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** ----------
Warnings and Precautions, 6/2020
Serious Skin Reactions (5.9)

---------- **INDICATIONS AND USAGE** ----------
Topiramate tablets are indicated for:

- Epilepsy: initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older (1.1), adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older (1.2)
- Preventive treatment 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 tablets (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 tablets if clinically appropriate (5.4)
- Suicidal behavior and ideation: antiepileptic drugs increase the risk of suicidal behavior or ideation (5.5)
- Cognitive/neuropsychiatric adverse reactions: use caution when operating machinery including cars; depression and mood problems may occur (5.6)
- Fetal Toxicity: use during pregnancy can cause cleft lip and/or palate and being small for gestational age (5.7)
- Withdrawal of AEDs: withdraw topiramate tablets gradually (5.8)
- Serious skin reactions: If SJS or TEN is suspected, discontinue topiramate tablets (5.9)
- Hyperammonemia/encephalopathy: measure ammonia if encephalopathic symptoms occur (5.10)
- Kidney stones: avoid use with other carbonic anhydrase inhibitors, drugs causing metabolic acidosis, or patients on a ketogenic diet (5.11)
- Hypothermia has been reported with and without hyperammonemia during topiramate treatment with concomitant valproic acid use (5.12)

---------- **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 (7.4)
- Monitor lithium levels if lithium is used with high-dose topiramate tablets (7.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2020

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Topiramate Tablets, USP

21084865

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy Epilepsy

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

1.2 Adjunctive Therapy Epilepsy

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

1.3 Migraine

Topiramate tablets are indicated for the preventive treatment of migraine in patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing in Monotherapy Epilepsy

Adults and Pediatric Patients 10 Years of Age and Older

The recommended dose for topiramate tablets 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

Pediatric Patients 2 to 9 Years of Age

Dosing in patients 2 to 9 years of age is based on weight. During the titration period, the initial dose of topiramate tablet is 25 mg/day 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 clinical response, 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
Up to 11	150	250
12–22	200	300
23–31	200	350
32–38	250	350
Greater than 38	250	400

*Administered in two equally divided doses

2.2 Dosing in Adjunctive Therapy Epilepsy

Adults (17 Years of Age and Older)

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 adults with partial-onset seizures.

Pediatric Patients 2 to 16 Years of Age

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 in 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. The total daily dose should not exceed 400 mg/day.

2.3 Dosing for the Preventive Treatment of Migraine

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

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

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

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

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 patients with renal impairment (creatinine clearance less than 70 mL/min/1.73 m^2), one-half of the usual adult dose of topiramate tablets 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 of the hemodialysis 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 tablets 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 improve 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 postmarketing 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 tablets should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when topiramate tablet is given 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 *[see Warnings and Precautions (5.11)]*. 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 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.

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 adjunctive 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 controlled trials for the preventive treatment of migraine, 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. The most common events included psychomotor slowing, difficulty with concentration/attention, speech disorders/related speech problems, and language problems. The most frequently reported cognitive/neuropsychiatric adverse reaction in pediatric epilepsy patients during adjunctive therapy double-blind studies were somnolence and fatigue. The most frequently reported cognitive/neuropsychiatric adverse reaction 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 patients receiving a fixed dose than in those receiving a titration regimen. 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 13 *[see Clinical Studies (14.2.)]*. 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 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) and for being small for gestational age (SGA). 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 when administering this drug in women of childbearing potential, particularly when topiramate is consider for a non-disease related indication (e.g., migraine) *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*. Topiramate 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 harm to a fetus *[see Use in Specific Populations (8.1)]*.

5.8 Withdrawal of Antiepileptic Drugs

In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including topiramate, 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 is medically required, appropriate monitoring is recommended.

5.9 Serious Skin Reactions

Serious skin reactions (Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)) have been reported in patients receiving topiramate. Topiramate should be discontinued at the first sign of a rash, unless the rash is clearly not drug related. Recurrence of severe signs and symptoms of SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. Inform patients about the signs of serious skin reactions.

5.10 Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid Use)

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 the preventive treatment of migraine trials was 28% 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. In these trials, no cases were reported 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 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.

5.11 Kidney Stones

Topiramate increases the risk of kidney stones. During adjunctive epilepsy trials, the risk for kidney stones in topiramate-treated patients was 1.5%, or approximately 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.

5.12 Hypothermia with Concomitant Valproic Acid Use

Hypothermia, defined as a drop in body core temperature to <35°C (95°F), has been reported in association with topiramate use with concomitant valproic acid 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 serious adverse reactions are discussed in more detail in other sections of the labeling:

- *Acute Myopia and Secondary Angle Closure Glaucoma [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)]*
- *Serious Skin Reactions [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 Use [see Warnings and Precautions (5.12)]*

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

6.1 Clinical Trials Experience

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.

