated with reductions in Z SCORES for length, weight, and head circumference *[see Warnings and Precautions (5.4), Adverse Reactions (6)]* .

In open-label, uncontrolled experience, increasing impairment of adaptive behavior was documented in behavioral testing over time in this population. There was a suggestion that this effect was dose-related. However, because of the absence of an appropriate control group, it is not known if this decrement in function was treatment-related or reflects the patient's underlying disease (e.g., patients who received higher doses may have more severe underlying disease) *[see Warnings and Precautions (5.6)]* .

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

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

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

Migraine Prophylaxis in Pediatric Patients 12 to 17 Years of Age

Safety and effectiveness of topiramate in the prophylaxis of migraine was studied in 5 double-blind, randomized, placebo-controlled, parallel-group trials in a total of 219 pediatric patients, at doses of 50 to 200 mg/day, or 2 to 3 mg/kg/day. These comprised a fixed dose study in 103 pediatric patients 12 to 17 years of age *[see Clinical Studies (14.3)]* , a flexible dose (2 to 3 mg/kg/day), placebo-controlled study in 157 pediatric patients 6 to 16 years of age (including 67 pediatric patients 12 to 16 years of age), and a total of 49 pediatric patients 12 to 17 years of age in 3 studies of migraine prophylaxis primarily in adults. Open-label extension phases of 3 studies enabled evaluation of long-term safety for up to 6 months after the end of the double-blind phase.

Efficacy of topiramate for migraine prophylaxis in pediatric patients 12 to 17 years of age is demonstrated for a 100 mg daily dose in Study 12 *[see Clinical Studies (14.3)]*. Efficacy of topiramate (2 to 3 mg/kg/day) for migraine prophylaxis was not demonstrated in a placebocontrolled trial of 157 pediatric patients (6 to 16 years of age) that included treatment of 67 pediatric patients (12 to 16 years of age) for 20 weeks.

In the pediatric trials (12 to 17 years of age) in which patients were randomized to placebo or a fixed daily dose of topiramate , the most common adverse reactions with topiramate that were seen at an incidence higher (≥5%) than in the placebo group were: paresthesia, upper respiratory tract infection, anorexia, and abdominal pain *[see Adverse Reactions (6)]* .

The most common cognitive adverse reaction in pooled double-blind studies in pediatric patients 12 to 17 years of age was difficulty with concentration/attention *[see Warnings and Precautions (5.6)]*.

Markedly abnormally low serum bicarbonate values indicative of metabolic acidosis were reported in topiramate-treated pediatric migraine patients *[see Warnings and Precautions (5.4)]* .

In topiramate-treated pediatric patients (12 to 17 years of age) compared to placebo-treated patients, abnormally increased results were more frequent for creatinine, BUN, uric acid, chloride, ammonia, total protein, and platelets. Abnormally decreased results were observed with topiramate vs placebo treatment for phosphorus and bicarbonate *[see Warnings and Precautions*

(5.12)] .

Notable changes (increases and decreases) from baseline in systolic blood pressure, diastolic blood pressure, and pulse were observed occurred more commonly in pediatric patients treated with topiramate compared to pediatric patients treated with placebo *[see Clinical Pharmacology*

(12.2)].

Migraine Prophylaxis in Pediatric Patients 6 to 11 Years of Age

Safety and effectiveness in pediatric patients below the age of 12 years have not been established for the prophylaxis treatment of migraine headache.

In a double-blind study in 90 pediatric patients 6 to 11 years of age (including 59 topiramate-treated and 31 placebo patients), the adverse reaction profile was generally similar to that seen in pooled double-blind studies of pediatric patients 12 to 17 years of age. The most common adverse reactions that occurred in topiramate -treated pediatric patients 6 to 11 years of age, and at least twice as frequently than placebo, were gastroenteritis (12% topiramate, 6% placebo), sinusitis (10% topiramate, 3% placebo), weight loss (8% topiramate, 3% placebo) and paresthesia (7% topiramate, 0% placebo). Difficulty with concentration/attention occurred in 3 topiramate-treated patients (5%) and 0 placebo-treated patients.

The risk for cognitive adverse reaction was greater in younger patients (6 to 11 years of age) thanin older patients (12 to 17 years of age) *[see Warnings and Precautions (5.6)]* .

Juvenile Animal Studies

When topiramate (30, 90, or 300 mg/kg/day) was administered orally to rats during the juvenile period of development (postnatal days 12 to 50), bone growth plate thickness was reduced in males at the highest dose, which is approximately 5-8 times the maximum recommended pediatric dose (9 mg/kg/day) on a body surface area (mg/m^2) basis.

