Topiramate is indicated for:

- Epilepsy  adjunctive therapy: adults with partial onset seizures or with primary generalized tonic-clonic seizures (2.1)
- Epilepsy  monotherapy: adults and pediatric patients (6-16 years old) with partial onset seizures or with primary generalized tonic-clonic seizures (2.1)

Dosage and Administration:

1. Epilepsy  monotherapy: adults and pediatric patients (6-16 years old) with partial onset seizures or with primary generalized tonic-clonic seizures (2.1)
   
   1.1 Initial Dose
   
   - Start with 25 mg/day administered nightly for the first week
   - The dosage should be increased to 50 mg/day (administered in two divided doses) for week 2
   - The dosage should be increased to 100 mg/day (administered in two divided doses) for week 3, and should be increased at weekly intervals of 25 to 50 mg, up to 200 mg/day (administered in two divided doses)

2. Epilepsy  adjunctive therapy: adults with partial onset seizures or with primary generalized tonic-clonic seizures (2.1)
   
   2.1 Initial Dose
   
   - Start with 25 mg/day administered nightly for the first week
   - The dosage should be increased to 50 mg/day (administered in two divided doses) for week 2
   - The dosage should be increased to 100 mg/day (administered in two divided doses) for week 3, and should be increased at weekly intervals of 25 to 50 mg, up to 200 mg/day (administered in two divided doses)

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.

HIGHLIGHTS OF PRESCRIBING INFORMATION

DOSAGE FORMS AND STRENGTHS

- Tablets: 25 mg, 50 mg, and 100 mg

CONTRAINDICATIONS

- Patients with a history of idiosyncratic reaction to topiramate
- Patients with a history of a general anesthetic reaction to topiramate
- Patients with a history of a generalized anesthetic reaction to topiramate

WARNINGS AND PRECAUTIONS

- Use in Acute and Refractory Angle-Closure Glaucoma: Topiramate should not be used in patients with acute angle-closure glaucoma
- Use in Inborn Errors of Metabolism: Topiramate should not be used in patients with inborn errors of metabolism
- Use in Cataracts: Topiramate should not be used in patients with cataracts
- Use in Renal Failure: Topiramate should not be used in patients with renal failure
- Use in Hepatic Failure: Topiramate should not be used in patients with hepatic failure
- Use in Pediatric Patients: Topiramate should not be used in pediatric patients

ADDITIONAL REGARDING USE IN SPECIFIC POPULATIONS

- Pregnancy: Increased risk of cleft lip and/or palate. (8.1)
- Breastfeeding: Decreased milk production. (8.3)

DRUG INTERACTIONS

- Other carbonic anhydrase inhibitors: Monitor the patient for the appearance or worsening of metabolic acidosis
- Oral contraceptives: Decreased contraceptive efficacy and increased breakthrough bleeding should be considered
- Metformin: Increased risk of lactic acidosis
- Phenytoin: Increased risk of phenytoin-induced hypocalcemia
- Sulfa drugs: Increased risk of acetonemia
- Lithium: Increased risk of lithium-induced hypokalemia
- Phenobarbital: Increased risk of phenobarbital-induced hypocalcemia
- Primidone: Increased risk of primidone-induced hypocalcemia
- Carbamazepine: Increased risk of carbamazepine-induced hypocalcemia

ADVERSE REACTIONS

- CNS: Headache, dizziness, somnolence, insomnia, paresthesias, fatigue, lethargy, memory impairment, confusion, speech disorder, dysarthria, tremor, hyperesthesia, decreased vision, visual disturbance, visual acuity decrease, diplopia, nystagmus, pinnalgia, lid twitching, eye pain
- GI: Nausea, vomiting, constipation, diarrhea, abdominal pain, anorexia, weight decrease, dysphagia, xerostomia, dry mouth, decreased salivary flow, oligohidrosis, hyperthermia
- Skin: Rash, Pruritus, alopecia, alopecia areata, paronychia, decreased sweating, increased sweating, dermatitis, urticaria, angioedema, photosensitivity, sweating, sweating disorders, sweating disorders associated with or without hyperthermia during exercise treatment, sweating, hyperhidrosis, hyperhidrosis associated with exercise treatment
- Metabolic: Hyperammonemia, hypokalemia, hypocalcemia, hypernatremia, increased blood urea nitrogen, increased serum creatinine, decreased serum creatinine, decreased serum sodium, decreased serum potassium, decreased serum chloride, increased serum creatinine, increased serum urea nitrogen
- Other: Cerebrovascular accident, chest pain, abdominal pain, decreased appetite, decreased water intake, increased thirst, increased liver enzyme levels, increased myoglobin, increased muscle mass, increased weight, increased height, increased blood pressure, increased pulse rate, increased respiratory rate, increased body temperature, increased heart rate, increased body weight, increased body mass index, increased waist circumference, increased height, increased body mass index, increased waist circumference

FULL PRESCRIBING INFORMATION: CONTENTS* 1 INDICATIONS AND USAGE 1.1 Adjunctive Therapy for Epilepsy 1.2 Adjunctive Therapy for Seizure 2 DOSAGE AND ADMINISTRATION 2.1 Epilepsy 2.1.1 Epilepsy Monotherapy 2.1.1.1 Initial Dose 2.1.1.2 Dose Titration 2.1.1.3 Dose Increment 2.1.1.4 Maximum Daily Dose 2.1.1.5 Other Use in Specific Populations 2.1.1.5.1 Pregnancy 2.1.1.5.2 Labor and Delivery 3 DOSAGE FORMS AND STRENGTHS 4 CONTRAINDICATIONS 4.1 Use in Acute and Refractory Angle-Closure Glaucoma 4.2 Use in Inborn Errors of Metabolism 4.3 Use in Cataracts 4.4 Use in Renal Failure 4.5 Use in Hepatic Failure 4.6 Use in Pediatric Patients 5 WARNINGS AND PRECAUTIONS 5.1 Use in Acute and Refractory Angle-Closure Glaucoma 5.2 Use in Inborn Errors of Metabolism 5.3 Use in Cataracts 5.4 Use in Renal Failure 5.5 Use in Hepatic Failure 5.6 Use in Pediatric Patients 6 ADVERSE REACTIONS 6.1 CNS 6.2 GI 6.3 Skin 6.4 Metabolic 6.5 Other 7 DRUG INTERACTIONS 8 ADDITIONAL REGARDING USE IN SPECIFIC POPULATIONS 8.1 Pregnancy 8.2 Labor and Delivery Revised: 10/2017
**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 seizures or primary generalized tonic-clonic seizures, based on a pharmacometric bridging approach [see Clinical Studies (14.1)].