Monotherapy Epilepsy

Adults 16 Years of Age and Older

The most common adverse reactions in the controlled clinical trial (Study 1) that occurred in adults in the 400 mg/day topiramate group and at an incidence higher ($\geq$ 10 %) than in the 50 mg/day group were: paresthesia, weight loss and anorexia (see Table 5).

Approximately 21% of the 159 adult patients in the 400 mg/day group who received topiramate as monotherapy in Study 1 discontinued therapy due to adverse reactions. The most common ($\geq$2% more frequent than low-dose 50 mg/day topiramate) adverse reactions causing discontinuation were difficulty with memory, fatigue, asthenia, insomnia, somnolence, and paresthesia.

Pediatric Patients 6 to 15 Years of Age

The most common adverse reactions in the controlled clinical trial (Study 1) that occurred in pediatric patients in the 400 mg/day topiramate group and at an incidence higher ($\geq$ 10%) than in the 50 mg/day group were fever and weight loss (see Table 5).

Approximately 14% of the 77 pediatric 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 ($\geq$2% more frequent than low-dose 50 mg/day topiramate) adverse reactions resulting in discontinuation were difficulty with concentration/attention, fever, flushing, and confusion.

Table 5 presents the incidence of adverse reactions occurring in at least 3% of adult and pediatric patients treated with 400 mg/day topiramate with greater incidence than 50 mg/day topiramate.

Table 5: Adverse Reactions in the High Dose Group As Compared to the Low Dose Group, in Monotherapy Epilepsy Trial (Study 1) in Adult and Pediatric Patients

	Age Group			
	Pediatric (6 to 15 Years)		Adult (Age ≥ 16 Years)	
	Topiramate Daily Dosage (mg/day)			
	50	400	50	400
	(N=74)	(N=77)	(N=160)	(N=159)
Body System Adverse Reaction	%	%	%	%
Body as a Whole-General Disorders				
Asthenia	0	3	4	6
Fever	1	12		
Leg pain			2	3
Central & Peripheral Nervous System Disorders				
Paresthesia	3	12	21	40
Dizziness			9	12
Ataxia			3	4
Hypoesthesia			4	5
Hypertonia			0	3
Involuntary muscle contractions	0	3		
Vertigo	0	3		
Gastro-Intestinal System Disorders				
Constipation			1	4
Diarrhea	8	9		
Gastritis			0	3
Dry mouth			1	3
Liver and Biliary System Disorders				
Increase in Gamma-GT			1	3
Metabolic and Nutritional Disorders				
Weight loss			7	14
Platelet, Bleeding & Clotting Disorders				
Epistaxis	0	4		
Psychiatric Disorders				
Anorexia			4	14
Anxiety			2	6
Cognitive problems	1	6	2	4
Confusion	0	3		
Depression	0	3	7	9
Difficulty with concentration or attention	7	10	7	8
Difficulty with memory	1	3	6	11
Insomnia			8	9
Decrease in libido			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
Viral infection	3	6	6	8
Respiratory System Disorders				
Bronchitis	1	5	3	4
Upper respiratory tract infection	16	18		
Rhinitis	5	6	2	4
Sinusitis	1	4		
Skin and Appendages Disorders				
Alopecia	1	4	3	4
Pruritus			1	4
Rash	3	4	2	4
Acne			2	3
Special Senses Other, Disorders				
Taste perversion			3	5
Urinary System Disorders				
Cystitis			1	3
Micturition frequency	0	3		
Renal calculus			0	3
Urinary incontinence	1	3		
Vascular (Extracardiac) Disorders				
Flushing	0	5		

Adjunctive Therapy Epilepsy:

Adults 17 Years of Age and Older

In pooled controlled clinical trials in adults with partial-onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, 183 patients received adjunctive therapy with topiramate in doses of 200 to 400 mg/day (recommended dosage range) and 291 patients received placebo. Patients in these trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to topiramate or placebo.

The most common adverse reactions in the controlled clinical trial that occurred in adult patients in the 200-400 mg/day topiramate group with an incidence higher ($\geq$ 10 %) than in the placebo group were: fatigue, psychomotor slowing, speech disorders/related speech problems, somnolence, nervousness, psychomotor slowing, and vision abnormal (Table 6).