8.5 Geriatric Use

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

8.6 Renal Impairment

The clearance of topiramate is reduced in patients with moderate (creatinine clearance 30 to 69 $mL/min/1.73\ m^2$) and severe (creatinine clearance <30 $mL/min/1.73\ m^2$) renal impairment. A dosage adjustment is recommended in patients with moderate or severe renal impairment *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]* .

8.7 Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than in a normal individual. A dosage adjustment may be required *[see Dosage and Administration (2.6), Clinical Pharmacology (12.3)]*.

8.8 Women of Childbearing Potential

Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk for cleft lip and/or cleft palate (oral clefts) *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1)]* . Consider the benefits and the risks of topiramate when prescribing this drug to women of childbearing potential, particularly when topiramate is considered for a condition not usually associated with permanent injury or death. Because of the risk of oral clefts to the fetus, which occur in the first trimester of pregnancy before many women know they are pregnant, all women of childbearing potential should be apprised of the potential hazard to the fetus from exposure to topiramate. If the decision is made to use topiramate, women who are not planning a pregnancy should use effective contraception *[see Drug Interactions (7.3)]* . Women who are planning a pregnancy should be counseled regarding the relative risks and benefits of topiramate use during pregnancy, and alternative therapeutic options should be considered for these patients.

10 OVERDOSAGE

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

Topiramate overdose has resulted in severe metabolic acidosis *[see Warnings and Precautions (5.4)]* .

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

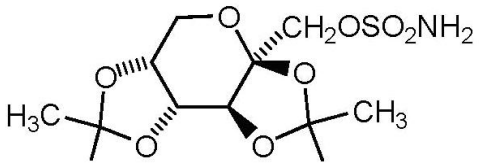
In acute topiramate overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate *in vitro*. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body

11 DESCRIPTION

Topiramate is a sulfamate-substituted monosaccharide. Topiramate tablets USP are available as 25mg, 50 mg and 100 mg circular tablets and 200 mg capsule shaped tablets for oral administration.

Topiramate USP is a white crystalline powder with a bitter taste. Topiramate USP is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and

a molecular weight of 339.36. Topiramate is designated chemically as 2,3:4,5Di- *O*-isopropylidene-ß-D-fructopyranose sulfamate and has the following structural formula:



Each tablet, for oral administration, contains 25 mg, 50 mg, 100 mg and 200 mg topiramate and has the following inactive ingredients: hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, sodium starch glycolate and titanium dioxide. In addition, the 25 mg also contains FD&C Blue #2; the 50 mg and 100 mg also contain red iron oxide and yellow iron oxide; and the 200 mg also contains red iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms by which topiramate exerts its anticonvulsant are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate efficacy for epilepsy. Electrophysiological and biochemical evidence suggests that Topiramate, at pharmacologically relevant concentrations, blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

12.2 Pharmacodynamics

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

Changes (increases and decreases) from baseline in vital signs (systolic blood pressure-SBP, diastolic blood pressure-DBP, pulse) occurred more frequently in pediatric patients (6 to 17 years) treated with various daily doses of topiramate (50 mg, 100 mg, 200 mg, 2 to 3 mg/kg) than in patients treated with placebo in controlled trials for migraine prophylaxis. The most notable changes were SBP <90 mm Hg, DBP <50 mm Hg, SBP or DBP increases or decreases ≥20 mm Hg, and pulse increases or decreases ≥30 beats per minute. These changes were often dose-related, and were most frequently associated with the greatest treatment difference at the 200 mg dose level. Systematic collection of orthostatic vital signs has not been conducted. The clinical significance of these various changes in vital signs has not been clearly established.

12.3 Pharmacokinetics

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

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

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

Metabolism and Excretion

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in adults following oral administration.

Special Populations

Renal Impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30 to 69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment *[see Dosage and Administration (2.4) and (2.5)* and *Warnings and Precautions (5.14)]* .

Hemodialysis

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

Hepatic Impairment

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

Age, Gender, and Race

The pharmacokinetics of topiramate in elderly subjects (65 to 85 years of age, N=16) were evaluated in a controlled clinical study. The elderly subject population had reduced renal function (creatinine clearance [-20%]) compared to young adults. Following a single oral 100 mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1 to 2 hours. Reflecting the primary renal elimination of topiramate, topiramate plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced. As recommended for all patients, dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate ≤70 mL/min/1.73 m^2) is evident. It may be useful to monitor renal function in the elderly patient *[see Dosage and Administration (2.4)* and *Warnings and Precautions (5.14)]* .

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

Pediatric Pharmacokinetics

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

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

Clearance was independent of dose.

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

Drug-Drug Interactions

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on mean plasma AUCs are summarized in Table 10.

In Table 13, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the co-administration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when topiramate was given alone.

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

[a]= Plasma concentration increased 25% in some patients, generally those on a twice a day dosing regimen of phenytoin.

[b]= Is not administered but is an active metabolite of carbamazepine.

In addition to the pharmacokinetic interaction described in the above table, concomitant administration of valproic acid and topiramate tablets has been associated with hyperammonemia with and without encephalopathy and hypothermia *[see Warnings and Precautions (5.10), (5.12)* and *Drug Interactions (7.1)]* .

CNS Depressants

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

Oral Contraceptives

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), topiramate tablets, given in the absence of other medications at doses of 50 to200 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, topiramate tablets (50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose-dependent decrease in EE exposure for doses between 200 and 800 mg/day, there was no significant dose-dependent change in EE exposure for doses of 50 to 200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with topiramate tablets. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding *[see Drug Interactions (7.3)]* .

Digoxin

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

Hydrochlorothiazide

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

Metformin

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

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin (500 mg every 12 hr) and topiramate in plasma when metformin was given alone and when metformin and topiramate (100 mg every 12 hr) were given simultaneously. The results of this study indicated that the mean metformin C_{max} and AUC_{0-12h} increased by 18%and 25%, respectively, when topiramate was added. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is not known. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear *[see Drug Interactions (7.4)]* .

Pioglitazone

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

Glyburide

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

Lithium

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

Haloperidol

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

Amitriptyline

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

Sumatriptan

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

Risperidone

When administered concomitantly with topiramate tablets at escalating doses of 100, 250, and 400 mg/day, there was a reduction in risperidone systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses of topiramate). No alterations of 9-hydroxyrisperidone levels were observed. Co-administration of topiramate 400 mg/day with risperidone resulted in a 14% increase in C_{max} and a 12% increase in AUC_{12} of topiramate. There were no clinically significant changes in the systemic exposure of risperidone plus 9-hydroxyrisperidone or of topiramate; therefore, this

interaction is not likely to be of clinical significance.

Propranolol

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

Dihydroergotamine

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

Diltiazem

Co-administration of diltiazem (240 mg Cardizem CD ®) with topiramate (150 mg/day) resulted in a 10% decrease in C_{max} and a 25% decrease in diltiazem AUC, a 27% decrease in C_{max} and an 18% decrease in des-acetyl diltiazem AUC, and no effect on N-desmethyl diltiazem. Co-administration of topiramate with diltiazem resulted in a 16% increase in C_{max} and a 19% increase in AUC_{12} of topiramate.

Venlafaxine

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

Other Carbonic Anhydrase Inhibitors

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

Drug/Laboratory Tests Interactions

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Topiramate did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Topiramate was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro*; and it did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo*.

Impairment of Fertility

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

14 CLINICAL STUDIES

The studies described in the following sections were conducted using topiramate tablets.

14.1 Monotherapy Epilepsy

Patients with Partial Onset or Primary Generalized Tonic-Clonic Seizures

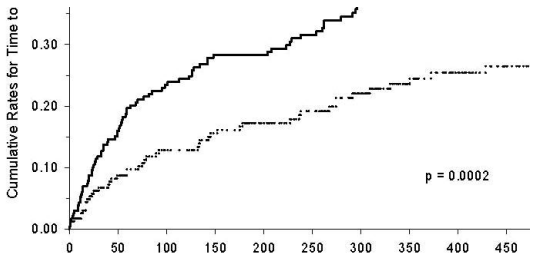
Adults and Pediatric Patients 10 Years of Age and Older

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

The trial was conducted in 487 patients diagnosed with epilepsy (6 to 83 years of age) who had 1 or 2 well-documented seizures during the 3-month retrospective baseline phase who then entered the study and received topiramate 25 mg/day for 7 days in an open-label fashion.

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

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



Children 2 to <10 Years of Age

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

14.2 Adjunctive Therapy Epilepsy

Adult Patients With Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for adults with partial onset seizures was established in six multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo and four comparing a single dosage with placebo, in patients

with a history of partial onset seizures, with or without secondarily generalized seizures.

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate 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 topiramate tablets in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. In five of the six studies, patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. In the sixth study (119), the 25 or 50 mg/day initial doses of topiramate were followed by respective weekly increments of 25 or 50 mg/day until the target dose of 200 mg/day was reached. After titration, patients entered a 4, 8 or 12-week stabilization period. The numbers of patients randomized to each dose and the actual mean and median doses in the stabilization period are shown in Table 11.