**1.2 Adjunctive Therapy Epilepsy**

Topiramate tablets, USP are indicated as adjunct therapy for adults and pediatric patients aged 2 to 16 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome [see Clinical Studies (14.2)].

**2 DOSAGE AND ADMINISTRATION**

**2.1 Epilepsy**

It is necessary to monitor topiramate plasma concentration to optimize topiramate tablets therapy. Observations, the addition of other AEDs to phenytoin may require adjustment of the dose of phenytoin to achieve optimal clinical outcome. Additions of withdrawal of phenytoin and carbamazepine during adjunct therapy with topiramate tablets may require adjustment of the dose of the other AEDs.

Because of the latter note, tablets should not be broken. Topiramate tablets can be taken without regard to meals.

**2.2 Adjunctive Therapy**

**2.2.1 Adult and Pediatric Patients 17 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. Approximately 58% of patients randomized to 400 mg/day dose were converted to monotherapy from a previous regimen of other anticonvulsant drugs. The actual dose that the monotherapy controlled trial was 275 mg/day. The dose should be achieved by titration according to the following schedule (Table 1).

**2.2.2 pediatric Patients Ages 2 to <10 Years**

During the titration period, the initial dose of topiramate tablets should be 5 mg/kg/day (25 mg twice daily) in the first week. Dosage should be increased by 25% at the end of each week in this titration period. The maximum maintenance dose for each range of body weight is 300 mg/day (25 mg/kg/day). The daily dose should not exceed the maximum maintenance dose for each range of body weight (Table 2).

**2.2.3 Children Ages 2 to <10 Years**

Topiramate tablets can be taken without regard to meals. Because of the bitter taste, tablets should not be broken. Tablets should be given at bedtime to minimize gastrointestinal complaints. It is not necessary to monitor topiramate plasma concentrations to optimize topiramate tablets therapy.

**3 DOSAGE FORMS AND STRENGTHS**

Topiramate tablets, USP are available in the following strengths:

- 25 mg white, square, scored tablets: NDC 0078-1503-01
- 50 mg white, square, scored tablets: NDC 0078-1504-01
- 100 mg white, square, scored tablets: NDC 0078-1505-01
- 200 mg white, square, scored tablets: NDC 0078-1506-01
- 300 mg white, square, scored tablets: NDC 0078-1507-01
- 400 mg white, square, scored tablets: NDC 0078-1508-01

Topiramate tablets, USP are indicated as initial monotherapy in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome [see Clinical Studies (14.1)].

**14 CLINICAL STUDIES**

**14.1 Monotherapy Epilepsy Controlled Trial**

The recommended daily dose of topiramate tablets in adults with partial onset or primary generalized tonic-clonic seizures was based on a pharmacometric bridging approach [see Clinical Studies (14.1)].

**14.2 Adjunctive Therapy Epilepsy Controlled Trials**

Dosing in patients 2 to <10 years is based on weight. During the titration period, the initial dose of topiramate tablets should be 12.5 mg/kg/day (5 mg twice daily) in the first week. Dosage should be increased by 25% at the end of each week in this titration period. The maximum maintenance dose for each range of body weight (Table 2).
Substantially by age (5 to 100 years) in the clinical trials analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of behavior Beyond 24 weeks could not be assessed. Most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because the increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about other drugs that predispose patients to behavior-related disorders, these drugs include, but are not limited to, other antiepileptic drugs and drugs with antihistaminic action.

4.3 Metabolic Acidosis

Hyperchloremic, normo- or metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acidosis is caused by reduced bicarbonate levels due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. The degree of hypochloremia is usually mild in incidence (average decrease of 1 mEq/L at daily doses greater than 5 mg/kg/day). An increase in urinary pCO2 has been observed in patients who experience severe decrements in bicarbonate below 10 mEq/L. Conditions other than topiramate can be excluded (such as acute or chronic respiratory disorders, severe dehydration, diabetic ketoacidosis, or metabolic encephalopathies) before metabolic acidosis is attributable to topiramate.

Topiramate use has been associated with hypochloremia and metabolic acidosis which may be sufficient to cause mild to moderate symptoms. Such symptoms include nausea, vomiting, fatigue, muscle cramps, and anorexia. Hypocloremic metabolic acidosis has been noted in patients with status epilepticus treated with a sodium channel blocker, which is associated with a high incidence of metabolic acidosis.

Measurement of Serum Bicarbonate in Epilepsy Patients

Measurement of serum bicarbonate is recommended in patients who are supine and have normal reference ranges for serum bicarbonate. Serum bicarbonate concentrations below 20 mEq/L indicate metabolic acidosis. Laboratory data from the post-marketing period have revealed that the incidence of metabolic acidosis, defined as a serum bicarbonate level <17 mEq/L, was 50% for 15 mg/kg/day, 45% for 25 mg/kg/day, 50% for 15 mg/kg/day, and 45% for 25 mg/kg/day. The incidence of markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in the adjunctive therapy trials was 5% for placebo. The incidence of metabolic acidosis in pediatric patients (≤15 years of age) with refractory partial onset seizures was 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 the pediatric trials was 0% for placebo, 30% for 5 mg/kg/day, 40% for 15 mg/kg/day, and 45% for 25 mg/kg/day. The incidence of metabolic acidosis (defined as a serum bicarbonate level <20 mEq/L) was 0% for placebo, 30% for 5 mg/kg/day, 40% for 15 mg/kg/day, and 45% for 25 mg/kg/day. The incidence of markedly abnormal changes (i.e., absolute value >17 mEq/L and >5 mEq/L decrease from pretreatment) in the pediatric trials was 0% for placebo, 30% for 5 mg/kg/day, 40% for 15 mg/kg/day, and 45% for 25 mg/kg/day.

In children aged 3 to 12 years, the incidence of metabolic acidosis in placebo-controlled trials was 0% for 5 mg/kg/day, 10% for 15 mg/kg/day, and 15% for 25 mg/kg/day. The incidence of metabolic acidosis in the pediatric controlled trials for monotherapy was 14% for 50 mg/day and 25% for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in the pediatric trials was 0% for placebo, 30% for 5 mg/kg/day, 40% for 15 mg/kg/day, and 45% for 25 mg/kg/day. The incidence of metabolic acidosis (defined as a serum bicarbonate level <20 mEq/L) was 0% for placebo, 30% for 5 mg/kg/day, 40% for 15 mg/kg/day, and 45% for 25 mg/kg/day. The incidence of markedly abnormal changes (i.e., absolute value >17 mEq/L and >5 mEq/L decrease from pretreatment) in the pediatric trials was 0% for placebo, 30% for 5 mg/kg/day, 40% for 15 mg/kg/day, and 45% for 25 mg/kg/day.