Table 6 presents the incidence of adverse reactions occurring in at least 3% of adult patients treated with 200 to 400 mg/day topiramate and was greater than placebo incidence. The incidence of some adverse reactions (e.g., fatigue, dizziness, paresthesia, language problems, psychomotor slowing, depression, difficulty with concentration/attention, mood problems) was dose-related and much greater at higher (up to the recommended topiramate dosing (i.e., 400 mg – 1000 mg daily) compared to the incidence of these adverse reactions at the rec

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.
- Take topiramate tablets 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 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, the risk of stopping 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?

- You should not drink alcohol while taking topiramate tablets. Topiramate tablets and alcohol can affect each other causing side effects such as sleepiness and dizziness.
- Do not drive a car or operate 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 attention, make you feel tired, or cause vomiting. This has happened when topiramate tablets is taken with a medicine called valproic acid (DEPAKENE and DEPAKOTE).
- **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 dizziness, tiredness, and sleepiness.
- **Dizziness or loss of muscle coordination.**
- **Serious skin reactions.** Topiramate tablets may cause a severe rash with blisters and peeling skin, especially around the mouth, nose, eyes, and genitals (Stevens-Johnson syndrome). Topiramate tablets may also cause a rash with blisters and peeling skin over much of the body that may cause death (toxic epidermal necrolysis). Call your healthcare provider right away if you develop a skin rash or blisters.
- **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, or can cause tiredness, confusion, or coma.

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)
- 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. 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. India. at 1-866-604-3268.

How should I store topiramate tablets?

- 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 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 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. You can ask your pharmacist or healthcare provider for information about topiramate tablets that is written for health professionals.

What are the ingredients in topiramate tablets?

Active ingredient: Topiramate USP

Inactive ingredients:

- Tablets - contain hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pre gelatinized 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.

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

Manufactured by: Cipla Ltd., Kurkumbh, India
Manufactured for: Cipla USA, Inc.
10 Independence Boulevard, Suite 300
Warren, NJ 07059
For more information, call 1-866-604-3268.

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

Revised: 6/2020

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 (5.10, 5.12), Clinical Pharmacology (12.3)]*.

7.2 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 carefully closely for the appearance or worsening of metabolic acidosis *[see Clinical Pharmacology (12.3)]*.

7.3 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 should be used with extreme caution if used in combination with alcohol and other CNS depressants.

7.4 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 pattern. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding *[see Clinical Pharmacology (12.3)]*.

7.5 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)]*.

7.6 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 significance 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)]*.

7.7 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)]*.

7.8 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)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to topiramate during pregnancy. 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 exposure 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.aedpregnancyregistry.org/.

Risk Summary

Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero are at a greater risk than infants not exposed to topiramate tablets given alone for oral clefts (and other birth defects) compared with the general population. The prevalence of SGA is greater in infants of women who received higher doses of topiramate during pregnancy. In addition, the prevalence of SGA in infants of women who continued topiramate use until later in pregnancy is higher compared to the prevalence in infants of women who stopped topiramate use before the third trimester.

In multiple animal species, topiramate produced developmental toxicity, including increased incidences of fetal malformations, in the absence of maternal toxicity at clinically relevant doses *[see Animal Data]*.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Consider the benefits and 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 when topiramate is used in the first trimester of pregnancy, all women of childbearing potential should be informed of the potential risk to the fetus from exposure to topiramate. Women who are pregnant should be informed of the available information regarding the relative risks and benefits of topiramate use during pregnancy, and alternative therapeutic options should be considered for these patients.

Labor or Delivery

Although the effect of topiramate 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.

Topiramate tablets 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's ability to tolerate labor. Pregnant women 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 tablets should be monitored for metabolic acidosis because of transfer of topiramate to the fetus and possible occurrence of transient metabolic acidosis following birth.

Based on limited information, topiramate has also been associated with pre-term labor and premature delivery.

Data

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 (0.38%) 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 8.6 (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 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 8 % in the comparison group unexposed to AEDs. The long-term consequences of the SGA findings are not known.

Animal Data

When topiramate (0, 20, 100, or 500 mg/kg/day) was administered to pregnant mice during the period of organogenesis, incidences of fetal malformations (primarily craniofacial defects) were increased at all doses. Fetal body weights and skeletal ossification were reduced at the highest dose tested in conjunction with decreased maternal body weight gain. A no-effect dose for embryofetal developmental toxicity in mice was not identified. The lowest dose tested, which was associated with increased maternal toxicities, is less than the maximum recommended human dose (MRHD) for epilepsy (400 mg/day) or migraine (100 mg/day) on a body surface area (mg/m²) basis.