Pediatric Patients Ages 2 to 16 Years with Partial Onset Seizures

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

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate 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 topiramate tablets in addition to their other AEDs.

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

Patients With Primary Generalized Tonic-Clonic Seizures

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

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate 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 topiramate in addition to their other AEDs.

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

Patients With Lennox-Gastaut Syndrome

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

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

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

* Dose-response studies were not conducted for other indications or pediatric partial onset seizures.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reductions in seizure rates and the responder rates (fraction of patients with at least a 50% reduction) by treatment group for each study are shown below in Table 12. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

Table 12 Efficacy Results in Double-Blind, Placebo-Controlled, Add-On Epilepsy Trials

		Target Topiramate Dosage (mg/day)					
Protocol Efficacy Results	**Placebo**	**200**	**400**	**600**	**800**	**1 , 000**	**≈6 mg/kg/day***
Comparisons with placebo:							
Partial Onset Seizures							
Studies in Adults							
1 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]	--	--	--
2 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]	--
3 N	24	--	23	--	--	--	--
Median % Reduction	1.1	--	40.7 [e]	--	--	--	--
% Responders	8	--	35 [d]	--	--	--	--
4 N	30	--	--	30	--	--	--
Median % Reduction	-12.2	--	--	46.4 [f]	--	--	--
% Responders	10	--	--	47 [§]	--	--	--
5 N	28	--	--	--	28	--	--
Median % Reduction	-20.6	--	--	--	24.3 [c]	--	--
% Responders	0	--	--	--	43 [c]	--	--
6 N	91	168	--	--	--	--	--
Median % Reduction	20.0	44.2 [c]	--	--	--	--	--
% Responders	24	45 [c]	--	--	--	--	--
Studies in Pediatric Patients							
7 N	45	--	--	--	--	--	41
Median % Reduction	10.5	--	--	--	--	--	33.1 [¶]
% Responders	20	--	--	--	--	--	39

Primary Generalized Tonic-Clonic [g]								
8	N	40	--	--	--	--	--	39
Median % Reduction		9.0	--	--	--	--	--	56.7 [d]
% Responders		20	--	--	--	--	--	56 [c]
Lennox-Gastaut Syndromeà								
9	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 patients 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 topiramate tablets in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

In clinical trials for epilepsy, daily dosages were decreased in weekly intervals by 50 to 100 mg/day in adults and over a 2- to 8-week period in children; transition was permitted to a new antiepileptic regimen when clinically indicated.

14.3 Migraine Prophylaxis

Adult Patients

The results of 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials established the effectiveness of topiramate in the prophylactic treatment of migraine headache. The design of both trials (Study 10 was conducted in the U.S. and Study 11 was conducted in the U.S. and Canada) was identical, enrolling patients with a history of migraine, with or without aura, for at least 6 months, according to the International Headache Society (IHS) diagnostic criteria. Patients with a history of cluster headaches or basilar, ophthalmoplegic, hemiplegic, or transformed migraine headaches were excluded from the trials. Patients were required to have completed up to a 2-week washout of any prior migraine preventive medications before starting the baseline phase.

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

Effectiveness of treatment was assessed by the reduction in migraine headache frequency, as measured by the change in 4-week migraine rate (according to migraines classified by HIS criteria) from the baseline phase to double-blind treatment period in each topiramate treatment group compared to placebo in the Intent-To-Treat (ITT) population.

In Study 10, a total of 469 patients (416 females, 53 males), ranging in age from 13 to 70 years, were randomized and provided efficacy data. Two hundred sixty-five patients completed the entire 26-week double-blind phase. The median average daily dosages were 48 mg/day, 88 mg/day, and 132 mg/day in the target dose groups of topiramate 50, 100, and 200 mg/day, respectively.

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

In Study 11, a total of 468 patients (406 females, 62 males), ranging in age from 12 to 65 years, were randomized and provided efficacy data. Two hundred fifty-five patients completed the entire 26-week double-blind phase. The median average daily dosages were 47 mg/day, 86 mg/day, and 150 mg/day in the target dose groups of topiramate 50, 100, and 200 mg/day, respectively.

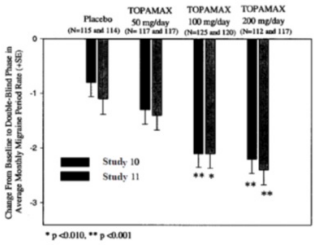
The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches/28 days and was similar across treatment groups. The change in the mean 4-week migraine headache period frequency from baseline to the double-blind phase was -1.4, -2.1, and -2.4 in the topiramate 50, 100,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

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

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

Figure 2: Reduction in 4-Week Migraine Headache Frequency

(Studies 10 and 11 for Adults and Adolescents)



Pediatric Patients 12 to 17 Years of Age

The effectiveness of topiramate as prophylaxis for migraine headache in pediatric patients 12 to 17 years of age was established in a multicenter, randomized, double-blind, parallel-group trial. The study enrolled 103 patients (40 male, 63 female) 12 to 17 years of age with episodic migraine headaches with or without aura. Patient selection was based on IHS criteria for migraines (using proposed revisions to the 1988 IHS pediatric migraine criteria [IHS-R criteria]).

Patients who experienced 3 to 12 migraine attacks (according to migraines classified by patient reported diaries) and ≤14 headache days (migraine and non-migraine) during the 4-week prospective baseline period were randomized to either topiramate 50 mg/day, 100 mg/day, or placebo and treated for a total of 16 weeks (4-week titration period followed by a 12-week maintenance period). Treatment was initiated at 25 mg/day for one week, and then the daily dosage was increased by 25 mg increments each week until reaching the assigned target dose or maximum tolerated dose (administered twice daily). Approximately 80% or more patients in each treatment group completed the study. The median average daily dosages were 45 and 79 mg/day in the target dose groups of topiramate 50 and 100 mg/day, respectively.

Effectiveness of treatment was assessed by comparing each topiramate treatment group to placebo (ITT population) for the percent reduction from baseline to the last 12 weeks of the double-blind phase in the monthly migraine attack rate (primary endpoint). The percent reduction from baseline to the last 12 weeks of the double-blind phase in average monthly migraine attack rate is shown in Table 13. The 100 mg topiramate dose produced a statistically significant treatment difference relative to placebo of 28% reduction from baseline in the monthly migraine attack rate.

The mean reduction from baseline to the last 12 weeks of the double-blind phase in average monthly attack rate, a key secondary efficacy endpoint in Study 12 (and the primary efficacy endpoint in Studies 10 and 11, of adults) was 3.0 for 100 mg topiramate dose and 1.7 for placebo. This 1.3 treatment difference in mean reduction from baseline of monthly migraine rate was statistically significant (p = 0.0087).

Table 13: Percent Reduction from Baseline to the Last 12 Weeks of Double-Blind Phase in Average Monthly Attack Rate: Study 12 (Intent-to-Treat Analysis Set)

Category	Placebo (N=33)	Topiramate 50 mg/day (N=35)	Topiramate 100 mg/day (N=35)
Baseline			

Median	3.6	4.0	4.0
Last 12 Weeks of Double-Blind Phase			
Median	2.3	2.3	1.0
Percent Reduction (%)			
Median	44.4	44.6	72.2
P-value versus		0.7975	0.0164 [c]
Placebo [a,b]			

[a] P-values (two-sided) for comparisons relative to placebo are generated by applying an ANCOVA model on ranks that includes subject's stratified age at baseline, treatment group, and analysis center as factors and monthly migraine attack rate during baseline period as a covariate.

[b] P-values for the dose groups are the adjusted p-value according to the Hochberg multiple comparison procedure.

[c] Indicates p-value is <0.05 (two-sided).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Topiramate tablets USP

Topiramate tablets USP are available in the following strengths and colors:

25 mg, White colored, circular, biconvex film-coated tablets, debossed with "122" on one side and "C" on the other side and are available in

Bottles of 60's (NDC 69097-122-03)

Bottles of 500's (NDC 69097-122-12)

Bottles of 1000's (NDC 69097-122-15)

50 mg, Light orange colored, circular, biconvex, film-coated tablets, debossed with "123" on one side and "C" on the other side and are available in

Bottles of 60's (NDC 69097-123-03)

Bottles of 500's (NDC 69097-123-12)

Bottles of 1000's (NDC 69097-123-15)

100 mg, Orange colored, circular, biconvex, film-coated tablets, debossed with "124" on one side and "Cipla" on the other side and are available in

Bottles of 60's (NDC 69097-124-03)

Bottles of 500's (NDC 69097-124-12)

Bottles of 1000's (NDC 69097-124-15)

200 mg, Pink colored, capsule shaped, biconvex, film-coated tablets, debossed with "125" on one side and "Cipla" on other side and are available in

Bottles of 60's (NDC 69097-125-03)

Bottles of 500's (NDC 69097-125-12)

Bottles of 1000's(NDC 69097-125-15)

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F) [See USP controlled room temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Eye Disorders

Instruct patient taking topiramate tablets should be told to seek immediate medical attention if they experience blurred vision, visual disturbances, or periorbital pain *[see Warnings and Precautions (5.1), (5.2)]* .

Oligohidrosis and Hyperthermia

Closely monitor topiramate tablets-treated pateints, especially pediatric patients, for evidence of decreased sweating and increased body temperature, especially in hot weather. Counsel patient to contact their healthcare professionals immediately if they develop a high or persistent fever, or decreased sweating *[see Warnings and Precautions (5.3)]* .

Metabolic Acidosis

Warn patients about the potential significant risk for metabolic acidosis that may be asymptomatic and may be associated with adverse effects on kidneys (e.g., kidney stones, nephrocalcinosis), bones (e.g., osteoporosis, osteomalacia, and/or rickets in children), and growth (e.g., growth delay/retardation) in pediatric patients, and on the fetus *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)]* .

Suicidal Behavior and Ideation

Counsel patients, their caregivers, and families that AEDs, including topiramate tablets, may increase the risk of suicidal thoughts and behavior, and advise of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior or the emergence of suicidal thoughts, or behavior or thoughts about self-harm. Instruct patients to immediately report behaviors of concern to their healthcare providers *[see Warnings and Precautions (5.5)]* .

Interference with Cognitive and Motor Performance

Warn patients about the potential for somnolence, dizziness, confusion, difficulty concentrating, or visual effects, and advise patients not to drive or operate machinery until they have gained sufficient experience on topiramate tablets to gauge whether it adversely affects their mental performance, motor performance, and/or vision *[see Warnings and Precautions (5.6)]* .

Even when taking topiramate tablets other anticonvulsants, some patients with epilepsy will continue to have unpredictable seizures. Therefore, advise all patients taking topiramate tablets for epilepsy to exercise appropriate caution when engaging in any activities where loss of consciousness could result in serious danger to themselves or those around them (including swimming, driving a car, climbing in high places, etc.). Some patients with refractory epilepsy will need to avoid such activities altogether. Discuss the appropriate level of caution with patients, before patients with epilepsy engage in such activities.

Fetal Toxicity

Inform pregnant women and women of childbearing potential that use of topiramate tablets during pregnancy can cause fetal harm, including an increased risk for cleft lip and/or cleft palate (oral clefts), which occur early in pregnancy before many women know they are pregnant. There may also be risks to the fetus from chronic metabolic acidosis with use of Topiramatedуring pregnancy *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1), (8.9)]* . When appropriate, counsel pregnant women and women of childbearing potential about alternative therapeutic options. This is particularly important when topiramate tablets is considered for a condition not usually associated with permanent injury or death.

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

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

Hyperammonemia and Encephalopathy

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

Kidney Stones

Instruct patients, particularly those with predisposing factors, to maintain an adequate fluid intake in order to minimize the risk of kidney stone formatio n *[see Warnings and Precautions (5.11)]*.

Instructions for a Missing Dose

Instruct patients that if they miss a single dose of topiramate tablets, it should be taken as soon as

possible. However, if a patient is within 6 hours of taking the next scheduled dose, tell the patient to wait until then to take the usual dose of topiramate tablets, and to skip the missed dose. Tell patients that they should not take a double dose in the event of a missed dose. Advise patients to contact their healthcare provider if they have missed more than one dose .

Manufactured by:

Cipla Ltd, Kurkumbh, India

Manufactured for:

Cipla USA, Inc., 1560 Sawgrass

Corporate Parkway, Suite 130, Sunrise, FL 33323

Revised on: 06/2017

MEDICATION GUIDE

Topiramate (toe pir'a mate) Tablets, USP

What is the most important information I should know about topiramate tablets?

Topiramate tablets may cause eye problems. Serious eye problems include:
- any sudden decrease in vision with or without eye pain and redness,
- a blockage of fluid in the eye causing increased pressure in the eye (secondary angle closure glaucoma).
- These eye problems can lead to permanent loss of vision if not treated.
- You should call your healthcare provider right away if you have any new eye symptoms, including any new problems with your vision.

Topiramate tablets may cause decreased sweating and increased body temperature (fever). People, especially children, should be watched for signs of decreased sweating and fever, especially in hot temperatures. Some people may need to be hospitalized for this condition. Call your healthcare provider right away if you have a high fever, a fever that does not go away, or decreased sweating.

Topiramate tablets can increase the level of acid in your blood (metabolic acidosis). If left untreated, metabolic acidosis can cause brittle or soft bones (osteoporosis, osteomalacia, osteopenia), kidney stones, can slow the rate of growth in children, and may possibly harm your baby if you are pregnant. Metabolic acidosis can happen with or without symptoms.

Sometimes people with metabolic acidosis will:
- feel tired
- not feel hungry (loss of appetite)
- feel changes in heartbeat
- have trouble thinking clearly

Your healthcare provider should do a blood test to measure the level of acid in your blood before and during your treatment with topiramate tablets. If you are pregnant, you should talk to your healthcare provider about whether you have metabolic acidosis.

Like other antiepileptic drugs, topiramate tablets may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Do not stop topiramate tablets without first talking to a healthcare provider.
- Stopping topiramate tablets suddenly can cause serious problems.
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?
- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Topiramate tablets can harm your unborn baby.
- If you take topiramate tablets during pregnancy, your baby has a higher risk for birth defects called cleft lip and cleft palate. These defects can begin early in pregnancy, even before you know you are pregnant.
- Cleft lip and cleft palate may happen even in children born to women who are not taking any medicines and do not have other risk factors.
- There may be other medicines to treat your condition that have a lower chance of birth defects.
- All women of childbearing age should talk to their healthcare providers about using other possible treatments instead of topiramate tablets. If the decision is made to use topiramate tablets, you should use effective birth control (contraception) unless you are planning to become pregnant. You should talk to your doctor about the best kind of birth control to use while you are taking topiramate tablets.
- If you take topiramate during pregnancy, your baby may be smaller than expected at birth. Talk to your healthcare provider if you have questions about this risk during pregnancy
- Tell your healthcare provider right away if you become pregnant while taking topiramate tablets. You and your healthcare provider should decide if you will continue to take topiramate tablets while you are pregnant.
- Metabolic acidosis may have harmful effects on your baby. Talk to your healthcare provider if topiramate tablet has caused metabolic acidosis during your pregnancy.
- Pregnancy Registry: If you become pregnant while taking topiramate tablets, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.

What is topiramate tablets ?

Topiramate tablets is a prescription medicine used:
- to treat certain types of seizures (partial onset seizures and primary generalized tonic-clonic seizures) in adults and children 2 years and older,
- with other medicines to treat certain types of seizures (partial onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children 2 years and older.

to prevent migraine headaches in adults and adolescents 12 years and older.

What should I tell my healthcare provider before taking topiramate tablets?

Before taking topiramate tablets, tell your healthcare provider about all of your medical conditions, including if you:
- have or have had depression, mood problems, or suicidal thoughts or behavior
- have kidney problems, have kidney stones, or are getting kidney dialysis
- have a history of metabolic acidosis (too much acid in the blood)
- have liver problems
- have weak, brittle, or soft bones (osteomalacia, osteoporosis, osteopenia, or decreased bone density)
- have lung or breathing problems
- have eye problems, especially glaucoma
- have diarrhea
- have a growth problem
- are on a diet high in fat and low in carbohydrates, which is called a ketogenic diet
- are having surgery
- are pregnant or plan to become pregnant
- are breastfeeding. Topiramate passes into breast milk. It is not known if the topiramate that passes into breast milk can harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take topiramate tablets.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Topiramate tablets and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:
- Valproic acid (such as DEPAKENE or DEPAKOTE)
- Any medicines that impair or decrease your thinking, concentration, or muscle coordination
- Birth control pills. Topiramate tablets may make your birth control pills less effective. Tell your healthcare provider if your menstrual bleeding changes while you are taking birth control pills and topiramate tablets.

Ask your healthcare provider if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without talking with your healthcare provider.

How should I take topiramate tablets?
- Take topiramate tablets exactly as prescribed.
- Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.
- Topiramate tablets should be swallowed whole. Do not chew the tablets. They may leave a bitter taste.
- Do not store any medicine and food mixture for later use.
- Topiramate tablets can be taken before, during, or after a meal. Drink plenty of fluids during the day. This may help prevent kidney stones while taking topiramate tablets
- If you take too much topiramate tablets, call your healthcare provider or poison control center right away or go to the nearest emergency room.
- If you miss a single dose of topiramate tablets, take it as soon as you can. However, if you are within 6 hours of taking your next scheduled dose, wait until then to take your usual dose of topiramate tablets, and skip the missed dose. Do not double your dose. If you have missed more than one dose, you should call your healthcare provider for advice.
- Do not stop taking topiramate tablets without talking to your healthcare provider. Stopping topiramate tablets suddenly may cause serious problems. If you have epilepsy and you stop taking topiramate tablets suddenly, you may have seizures that do not stop. Your healthcare provider will tell you how to stop taking topiramate tablets slowly.
- Your healthcare provider may do blood tests while you take topiramate tablets.

What should I avoid while taking topiramate tablets ?
- Do not drink alcohol while taking topiramate tablets. Topiramate and alcohol can affect each other causing side effects such as sleepiness and dizziness.
- Do not drive a car or operate heavy machinery until you know how topiramate tablets affects you. Topiramate tablets can slow your thinking and motor skills, and may affect vision.

What are the possible side effects of topiramate tablets?

Topiramate tablets may cause serious side effects including:

See "what is the most important information i should know about topiramate tablets?"

● **High blood ammonia levels.** High ammonia in the blood can affect your mental activities, slow your alertness, make you feel tired, or cause vomiting. This has happened when topiramate tablets is taken with a medicine called valproic acid (DEPAKENE and DEPAKOTE).

● **Kidney stones.** Drink plenty of fluids when taking topiramate tablets to decrease your chances of getting kidney stones.

● **Low body temperature.** Taking topiramate tablets when you are also taking valproic acid can cause a drop in body temperature to less than 95°F, feeling tired, confusion, or coma.

● **Effects on thinking and alertness.** Topiramate tablets may affect how you think and cause confusion, problems with concentration, attention, memory, or speech. Topiramate tablets may cause depression or mood problems, tiredness, and sleepiness.

● **Dizziness or loss of muscle coordination.**

Call your healthcare provider right away if you have any of the symptoms above.

The most common side effects of topiramate tablets include:
- tingling of the arms and legs (paresthesia)
- not feeling hungry
- nausea
- a change in the way foods taste
- diarrhea
- weight loss
- nervousness
- upper respiratory tract infection
- speech problems
- tiredness
- dizziness
- sleepiness/drowsiness
- slow reactions
- difficulty with memory
- pain in the abdomen
- fever
- abnormal vision
- decreased feeling or sensitivity, especially in the skin

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of topiramate tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Cipla Ltd. at **1-866-604-3268**

How should I store topiramate tablets USP
- Store topiramate tablets USP at room temperature, 20°C to 25°C (68°F to 77°F) [See USP controlled room temperature].
- Keep topiramate tablets in a tightly closed container.
- Keep topiramate tablets dry and away from moisture.
- **Keep topiramate tablets and all medicines out of the reach of children.**

General information about the safe and effective use of topiramate tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use topiramate tablets for a condition for which it was not prescribed. Do not give topiramate tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about topiramate tablets. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about topiramate tablets that is written for health professionals.

For more information, call **1-866-604-3268**

What are the ingredients in topiramate tablets USP ?

Active ingredient: Topiramate USP

Inactive ingredients:
- **Tablets -** Tablets - contain hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, sodium starch glycolate and titanium dioxide. In addition, the 25 mg also contains FD&C Blue #2; the 50 mg and 100 mg also contain red iron oxide and yellow iron oxide; and the 200 mg also contains red iron oxide.

Additional pediatric use information for patients ages 12 to 17 years is approved for Janssen Pharmaceuticals, Inc.'s TOPAMAX (topiramate) Tablets and Sprinkle Capsules. However, due to Janssen Pharmaceuticals, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Disclaimer: Other brands listed are the registered trademarks of their respective owners and are not trademarks of Cipla Limited

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Cipla Ltd Kurkumbh, India

Manufacture for:

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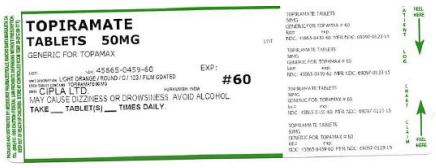
Corporate Parkway, Suite 130, Sunrise, FL 33323

Revised: 06/2017

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 60 count



TOPIRAMATE

topiramate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:45865-459(NDC:69097-123)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TOPIRAMATE (UNII: 0H73WJJ391) (TOPIRAMATE - UNII:0H73WJJ391)	TOPIRAMATE	50 mg

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
STARCH, PREGELATINIZED CORN (UNII: O8232NY3SJ)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMYB2)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics			
Color	orange (Light orange)	**Score**	no score
Shape	ROUND (Circular, biconvex)	**Size**	7mm
Flavor		**Imprint Code**	123;C
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:45865-459-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2018	
2	NDC:45865-459-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2018	

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
ANDA	ANDA076343	06/12/2014	

Labeler - Medsource Pharmaceuticals (833685915)

Establishment			
Name	**Address**	**ID/FEI**	**Business Operations**
Medsource Pharmaceuticals		833685915	repack(45865-459)

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