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

Anyone considering prescribing topiramate or any other AED must balance the risks of suicidal thoughts or behavior with the risks 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 is likely to be related to the illness being treated.

Parents, caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised that the need to be alert for the emergence of such behavior or for any symptoms of depression, any unusual change in behavior or worsening of behavior or mood should be reported to the prescriber immediately.

5.5 Cognitive/Neuropsychiatric Adverse Reactions

Adverse reactions most often associated with the use of topiramate were related to the central nervous system (CNS). The most frequent of these were dizziness, somnolence, and ataxia. Other CNS events commonly observed with topiramate in the add-on epilepsy population included headache, dizziness, somnolence, and anxiety.

5.6 Cognitive/Neuropsychiatric Adverse Reactions

Additional nonspecific CNS events commonly observed with topiramate in the add-on epilepsy population included headache and anxiety.

5.7 Cognitive/Neuropsychiatric Adverse Reactions

Topiramate treatment has produced histological abnormalities in the cortex of some human brains examined post-mortem. These abnormalities include gliosis, neuronal loss, changes in the neuronal and glial cytoskeleton, and synaptic loss. The abnormalities were more severe in patients with a history of seizures or other neurological disorders. The significance of these abnormalities is unknown.

Topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk. If topiramate is used during pregnancy, or if the onset of pregnancy occurs within 3 months of the end of topiramate treatment,出生缺陷 registry data indicate an increased risk of cleft lip with or without cleft palate in the offspring of women exposed to topiramate during pregnancy. Routine newborn screening programs should be arranged for infants born to women who have been treated with topiramate during pregnancy. The adverse effect of topiramate on the developing fetus is not confined to cleft palate. Clinical and post-mortem studies have demonstrated adverse effects on CNS development that are not limited to the facial region.

5.8 Withdrawal of Antiepileptic Drugs (AEDs)

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. In about 1 out of 5 patients not treated with AEDs, seizures recur when the medication is discontinued. These patients should be monitored carefully during withdrawal. The risk of potential withdrawal seizures increases with the length of treatment and the dose of the medication. 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. In about 1 out of 5 patients not treated with AEDs, seizures recur when the medication is discontinued. These patients should be monitored carefully during withdrawal. The risk of potential withdrawal seizures increases with the length of treatment and the dose of the medication.

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

<table>
<thead>
<tr>
<th>Table 4. Risk by Indication for Antiepileptic Drugs in Pooled Analysis</th>
<th>Placebo Patients</th>
<th>Drug Patients with Events per 1000 Patients</th>
<th>Relative Risk Increase/Decrease in Events per 1000 Patients</th>
<th>Relative Risk Increase/Decrease in Patients with Events per 1000 Patients</th>
<th>Risk Difference/Increase/Decrease in Placebo Patients</th>
<th>Risk Difference/Increase/Decrease in Patients with Events per 1000 Patients</th>
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</thead>
<tbody>
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<td>2.4</td>
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<td>Psychiatric</td>
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<td>8.5</td>
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<td>2.9</td>
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<tr>
<td>Other</td>
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<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
</tr>
</tbody>
</table>

5.9 Stomach Unexplained Death in Epilepsy (SUDEP)

The majority of cognitive-related adverse reactions were mild to moderate in severity, and they frequently occurred even in patients with normal renal function or dialysis. These adverse reactions were dose-related and higher initial doses were associated with higher incidences of these reactions. Many of these reactions contributed to withdrawal from treatment (see Adverse Reactions). In the add-on epilepsy controlled trials (using rapid titration such as 100 to 200 mg weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reaction was 62% for 200 mg/day, 61% for 400 mg/day, 52% for 600 mg/day, 50% for 800 to 1000 mg/day, and 18% for placebo. These dose-related adverse reactions began at a similar frequency in the titration and the maintenance phase, although more patients in the maintenance phase experienced these reactions. For example, in pediatric epilepsy patients, 6% experienced one or more cognitive-related adverse reactions in the titration phase and 26% experienced one or more cognitive-related adverse reactions in the maintenance phase. For the monotherapy epilepsy trial, the proportion of patients who experienced one or more cognitive-related adverse reactions was 26% for 50 mg/day and 26% for 400 mg/day.

5.10 Hypersalivation and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use)

Topiramate has been associated with the development of hypertrophic cardiomyopathy and valvular heart disease. The risk of these events is increased in patients with pre-existing cardiovascular disease or in patients who are treated with concomitant valproic acid and topiramate. In addition, patients with pre-existing hypertension are at risk for the development of hypertensive crisis. In patients with pre-existing hypertension, the risk of hypertensive crisis is increased with concomitant valproic acid and topiramate.

Concomitant administration of topiramate and valproic acid (VPA) has been associated with an increased risk of serious or life-threatening adverse events, including death. In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including topiramate, should be used in combination with concomitant valproic acid with caution and close monitoring. In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including topiramate, should be used in combination with concomitant valproic acid with caution and close monitoring. In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including topiramate, should be used in combination with concomitant valproic acid with caution and close monitoring.
Hyperammonemia, which is due to decreased urea cycle capacity and increased hepatic neurotransmitter activity, may be an increased risk for hyperammonemia with or without nephropathy. Administration of topiramate to renal failure patients was reported in clinical studies of adults with chronic kidney disease (e.g., diabetic nephropathy) and in pediatric patients with kidney failure due to congenital anomalies. Changes in several clinical laboratory analytes (i.e., increased creatinine, BUN, alkaline phosphatase, and decreased serum bicarbonate and increased serum chloride) are associated with topiramate use and can occur in patients with normal baseline laboratory values or in those with pre-existing abnormalities. A dose-related decrease in urine volume and an increase in serum chloride has been observed in pediatric patients with kidney failure. A dose-related decrease in urine volume and an increase in serum chloride has been observed in pediatric patients with kidney failure. Measurement of baseline and periodic serum bicarbonate and serum chloride is recommended for patients with kidney failure. Measurement of baseline and periodic serum bicarbonate and serum chloride is recommended for patients with kidney failure.

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condition that increased the risk for bleeding were often present, or were taking other drugs that cause thrombocytopenia (either anticoagulant drugs or affected platelet function or coagulation [e.g., aspirin, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, or warfarin or other anticoagulants]).


drug interactions

Pediatric Patients 6 to <16 Years of Age

The adverse reaction in the controlled trial that occurred most commonly in pediatric patients in the 400 mg/day group and at an incidence higher (≥ 5%) than in the 50 mg/day group was fever. The other common (≥ 2% more frequent than low-dose 50 mg/day topiramate) adverse reactions resulting in discontinuation in this trial were difficulty with memory, fatigue, somnolence, and headache. 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 resulting in discontinuation in this trial were difficulty with memory, fatigue, somnolence, and headache.

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 (≥ 2% more frequent than low-dose 50 mg/day topiramate) adverse reactions resulting in discontinuation in this trial were difficulty with memory, fatigue, somnolence, and headache.

Approximately 13% of the 404 pediatric patients who received topiramate at dosages up to 30 mg/kg/day discontinued due to adverse reactions. This rate appeared to increase at dosages above 400 mg/day. Adverse reactions associated with discontinuing therapy included somnolence, weight decrease, and paresthesia.

The adverse reactions in the controlled clinical trial that occurred most commonly in adults in the 400 mg/day group were: paresthesia, weight decrease, anorexia, somnolence, and difficulty with memory (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 and occurring with greater incidence determined to be adverse reactions in the controlled clinical trial.

Approximately 11% of the 1757 adults with epilepsy who received topiramate 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: fatigue, somnolence, anorexia, difficulty with memory, cognitive problems, infection, dizziness, and pneumonia (see Table 5). Dose-related adverse reactions at dosages of 200 to 1,000 mg/day are shown in Table 8.

In controlled clinical trials in adults, 11% of patients receiving topiramate 200 to 400 mg/day as monotherapy in the controlled clinical trial discontinued therapy due to adverse reactions. This rate appeared to increase at dosages above 400 mg/day. Adverse reactions associated with discontinuing therapy included somnolence, anxiety, dizziness, confusion, ataxia, speech disorders and related speech problems, language problems, psychotic disorders, depression, vomiting, and paresthesia (see Table 8). Adverse reactions associated with discontinuing therapy included somnolence, weight decrease, anorexia, difficulty with memory, cognitive problems, infection, dizziness, and pneumonia (see Table 5). 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 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, difficulty with memory, cognitive problems, infection, dizziness, and pneumonia (see Table 8).

In controlled clinical trials in adults, 11% of patients receiving topiramate 200 to 400 mg/day as monotherapy in the controlled clinical trial discontinued therapy due to adverse reactions. This rate appeared to increase at dosages above 400 mg/day. Adverse reactions associated with discontinuing therapy included somnolence, anxiety, dizziness, confusion, ataxia, speech disorders and related speech problems, language problems, psychotic disorders, depression, vomiting, and paresthesia (see Table 8). Adverse reactions associated with discontinuing therapy included somnolence, weight decrease, anorexia, difficulty with memory, cognitive problems, infection, dizziness, and pneumonia (see Table 5). Dose-related adverse reactions at dosages of 200 to 1,000 mg/day are shown in Table 8.
pediatric patients treated with 5 to 9 mg/kg topiramate in controlled trials and that was numerically greater than the incidence in patients treated with placebo.

The prescriber should be aware that these data were obtained when topiramate 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 trials. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, doses, or investigator. 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, rash, pain, confusion, agitation, coughing, fever, chills, vomiting, muscle weakness, insomnia, personality disorder, dysmenorrhea, upper respiratory tract infections, and eye pain.

Table 6: Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Add-On Epilepsy Trials in Adults: Other Incidence at ≥ 1% in Any Topiramate Treatment Group and Greater Than the Incidence in Placebo-Treated Patients

<p>| Table 6: Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Add-On Epilepsy Trials in Adults: Other Incidence at ≥ 1% in Any Topiramate Treatment Group and Greater Than the Incidence in Placebo-Treated Patients |</p>
<table>
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<tr>
<th>Study Number</th>
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<th>Placebo (%)</th>
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Incidence in Study 119: Add-On Therapy - Adults with Partial Onset Seizures

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

The most commonly observed adverse reaction associated with the use of topiramate that was seen at an incidence of 5% or more in the placebo group was somnolence, nervousness, confusion, difficulty with concentration/attention, and fatigue (see Table 7). Because these topiramate treatment difference incidence (topiramate % - 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 3. Incidence of Treatment-Emergent Adverse Reactions Observed During All Epilepsy Clinical Trials

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The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was determined. The prevalence of oral clefts in infants exposed to a reference AED was 0.39%. In infants of mothers without epilepsy or pregnancies, the risk of oral clefts was increased. Data from the NAAED Pregnancy Registry (425 prospective topiramate monotherapy-exposed pregnancies) indicate an increased risk of oral clefts in infants exposed during the first trimester of pregnancy.

Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries suggest an increased risk of oral clefts in infants exposed during the first trimester of pregnancy. The prevalence of oral clefts among topiramate-exposed infants was 2.8% compared to a prevalence of 0.8% for infants exposed to a reference AED. Infants of mothers taking topiramate and at least one other AED had a prevalence of 7.2%.

Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries suggest an increased risk of oral clefts in infants exposed during the first trimester of pregnancy. The prevalence of oral clefts among topiramate-exposed infants was 2.8% compared to a prevalence of 0.8% for infants exposed to a reference AED. Infants of mothers taking topiramate and at least one other AED had a prevalence of 7.2%.

Additional interactions have been identified with other AEDs, including levetiracetam and valproic acid. Concomitant administration of levetiracetam and topiramate has been associated with a decrease in levetiracetam plasma concentrations. In patients taking valproic acid, the potential for drug-drug interactions with topiramate should be considered.
Data from pregnancy registries indicate that infants exposed to topiramate during pregnancy have a higher incidence of cleft lip and/or cleft palate (oral clefts) than infants of women not exposed to topiramate. The incidence of oral clefts was 16 times higher than the background rate in the UK, which is approximately 0.2%. This increased incidence was observed in infants born to women who took topiramate, even at lower doses. The risk of oral clefts is not dose-related and is present even at lower doses of topiramate. Women of Childbearing Potential should be informed of the potential risk and advised to discontinue treatment as early in pregnancy as possible.

8.9 Women of Childbearing Potential

There is no evidence from animal studies that topiramate has a teratogenic potential. However, the potential for topiramate to cause harm to the fetus is unknown. It is not known whether topiramate crosses the placenta, and there is no information on whether topiramate accumulates in the fetus. Therefore, topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.10 Labor and Delivery

Topiramate treatment can cause metabolic acidosis, which can lead to fetal acidosis. Topiramate treatment during pregnancy can cause increased incidence of decreased potassium, BUN, and protein. In a post-marketing study, the mortality rate among infants born to mothers treated with topiramate was higher than the background mortality rate. Therefore, topiramate treatment during pregnancy should be avoided if possible.

8.11 Neonates

Topiramate treatment can cause metabolic acidosis, which can lead to fetal acidosis. Topiramate treatment during pregnancy can cause increased incidence of decreased potassium, BUN, and protein. In a post-marketing study, the mortality rate among infants born to mothers treated with topiramate was higher than the background mortality rate. Therefore, topiramate treatment during pregnancy should be avoided if possible.

8.12 Pediatric Use

Topiramate treatment can cause metabolic acidosis, which can lead to fetal acidosis. Topiramate treatment during pregnancy can cause increased incidence of decreased potassium, BUN, and protein. In a post-marketing study, the mortality rate among infants born to mothers treated with topiramate was higher than the background mortality rate. Therefore, topiramate treatment during pregnancy should be avoided if possible.

8.2 Labor and Delivery

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8.3 Neonatal and Infant Exposures

Topiramate treatment can cause metabolic acidosis, which can lead to fetal acidosis. Topiramate treatment during pregnancy can cause increased incidence of decreased potassium, BUN, and protein. In a post-marketing study, the mortality rate among infants born to mothers treated with topiramate was higher than the background mortality rate. Therefore, topiramate treatment during pregnancy should be avoided if possible.

8.4 Pediatric Use

Topiramate treatment can cause metabolic acidosis, which can lead to fetal acidosis. Topiramate treatment during pregnancy can cause increased incidence of decreased potassium, BUN, and protein. In a post-marketing study, the mortality rate among infants born to mothers treated with topiramate was higher than the background mortality rate. Therefore, topiramate treatment during pregnancy should be avoided if possible.

8.5 Drug Interactions

Topiramate treatment can cause metabolic acidosis, which can lead to fetal acidosis. Topiramate treatment during pregnancy can cause increased incidence of decreased potassium, BUN, and protein. In a post-marketing study, the mortality rate among infants born to mothers treated with topiramate was higher than the background mortality rate. Therefore, topiramate treatment during pregnancy should be avoided if possible.

8.6 Human Milk Feeding

Topiramate treatment can cause metabolic acidosis, which can lead to fetal acidosis. Topiramate treatment during pregnancy can cause increased incidence of decreased potassium, BUN, and protein. In a post-marketing study, the mortality rate among infants born to mothers treated with topiramate was higher than the background mortality rate. Therefore, topiramate treatment during pregnancy should be avoided if possible.
Overdosage

Overdosage of topiramate has been reported. Signs and symptoms included dizziness, drowsiness, speech disturbance, blurred vision, diplopia, confusion, impaired motor and coordination skills, ataxia, tremor, nystagmus, diplopia, and other visual disturbances. The symptoms were generally transient and reversible with discontinuation of the drug. No fatalities have been reported. No specific treatment for overdose is known. In the event of an overdose, general supportive measures should be employed to maintain adequate respiratory and cardiovascular function. Administration of an activated charcoal suspension may be useful. Decontamination with a cathartic should be avoided because of the risk of intestinal perforation. The use of the drug for at least 2 weeks prior to overdose can complicate the diagnosis of metabolic acidosis, since the plasma concentrations of organic acids are increased. Topiramate is a metabolic inhibitor and the degree of acidosis is dependent on the plasma concentration. Third-degree burns have occurred in 2 dogs that ingested topiramate solution from an esophageal catheter. In patients treated with topiramate and frozen oral fluid, increased AST, ALT, and ALP have been observed. The plasma concentration is reduced. In overdose, the plasma concentration is reduced.
Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 males, 12 females) did not result in clinically significant changes in pharmacokinetics. Similarly, in 34 healthy volunteers (17 males, 17 females) treated with topiramate (200 mg/day) for 14 days, no clinically significant changes in pharmacokinetics were observed.

Propranolol co-administration with topiramate resulted in a 48% decrease in mean plasma concentrations of propranolol, without any clinically significant changes in pharmacokinetics of topiramate.

Risperidone, when co-administered with topiramate (400 mg/day), resulted in a 14% increase in Cmax and a 33% decrease in AUC of risperidone.

Co-administration of topiramate 400 mg/day with risperidone resulted in a 14% increase in Cmax of risperidone and a 33% decrease in AUC of topiramate; therefore, this interaction is not likely to be of clinical significance.

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

Pharmacokinetics of topiramate were evaluated in patients age 2 to <16 years. Patients received either topiramate tablets or topiramate solution (5 mg/mL). The results of this study indicated that topiramate Cmax and AUC were independent of dose and sex, with no age-related differences observed.

Table 13: Summary of AED Interactions with Topiramate

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<tr>
<td>13% decrease</td>
<td>NE</td>
</tr>
</tbody>
</table>

The clinical relevance of this observation has not been established.
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 (Study YP), comparing a single dosage of topiramate and placebo (see Table 15). The primary efficacy assessment was 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 100 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 pharmacodynamic approach using data from controlled epilepsy trials described in labeling. This approach consisted of first showing a similar exposure-response relationship between pediatric patients 2 to 12 years of age and adults when topiramate was given as adjunctive therapy. The next step was to determine if the therapeutic ratio (i.e., the ratio of the dose at which the response is judged to be adequate to the dose at which intolerable adverse effects occur) was maintained in pediatric patients. Finally, the time to achieve steady-state exposures in children 2 to 12 years of age was demonstrated. The adult comparative trial was performed in double-blind, parallel-group, placebo-controlled fashion, with the dosing regimen established in the 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 topiramate. In each 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 were randomly assigned to each dose and the actual mean and median doses in the stabilization period are presented in Table 15.

14.3 Monotherapy Epilepsy Controlled Trial

Patients with Partial Onset or 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 or primary generalized tonic-clonic seizures was established in a multicenter, randomized, double-blind, parallel-group trial.

The trial was conducted in 147 patients diagnosed with epilepsy 8 to 83 years of age who had had 1 or 2 well-documented seizures during the 3-month retrospective base line period who then entered the study and received topiramate 25 mg/day for 7 days in an open-label fashion. Forty-nine percent of patients had 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 this study, randomization was stratified by geographic region and on the basis of total seizure frequency. Patients were randomized to 1 of 3 groups on the basis of the total seizure frequency. Patients were randomized to 1 of 3 groups on the basis of the total seizure frequency. Patients who tolerated 150 mg/day were discontinued. The primary efficacy assessment was 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 100 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 pharmacodynamic approach using data from controlled epilepsy trials described in labeling. This approach consisted of first showing a similar exposure-response relationship between pediatric patients 2 to 12 years of age and adults when topiramate was given as adjunctive therapy. The next step was to determine if the therapeutic ratio (i.e., the ratio of the dose at which the response is judged to be adequate to the dose at which intolerable adverse effects occur) was maintained in pediatric patients. Finally, the time to achieve steady-state exposures in children 2 to 12 years of age was demonstrated. The adult comparative trial was performed in double-blind, parallel-group, placebo-controlled fashion, with the dosing regimen established in the 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 topiramate. In each 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 were randomly assigned to each dose and the actual mean and median doses in the stabilization period are presented in Table 15.

14.4 Adjunctive Therapy Epilepsy Controlled Trials

Adult Patients With Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for adults with partial onset seizures was established in 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 epilepsy) or with topiramate (in patients with absence seizures), with or without secondary-generализed seizures. Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate. In all studies, patients were stabilized on their other AEDs before randomization. Patients who tolerated 150 mg/day were discontinued. The primary efficacy assessment was 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 100 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

Pediatric Patients Aged 2 to 16 Years With Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for pediatric patients aged 2 to 16 years with partial onset seizures was established in multicenter, randomized, double-blind, placebo-controlled trials (Study YP), comparing topiramate and placebo in patients with a history of partial onset seizures, with or without secondary generalized seizures (Table 16). Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate. The trial was designed to establish the comparative safety and efficacy of topiramate 25 mg/day and placebo. The primary efficacy assessments were 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 25 mg/day group (p = 0.0025, 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

This product is not indicated for the treatment of generalized tonic-clonic seizures in patients 2 years old and older who are stabilized in a multicenter, randomized, double-blind, placebo-controlled trial (Study YP), comparing a single dosage of topiramate and placebo (Table 15).
In this study, patients were randomly assigned to placebo or active drug. Patients who experienced at least three primary generalized tonic-clonic seizures during the baseline phase were randomly assigned to placebo or active drug. Patients who experienced at least one primary generalized tonic-clonic seizure during the baseline phase were randomly assigned to placebo or active drug. Patients who experienced at least two primary generalized tonic-clonic seizures during the baseline phase were randomly assigned to placebo or active drug.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 50 mg/day for one week; the dose was then increased by 50 mg to 150 mg/day increments every other week until the assigned dose of 175 mg, 225 mg, or 400 mg/day based on patients' body weight was approached. A dosage of 400 mg/day was reached, unless intolerance occurred or seizures occurred. After titration, patients entered an 8-week stabilization period.

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 (Study 119) comparing a single dosage of topiramate with placebo in patients 2 years of age and older (see Table 15).

In this study, patients were randomly assigned to placebo or active drug. Patients who experienced at least 60 seizures per month before study entry were randomized to optimal dosages of their concomitant AEDs during a 4-week baseline phase. Following baseline, patients were randomly assigned to placebo or active drug in addition to their other AEDs. Active drug was started 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 global rating of seizure severity.

### Table 14: Topiramate Dose Summary During the Stabilization Periods of Each of Six Double-Blind, Placebo-Controlled, Add-On Trials in Adults with Partial Onset Seizures

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Stabilization Dose</th>
<th>200 mg</th>
<th>400 mg</th>
<th>600 mg</th>
<th>800 mg</th>
<th>1,000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>YD</td>
<td>N</td>
<td>42</td>
<td>32</td>
<td>35</td>
<td>47</td>
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</tr>
<tr>
<td></td>
<td>Mean Dose</td>
<td>5.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>Median Dose</td>
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<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>YE</td>
<td>N</td>
<td>44</td>
<td>--</td>
<td>40</td>
<td>65</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Mean Dose</td>
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<tr>
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<td>25</td>
<td>19</td>
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<td>--</td>
</tr>
<tr>
<td></td>
<td>Mean Dose</td>
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<td>3.8</td>
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<td>--</td>
</tr>
<tr>
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<td>Median Dose</td>
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<td>4.0</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Y2</td>
<td>N</td>
<td>30</td>
<td>--</td>
<td>26</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Mean Dose</td>
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<td>--</td>
<td>32</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Median Dose</td>
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<td>--</td>
<td>60</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Y3</td>
<td>N</td>
<td>20</td>
<td>--</td>
<td>15</td>
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<td>--</td>
</tr>
<tr>
<td></td>
<td>Mean Dose</td>
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<td>--</td>
<td>--</td>
<td>56</td>
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</tr>
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<td>--</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>119</td>
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<td>127</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Mean Dose</td>
<td>8.2</td>
<td>10.8</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
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<td>Median Dose</td>
<td>8.0</td>
<td>10.0</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

* Placebo studies were not conducted for other indications or pediatric partial onset seizures.

** Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocols YD and Y2, 6 tablets/day; Protocols Y3 and 119, 8 tablets/day; Protocol YE, 10 tablets/day.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reduction 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 15. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Median Dose</th>
<th>Mean Dose</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>YD</td>
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<td>6.0</td>
<td>157</td>
</tr>
<tr>
<td>YE</td>
<td>9.7</td>
<td>10.0</td>
<td>28</td>
</tr>
<tr>
<td>Y1</td>
<td>5.7</td>
<td>6.0</td>
<td>28</td>
</tr>
<tr>
<td>Y2</td>
<td>5.7</td>
<td>6.0</td>
<td>28</td>
</tr>
<tr>
<td>Y3</td>
<td>5.7</td>
<td>6.0</td>
<td>28</td>
</tr>
<tr>
<td>119</td>
<td>5.7</td>
<td>6.0</td>
<td>44</td>
</tr>
</tbody>
</table>

### Table 15: Primary Efficacy Results in Double-Blind, Placebo-Controlled, Add-On Trials in Adults with Partial Onset Seizures

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Placebo</th>
<th>200 mg</th>
<th>400 mg</th>
<th>600 mg</th>
<th>800 mg</th>
<th>1,000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>YD</td>
<td>N</td>
<td>45</td>
<td>45</td>
<td>46</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>% Reduction</td>
<td>11.6</td>
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</tr>
<tr>
<td></td>
<td>% Improvement</td>
<td>28</td>
<td>26</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>YE</td>
<td>N</td>
<td>47</td>
<td>47</td>
<td>47</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>% Reduction</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>% Improvement</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Y1</td>
<td>N</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>% Reduction</td>
<td>5.7</td>
<td>4.7</td>
<td>1.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>% Improvement</td>
<td>20</td>
<td>20</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Y2</td>
<td>N</td>
<td>30</td>
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<td>30</td>
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</tr>
<tr>
<td></td>
<td>% Reduction</td>
<td>12.2</td>
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<td>% Improvement</td>
<td>15</td>
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<td>15</td>
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<td>119</td>
<td>N</td>
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<td>28</td>
<td>28</td>
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</tr>
<tr>
<td></td>
<td>% Reduction</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>% Improvement</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
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</tr>
</tbody>
</table>

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reduction 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 15. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

### Table 16: Topiramate Dose Summary During the Stabilization Periods of Each of Six Double-Blind, Placebo-Controlled, Add-On Trials in Adults with Partial Onset Seizures

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Placebo</th>
<th>200 mg</th>
<th>400 mg</th>
<th>600 mg</th>
<th>800 mg</th>
<th>1,000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>YD</td>
<td>N</td>
<td>42</td>
<td>32</td>
<td>35</td>
<td>47</td>
<td>--</td>
</tr>
<tr>
<td>YE</td>
<td>N</td>
<td>44</td>
<td>--</td>
<td>40</td>
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<tr>
<td>Y1</td>
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<tr>
<td>Y2</td>
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</tr>
<tr>
<td>119</td>
<td>N</td>
<td>90</td>
<td>127</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

* Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocols YD and Y2, 6 tablets/day; Protocols Y3 and 119, 8 tablets/day; Protocol YE, 10 tablets/day.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reduction 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 15. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.
Topiramate tablets can harm your unborn baby. How can I watch for early symptoms of suicidal thoughts and actions? Do not stop topiramate tablets without first talking to a healthcare provider.

Topiramate tablets can increase the level of acid in your blood (metabolic acidosis). If left untreated, metabolic acidosis can cause fever, confusion, breathing problems, or death. Your healthcare provider should do a blood test to measure the level of acid in your blood before and during treatment with topiramate tablets.

Some people with metabolic acidosis will:

- have trouble thinking clearly
- have changes in heartbeat
- not feel hungry (loss of appetite)
- feel changes in heartbeat
- have trouble breathing
- have unusual muscle cramps
- have unusual weakness
- feel changes in vision
- have stomach pain
- have vomiting
- have diarrhea
- feel changes in feelings
- have feelings of depression
- have unusual or uncontrollable excitement
- have changes in behavior or thoughts about self-harm
- have difficulty concentrating
- feel agitated or restless
- new or worse irritability
- acting aggressive, being angry, or violent
- acting out of character
- feeling agitated or restless
- new or worse irritability

The most important information I should know about topiramate tablets?

- 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. If you become pregnant while taking topiramate tablets, you should talk to your healthcare provider about how to prevent these birth defects. Even if you start taking topiramate tablets after pregnancy begins, there may also be risks to the fetus.
- If you take topiramate tablets while you are breastfeeding, it may harm your baby. You should not breastfeed while you are taking topiramate tablets.
- You should not start taking topiramate tablets without first talking to a healthcare provider. You should not stop taking topiramate tablets without first talking to a healthcare provider.
- You should not take topiramate tablets if you are allergic to topiramate.
- You should not take topiramate tablets if you have any of the following conditions:
  - acidosis (excess amount of acid in the blood)
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
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  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
  - any sudden decrease in vision with or without eye pain and redness,
What are the ingredients in topiramate tablets?

Topiramate tablets contain the active ingredient, topiramate, USP, and the following inactive ingredients: lactose monohydrate, magnesium stearate, precipitated calcium carbonate, and povidone. In addition, there is an excipient in different strengths of topiramate tablets:

- For 100 mg tablets, opadry white (titanium dioxide, hypromellose 3cp, hypromellose 6cp, PEG 400, polysorbate 80) for 25 mg tablets, opadry yellow (titanium dioxide, hypromellose 3cp, hypromellose 6cp, PEG 400, polysorbate 80) for 50 mg tablets, opadry pink (titanium dioxide, hypromellose 6cp, PEG 400, iron oxide red) for 100 mg tablets, opadry yellow (titanium dioxide, hypromellose 3cp, hypromellose 6cp, PEG 400, iron oxide yellow, polysorbate 80, iron oxide red) for 150 mg tablets, opadry white (titanium dioxide, hypromellose 3cp, hypromellose 6cp, PEG 400, polysorbate 80) for 200 mg tablets.

What are the possible side effects of topiramate tablets?

Topiramate tablets may cause serious side effects including:

- Fevers
- Low body temperature
- Seizures/convulsions
- Severe or persistent vomiting
- Mental or mood changes
- Changes in the way you think or act
- Vision changes, especially loss of vision or eye color changes
- Disorientation
- Nausea
- Loss of appetite
- Weight loss
- Increased sweating
- Fatigue
- Tiredness
- Headache
- Nervousness
- Insomnia
- Dizziness
- Frustration
- Depression
- Irritability
- Difficulty concentrating
- Changes in mood or feeling
- Hypersensitivity reactions
- Stevens-Johnson syndrome or toxic epidermal necrolysis
- Speech problems
- Changes in skin sensation
- Abnormal vision
- Changes in the way you feel: painful and disturbing sensations and other causes such as dry mouth, changes in taste or smell, and numbness

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

How should topiramate tablets be used?

- Take topiramate tablets exactly as prescribed by your healthcare provider.
- For topiramate tablets, you may take it with or without food. It is best to take it at the same time each day.
- Do not cut or open the tablets.
- Store topiramate tablets at room temperature, in a tightly closed container, out of the reach of children.
- Do not change your dose without talking to your healthcare provider.
- You may need to take topiramate tablets during pregnancy if you have epilepsy. It is important to talk to your healthcare provider before you stop taking topiramate tablets.
- Do not stop taking topiramate tablets suddenly, especially if you have epilepsy. It is important to talk to your healthcare provider before you stop taking topiramate tablets.
- Your healthcare provider may change your dose.
- Topiramate tablets can change the way other medicines work. Talk to your healthcare provider before you start taking any new medicines.
- Topiramate tablets can cause metabolic acidosis, a condition in which the body has too little bicarbonate in the blood.
- Topiramate tablets can cause low blood pressure and sometimes fainting.
- Topiramate tablets can cause serious side effects including:
  - Seizures
  - Fever
  - Low body temperature
  - Seizures/convulsions
  - Severe or persistent vomiting
  - Mental or mood changes
  - Changes in the way you think or act
  - Vision changes, especially loss of vision or eye color changes
  - Disorientation
  - Nausea
  - Loss of appetite
  - Weight loss
  - Increased sweating
  - Fatigue
  - Tiredness
  - Headache
  - Nervousness
  - Insomnia
  - Dizziness
  - Frustration
  - Depression
  - Irritability
  - Difficulty concentrating
  - Changes in mood or feeling
  - Hypersensitivity reactions
  - Stevens-Johnson syndrome or toxic epidermal necrolysis
  - Speech problems
  - Changes in skin sensation
  - Abnormal vision
  - Changes in the way you feel: painful and disturbing sensations and other causes such as dry mouth, changes in taste or smell, and numbness

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

What is topiramate tablets used for?

Topiramate tablets are used to:

- Treat seizures in adults and children 2 years and older
- Treat seizures associated with Lennox-Gastaut syndrome in adults and children 2 years and older
- Treat seizures associated with temporal lobe epilepsy in children 2 years and older

What is topiramate tablets used to treat in adults and children?

Topiramate tablets are used to:

- Treat seizures in adults and children 2 years and older
- Treat seizures associated with temporal lobe epilepsy in children 2 years and older
- Treat seizures associated with Lennox-Gastaut syndrome in adults and children 2 years and older

What is topiramate tablets used to treat in adults?

Topiramate tablets are used to:

- Treat seizures in adults
- Treat seizures associated with temporal lobe epilepsy in adults
- Treat seizures associated with Lennox-Gastaut syndrome in adults

What are topiramate tablets used for?

Topiramate tablets are used to:

- Treat seizures in adults
- Treat seizures associated with temporal lobe epilepsy in adults
- Treat seizures associated with Lennox-Gastaut syndrome in adults

What are topiramate tablets used to treat in children?

Topiramate tablets are used to:

- Treat seizures in children
- Treat seizures associated with temporal lobe epilepsy in children
- Treat seizures associated with Lennox-Gastaut syndrome in children

Who should not take topiramate tablets?

- It is not known if topiramate tablets are safe and effective for children under 2 years of age.
- It is not known if topiramate tablets are safe and effective for children under 12 years of age.
- Topiramate tablets are not recommended for children under 6 months of age.
- Children with kidney problems should not take topiramate tablets.
- Children with liver problems should not take topiramate tablets.
- Children with certain eye problems, especially glaucoma, should not take topiramate tablets.
- Children with certain lung or breathing problems should not take topiramate tablets.
- Children who are breastfeeding should not take topiramate tablets.
- Children who are pregnant or plan to become pregnant should not take topiramate tablets.
- Children who are planning to have surgery should not take topiramate tablets.

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

- Before taking topiramate tablets, tell your healthcare provider about all your medical conditions, including:
  - Allergy to topiramate tablets or any other ingredients in this medicine
  - Heart or liver problems
  - Enlarged prostate
  - Kidney disease
  - Asthma
  - Seizures
  - Eye problems, especially glaucoma
  - Lung or breathing problems
  - Mental or mood changes, especially depression or suicidal thoughts or behavior
  - Alcohol or drug use
  - History of kidney stones
  - History of diabetes
  - History of certain blood disorders
  - History of certain bone problems
  - History of certain immune system problems
  - History of any other causing side effects such as dry mouth, changes in taste or smell, and numbness
  - History of certain infections
  - History of certain blood disorders
  - History of certain bone problems
  - History of certain immune system problems

What is the most important information I should know about topiramate tablets if I take topiramate tablets with other medicines or supplements?

- Topiramate tablets may cause serious side effects, including:
  - Fever
  - Low body temperature
  - Seizures/convulsions
  - Severe or persistent vomiting
  - Mental or mood changes
  - Changes in the way you think or act
  - Vision changes, especially loss of vision or eye color changes
  - Disorientation
  - Nausea
  - Loss of appetite
  - Weight loss
  - Increased sweating
  - Fatigue
  - Tiredness
  - Headache
  - Nervousness
  - Insomnia
  - Dizziness
  - Frustration
  - Depression
  - Irritability
  - Difficulty concentrating
  - Changes in mood or feeling
  - Hypersensitivity reactions
  - Stevens-Johnson syndrome or toxic epidermal necrolysis
  - Speech problems
  - Changes in skin sensation
  - Abnormal vision

These side effects are not all the possible side effects of topiramate tablets. For more information, ask your healthcare provider or pharmacist.
This Medication Guide has been approved by the U.S. Food and Drug Administration.

All brand names listed are the registered trademarks of their respective owners and are not trademarked by Cipla Limited.

Manufactured for:

Cipla USA Inc.,
900 S. Dadeland Blvd., Suite 500
Miami, FL 33156

Manufactured by:

Accord Pharmaceuticals, Inc.
Central Islip, NY 11722

Manufactured by:

InvaGen Pharmaceuticals, Inc.
(a subsidiary of Cipla Ltd.)
Hauppauge, NY 11788

Revised: 07/2016

Marketed/Packaged by:

GSMS, Inc.
Camarillo, CA 93012 USA

Repackaging Information

Please reference the How Supplied section listed above for a description of individual tablets. This drug product has been received by Aphena Pharma - TN in a manufacturer or distributor packaged configuration and repackaged in full compliance with all applicable cGMP regulations. The package configurations available from Aphena are:

- 200 mg
  - 30: 43353-697-30
  - 90: 43353-697-60

Store between 20°-25°C (68°-77°F). See USP Controlled Room Temperature.

Dispense in a tight light-resistant container as defined by USP.

Keep this and all drugs out of the reach of children.

Repackaged by:

Cookeville, TN 38506
20190129JH

PRODUCT INFORMATION

Product Type
HUMAN PRESCRIPTION DRUG

Route of Administration
ORAL

Active Ingredient/Active Moiety

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<th>Ingredient Name</th>
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<td>TOPIRAMATE</td>
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Inactive Ingredients

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<tr>
<td>TITANIUM DIOXIDE</td>
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<tr>
<td>LACTOSE MONOHYDRATE</td>
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<tr>
<td>MICROCRYSTALLINE CELLULOSE</td>
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Product Characteristics

- Color: pink
- Score: no score
- Shape: ROUND
- Size: 11mm
- Flavor: Imprint Code: IG;281

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Packaging

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Marketing Information

Marketing Category: Reproducing Number on Monograph
Marketing Start Date: 07/2016
Marketing End Date: 07/2019

Labeler:
Aphena Pharma Solutions - Tennessee, LLC

Establishment

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