In pregnant rats administered topiramate (0, 20, 100, and 500 mg/kg/day or 0, 0.2, 2.5, 30, and 400 mg/kg/day) orally during the period of organogenesis, the frequency of fetal malformations (ectrodactyly, micromelia, and anasta) was increased in fetuses at 400 and 500 mg/kg/day. Embryotoxicity (reduced fetal body weights, increased incidences of structural variations) was observed at doses as low as 20 mg/kg/day. Clinical signs of maternal toxicity were seen at 400 mg/kg/day and above, and maternal body weight gain was reduced at doses of 100 mg/kg/day or greater. The no-effect dose (2.5 mg/kg/day) for embryofetal developmental toxicity in rats is less than the MRHD for epilepsy or migraine on a mg/m² basis.

In pregnant rabbits administered topiramate (0, 20, 60, and 180 mg/kg/day or 0, 10, 35, and 120 mg/kg/day) orally during organogenesis, embryofetal mortality was increased at 35 mg/kg/day, and increased incidences of fetal malformations (primarily rib and vertebral malformations) were observed at 120 mg/kg/day. Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg/day and above. The no-effect dose (20 mg/kg/day) for embryofetal developmental toxicity in rabbits is equivalent to the MRHD for epilepsy and approximately 4 times the MRHD for migraine on a mg/m² basis.

When topiramate (0, 0.2, 4, 20, and 100 mg/kg/day or 0, 2, 20, and 200 mg/kg/day) was administered orally to female rats during the latter part of gestation and throughout lactation, offspring exhibited decreased viability and delayed physical development at 200 mg/kg/day and reductions in pre- and/or postweaning body weight gain at 2 mg/kg/day and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg/day or greater. In a rat embryofetal development study which included cross-fostering and assessment of offspring, oral administration of topiramate (0, 0.2, 2.5, 30, and 400 mg/kg) to pregnant animals during the period of organogenesis resulted in delayed physical development in offspring at 400 mg/kg/day and persistent reductions in body weight gain in offspring at 30 mg/kg/day and higher. The no-effect dose (0.2 mg/kg/day) for pre- and postnatal developmental toxicity in rats is less than the MRHD for epilepsy or migraine on a mg/m² basis.

8.2 Lactation

Risk Summary

Topiramate is excreted in human milk *[see Data]*. The effects of topiramate on milk production are unknown. Diarrhea and somnolence have been reported in breastfed infants whose mothers receive topiramate treatment.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for topiramate tablets and any potential adverse effects on the breastfed infant from topiramate tablets or from the underlying maternal condition.

Data

Human Data

Limited data from 5 women with epilepsy treated with topiramate during lactation showed drug levels in milk similar to those in maternal plasma.

8.3 Females and Males of Reproductive Potential

Contraception

Women of childbearing potential who are not planning a pregnancy should use effective contraception because of the risks of oral clefts and SGA *[see Drug Interactions (7.4) and Use in Specific Populations (8.1)]*.

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 doses daily doses of topiramate (50 mg, 100 mg, 200 mg, 2 to 3 mg/kg) has 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/weight retardation, certain clinical chemistry abnormalities, and other adverse reactions/toxicities that occurred with a greater frequency and/or greater severity than had been observed previously from studies in older pediatric patients or adults for various indications.

These strong 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 18%). 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 analysis 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, 12% 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 (5.10)]*.

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 population of epileptic drug-resistant children (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.

Adjunctive Therapy Treatment in Pediatric Patients 12 to 17 Years of Age

Safety and effectiveness of topiramate for the preventive treatment of migraine was studied in 5 double-blind, randomized, placebo-controlled, parallel-group trials in a total of 219 pediatric patients (ages 12 to 17 years) 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 (all topiramate-treated patients received 2 mg/kg/day), a flexible dose study in 54 pediatric patients 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 for the prevention treatment of migraine 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 the preventive treatment of migraine in pediatric patients 12 to 17 years of age is demonstrated for a 100 mg daily dose in Study 13 *[see Clinical Studies (14.3)]*. Efficacy of topiramate (2 to 3 mg/kg/day) for the preventive treatment of migraine was not demonstrated in a fixed dose study in a total of 157 pediatric patients (6 to 16 years of age) that included treatment of 67 pediatric patients (12 to 16 years of age) for 26 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 reaction in topiramate-treated patients was upper respiratory tract infection, 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 Clinical Trials Experience (6.1)]*.

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)]*.

Preventive Treatment of Migraine 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 preventive treatment of migraine.

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) than in older patients (12 to 17 years of age) *[see Warnings and Precautions (5.6)]*.

Juvenile Animal Studies

When topiramate (0, 30, 90, and 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. The no-effect dose (30 mg/kg/day) for adverse developmental effects is approximately 2 times the maximum recommended pediatric dose (9 mg/kg/day) on a body surface area (mg/m²) basis.

8.5 Geriatric Use

In clinical trials, 3% of patients were over age 60. No age-related differences in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with age-related renal impairment *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

The clearance of topiramate is reduced in patients with moderate (creatinine clearance 30 to 69 mL/min/1.73 m²) and severe (creatinine clearance <30 mL/min/1.73 m²) 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)]*.

10 OVERDOSAGE

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, impaired mentation, 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 overdoses involving topiramate.

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

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

In the event of overdose, topiramate should be discontinued and general supportive treatment given until clinical toxicity has been diminished or resolved. 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 25 mg, 50 mg, and 100 mg circular tablets and 200 mg capsule shaped tablets for oral administration.

Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and which included crystal at ambient temperature, and molecular weight is 339.36. Topiramate is 2,3-4,5-Di-*O*-isopropylidene-2-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 and preventive migraine effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and the preventive treatment of migraine. Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant concentrations, blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyric acid 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 pediatric patients treated with placebo in controlled trials for the preventive treatment of migraine. The most notable changes were SBP and DBP increases or decreases ≥20 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 daily dose. Significant clinical chemistry or 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 and is 23 to 29 L/kg. The fraction bound decreases with increasing topiramate concentration.

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 include oxamic acid hydroxylamine, 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 clearance (CL/F) is approximately 20 to 30 mL/min in adults following oral administration.

Specific Populations

Renal Impairment

The clearance of topiramate was reduced by 42% in subjects with moderate renal impairment (creatinine clearance 30 to 69 mL/min/1.73 m²) and by 54% in subjects with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²) compared to subjects with normal renal function (creatinine clearance >70 mL/min/1.73 m²) *[see Dosage and Administration (2.4) and (2.5)]*.

Hemodialysis

Topiramate is cleared by hemodialysis. Using a high-efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate plasma clearance was 120 mL/min with blood flow rate of 400 mL/min and dialyzer at 400 mL/min. This high clearance (compared to 20 to 30 mL/min total oral clearance in healthy subjects) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period *[see Dosage and Administration (2.6), Use in Specific Populations (8.7)]*.

Hepatic Impairment

Plasma clearance of topiramate decreased a mean of 26% in patients with moderate to severe hepatic impairment.

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 for the same dose. Therefore, topiramate clearance is decreased in the elderly only to the extent that renal function is reduced *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

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

Pediatric Pharmacokinetics

Pharmacokinetics of topiramate were evaluated in patients age 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 included data from 1217 subjects including 258 pediatric patients age 2 to <16 years (96 pediatric patients <10 years of age).

Pediatric patients, with adjunctive treatment, had a 60% higher topiramate oral clearance (CL/F) when compared to patients on monotherapy, presumably because of increased clearance from concomitant enzyme-inducing antiepileptic drugs. In comparison, topiramate clearance was about 5 times higher in patients than in adults and in young pediatric patients (down to 2 years) than in older pediatric patients. Consequently, the plasma drug concentration for a given topiramate 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 Interactions

In vitro studies indicate that topiramate does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP3A4, or CYP3A4/5 isozymes. *In vitro* studies indicate that topiramate is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4.

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 10, the second column (AED concentration) describes what happens to the concentration of the co-administered 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 when compared to topiramate tablets given alone.

Table 10: Summary of AED Interactions with Topiramate

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase*	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide†	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

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

† = Is not administered but is an active metabolite of carbamazepine.

NC = Less than 10% change in plasma concentration.

AED = Antiepileptic drug.

NE = Not Evaluated.

TPM = Topiramate

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, given in the absence of other medications at doses of 50 to 200 mg/day, was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, topiramate (50 mg/day to 800 mg/day) did not significantly affect exposure to NET and 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 *[see Drug interactions (7.4)]*.

Digoxin

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

Lithium/Hydrochlorothiazide

A drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of hydrochlorothiazide (HCT) (25 mg every 24 hours) and topiramate (96 mg every 12 hours) 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 steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin

A drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin (500 mg every 12 hours) and topiramate (256 mg every 12 hours) when topiramate was given alone and when metformin and topiramate (100 mg every 12 hours) were given simultaneously. The results of this study indicated that the mean metformin C_{max} and $AUC_{(0-12)}$ 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. Patients taking metformin with topiramate should be monitored to be reduced when administered with metformin. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear.

Pioglitazone

A drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics