TOPIRAMATE- topiramate tablet
Lake Erie Medical DBA Quality Care Products LLC

INDICATIONS AND USAGE

Topiramate tablets are indicated for:

- Monotherapy epilepsy: Initial monotherapy in patients ≥ 2 years of age with partial onset seizures (1.2).
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures, primary generalized tonic-clonic seizures, and in patients ≥2 years of age with rocamoxid associated with Lennox-Gastaut syndrome (1.3).
- Migraine prophylaxis: Migraine prophylaxis in premenopausal women ≥ 18 years of age with primary or secondary migrainous headaches (1.4).

DOSAGE FORMS AND STRENGTHS

Topiramate tablets USP are available in the following strengths:

- Tablets: 35 mg, 50 mg, 100 mg, and 200 mg.

DOSAGE AND ADMINISTRATION

- Monotherapy epilepsy: Initial monotherapy in patients ≥ 2 years of age with partial onset seizures.
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures, primary generalized tonic-clonic seizures, and in patients ≥2 years of age with rocamoxid associated with Lennox-Gastaut syndrome.
- Migraine prophylaxis: Migraine prophylaxis in premenopausal women ≥ 18 years of age with primary or secondary migrainous headaches.

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions: Hypersensitivity reactions including rash, angioedema, serum sickness-like syndrome, and eosinophilia have been reported with topiramate administration. Discontinue if a hypersensitivity reaction occurs.
- Central nervous system effects: Cerebrovascular accidents, including stroke, have been reported with topiramate administration, especially in pediatric patients. Monitor for these adverse events.
- Cognitive/neuropsychiatric: Use caution when operating machinery including automobiles. Depression, suicidal ideation, and mood problems may occur in epilepsy populations.
- Metabolic acidosis: Baseline and periodic measurement of serum bicarbonate is recommended. Monitor for this adverse event.
- Bonework growth delay: bonework growth delay has been reported in children and adolescents. Monitor for this adverse event.
- Kidney stones: Avoid use with other carbonic anhydrase inhibitors, drugs causing metabolic acidosis, lithium, or in patients on a ketogenic diet. Hyperammonemia and encephalopathy: Measure ammonia if encephalopathic symptoms occur. Migraine prophylaxis: Avoid use with other carbonic anhydrase inhibitors, drugs causing metabolic acidosis, lithium, or in patients on a ketogenic diet. Withdrawal of AEDs: Withdrawal of topiramate should be done gradually over a minimum of 14 days. Use caution when switching to or from a ketogenic diet.

DRUG INTERACTIONS

- Antiepileptic drugs: Use caution when using topiramate with other antiepileptic drugs. Increased risk of rhabdomyolysis when used with valproic acid. Use caution when using topiramate with lamotrigine.
- Oral contraceptives: Decreased contraceptive efficacy and increased breakthrough bleeding, especially in female patients with renal impairment.
- Oral corticosteroids: Use caution when using topiramate with oral corticosteroids.
- Lithium: Monitor lithium levels if lithium is used with high-dose topiramate tablets.
- Hypothyroidism: Uncomplicated hypothyroidism has been reported with topiramate treatment in patients with renal impairment, geriatric patients, and patients undergoing hemodialysis.
- Migraine prophylaxis: Caution should be exercised when administering topiramate to a nursing mother.
- Pregnancy: Use caution when using topiramate in pregnant women.

ADVERSE REACTIONS

- Hypersensitivity reactions: Hypersensitivity reactions including rash, angioedema, serum sickness-like syndrome, and eosinophilia have been reported with topiramate administration. Discontinue if a hypersensitivity reaction occurs.
- Central nervous system effects: Cerebrovascular accidents, including stroke, have been reported with topiramate administration, especially in pediatric patients. Monitor for these adverse events.
- Cognitive/neuropsychiatric: Use caution when operating machinery including automobiles. Depression, suicidal ideation, and mood problems may occur in epilepsy populations.
- Metabolic acidosis: Baseline and periodic measurement of serum bicarbonate is recommended. Monitor for this adverse event.
- Bonework growth delay: bonework growth delay has been reported in children and adolescents. Monitor for this adverse event.
- Kidney stones: Avoid use with other carbonic anhydrase inhibitors, drugs causing metabolic acidosis, lithium, or in patients on a ketogenic diet. Hyperammonemia and encephalopathy: Measure ammonia if encephalopathic symptoms occur. Migraine prophylaxis: Avoid use with other carbonic anhydrase inhibitors, drugs causing metabolic acidosis, lithium, or in patients on a ketogenic diet. Withdrawal of AEDs: Withdrawal of topiramate should be done gradually over a minimum of 14 days. Use caution when switching to or from a ketogenic diet.
Elevated intraocular pressure of any etiology, if left untreated, can lead to serious
crances with discontinuation of topiramate tablets, may be helpful.
treatment to reverse symptoms is discontinuation of topiramate tablets as rapidly as
a primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-
Topiramate tablets are indicated for patients 12 years of age and older for the prophylaxis of migraine headache.

tablets. The primary ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased
glaucoma has been reported in patients receiving topiramate tablets. Symptoms include
typically occur within 1 month of
Topiramate tablets have been reported in pediatric patients as well as adults. The primary
Topiramate tablets can be taken without regard to meals.

The recommended total daily dose of topiramate tablets as adjunctive therapy in adults with partial onset seizures or Lennox-Gastaut syndrome is

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

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Total Daily Dosing (mg/day)**</th>
<th>Total Daily Dosing (mg/day)***</th>
<th>Minimum Maintenance</th>
<th>Maximum Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 – 22</td>
<td>200 mg</td>
<td>300 mg</td>
<td>50 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>23 – 31</td>
<td>300 mg</td>
<td>350 mg</td>
<td>75 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>32 – 38</td>
<td>350 mg</td>
<td>400 mg</td>
<td>100 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Greater Than 38</td>
<td>400 mg</td>
<td>500 mg</td>
<td>125 mg</td>
<td>250 mg</td>
</tr>
</tbody>
</table>

*Administered in two equally divided doses
**Half the dose of the previous week
***If additional titration is needed, the maximum maintenance dose can be achieved at 25 mg/day increments.
Psychiatric/Behavioral Disturbances placebo. Cognitive adverse reactions most commonly developed during titration and one or more cognitive-related adverse reactions was 19% for topiramate 50 mg/day and in the monotherapy epilepsy controlled trial, the proportion of patients who experienced reactions began in the titration or in the maintenance phase, and in some patients these patients in the 800 mg/day and 1000 mg/day dose groups experienced cognitive-related dysfunction.

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

Topiramate can cause cognitive/neuropsychiatric adverse reactions. The most frequent is decreased serum bicarbonate below the normal reference range in the absence of other causes, such as renal disease or metabolic alkalosis. Decreased serum bicarbonate may also be 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 4-5 mEq/L in pediatric patients) but may increase in some patients with a history of renal disease, metabolic acidosis, or other conditions that predispose patients to acidosis (such as renal disease, severe respiratory disorders, iotia, electrolyte abnormalities, or acidosis). These decrements may be additive to the bicarbonate lowering effects of topiramate.

The majority of the reports have been in pediatric patients. Patients, especially pediatric patients, treated with topiramate should be monitored closely for evidence of decreased serum bicarbonate and increased body temperature. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disorders, iotia electrolyte abnormalities, or acidosis) 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 and adult patients was 5-10% and 1-3% respectively. Metabolic acidosis was more common in pediatric patients and was associated with rapid titration rate and higher initial dose. The risk was not increased in patients with a history of renal disease, severe respiratory disorders, iotia, electrolyte abnormalities, or acidosis. The relative risk for metabolic acidosis in patients treated with topiramate was 2.3 compared to placebo in pediatric patients and 2.4 in adult patients. The risk did not vary substantially by age (5 to 100 years) in the clinical trials assessed.

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 during dose tapering. If the decision is made to continue patients on topiramate in the face of persistent acidosis, usual treatment should be considered. The risk of metabolic acidosis in adult and pediatric patients treated with topiramate was similar. The incidence of decreased serum bicarbonate in pediatric and adult patients was 5-10% and 1-3% respectively. The risk was not increased in patients with a history of renal disease, severe respiratory disorders, iotia, electrolyte abnormalities, or acidosis. The relative risk for metabolic acidosis in patients treated with topiramate was 2.3 compared to placebo in pediatric patients and 2.4 in adult patients. The risk did not vary substantially by age (5 to 100 years) in the clinical trials assessed. The risk of metabolic acidosis in adult and pediatric patients treated with topiramate was similar. The incidence of decreased serum bicarbonate in pediatric and adult patients was 5-10% and 1-3% respectively. The risk was not increased in patients with a history of renal disease, severe respiratory disorders, iotia, electrolyte abnormalities, or acidosis. The relative risk for metabolic acidosis in patients treated with topiramate was 2.3 compared to placebo in pediatric patients and 2.4 in adult patients. The risk did not vary substantially by age (5 to 100 years) in the clinical trials assessed.

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

<table>
<thead>
<tr>
<th>Indication/Placode Patients with Events per 1000 Patients</th>
<th>Drug Patients with Events per 1000 Patients</th>
<th>Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients</th>
<th>Risk Difference: Additional Drug Patients with Events per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.8</td>
<td>2.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>

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

Anyone considering prescribing topiramate tablets or any other AED must balance the risk of suicidal thoughts and behavior with the risk of untreated illness. Epilepsy and many other diseases for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of depression, any unusual changes in mood or behavior, or any unusual thoughts or preoccupation with death. Should suicidal thoughts or behavior become apparent or worsen, the prescriber needs to consider whether the treatment needs to be reevaluated.

5.5 Suicide-related 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 should be monitored closely for evidence of suicidal ideation or behavior. Anyone considering prescribing topiramate tablets or any other AED must balance the risk of suicidal thoughts and behavior with the risk of untreated illness. Epilepsy and many other diseases for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of depression, any unusual changes in mood or behavior, or any unusual thoughts or preoccupation with death. Should suicidal thoughts or behavior become apparent or worsen, the prescriber needs to consider whether the treatment needs to be reevaluated.

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.

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/impaired attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g., depression or mood problems); and 3) Somnolence or fatigue.

Adult Patients

Cognitive-Related Dysfunction

Rapid titration rate and higher initial dose were associated with higher incidences of cognitive-related dysfunction. In adult epilepsy add-on controlled trials, which used rapid titration (100-200 mg/day weekly increments), and large titration doses of 200-400 mg/day, 56% of patients treated with topiramate had at least one cognitive adverse reaction compared to approximately 42% of patients in the 200-400 mg/day groups and 34% for placebo. In the rapid titration regimen, these dose-related adverse reactions began in the titration or in the maintenance phase, and in some patients these events began during titration and persisted into the maintenance phase. In the monotherapy epilepsy controlled trial, the proportion of patients who experienced one or more cognitive-related adverse reactions was 19% for topiramate 50 mg/day and 26% for 400 mg/day. In the 6-month migraine prophylaxis controlled trial, 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), 26% for 200 mg/day, and 32% for 400 mg/day. Cognitive adverse reactions most commonly developed during titration and were not generally reported after completion of titration.

Table 4: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis
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, related dose-related, for the monotherapy epilepsy population, the incidence of somnolence was dose-related. For the migraine population, the incidences of both fatigue and somnolence were dose-related and more common in the titration phase.

Pediatric Patients

In pediatric epilepsy trials (adjunctive and monotherapy), the incidence of cognitive/neuropsychiatric adverse reactions was generally lower than that observed in adults. These reactions included psychomotor slowing, difficulty with concentration/attention, speech disorders/reduced speech problems, and language problems. The most frequently reported cognitive/neuropsychiatric reactions in pediatric epilepsy patients during adjunctive therapy double-blind studies were somnolence and fatigue. The most frequently reported cognitive/neuropsychiatric reactions in pediatric migraine patients during prophylaxis double-blind studies 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). The risk for cognitive/neuropsychiatric adverse reactions was greater in patients less than 12 years of age treated with topiramate monotherapy for a mean duration of 24 weeks (5.4). 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.

5.7 Fetal Toxicity

Topiramate tablets can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries show that exposure to topiramate does not increase the risk of specific birth defects. Topiramate is teratogenic in rats when administered on days 6 through 18 of gestation. In a rat study in which topiramate was administered once daily to pregnant rats throughout gestation, the incidence of congenital malformations was increased in the offspring of rats treated at doses equivalent to 1.5, 3, 6, or 12 times the recommended human dose. In addition, some rat pups exhibited neurological hypoplasia and developmental delays. The drug is not indicated for use in pregnant women during labor and delivery.

5.8 Withdrawal of Antiepileptic Drugs

In patients who have been stabilized on antiepileptic drugs (AEDs) and who are then discontinued, the abrupt discontinuation of AEDs has been associated with seizures in patients with epilepsy. Abrupt withdrawal of AEDs in patients taking topiramate or valproate may result in psychomotor slowing and decreased verbal fluency.

5.9 Hypermnemonemia and Encephalopathy (Without and With Concomitant Valproic Acid)

Topiramate treatment can cause hyperammonemia with or without encephalopathy. See Adverse Reactions (8.7). This risk for hyperammonemia with concomitant valproic acid therapy 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 hyperammonemia often include acute alterations in level of consciousness and/or cognitive function with lethargy and/or vomiting. In most cases, hyperammonemia was associated with altered states of consciousness and seizures. The incidence of hyperammonemia in pediatric patients 12 to 17 years of age in migraine prophylaxis trials was 26% in patients taking topiramate monotherapy at 100 mg/day, and 13% in patients taking topiramate at 50 mg/day, compared to 9% in patients taking placebo. In patients who previously tolerated either drug alone, the incidence of hyperammonemia in pediatric patients treated concomitantly with topiramate and valproic acid was 5%.

Topiramate treatment can cause hyperammonemia with or without encephalopathy. See Adverse Reactions (8.7). This risk for hyperammonemia with concomitant valproic acid therapy 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)).

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Hypothermia defined as an unintentional drop in body core temperature to <35°C (95°F) is a side effect noted in some patients on topiramate therapy. The concomitant use of topiramate with any other drug that may cause hypothermia is not recommended.

5.10 Kidney Stones

Topiramate increases the risk of kidney stones. During adjunctive epilepsy trials, the risk for kidney stones in topiramate-treated adults was 1.5%, an incidence about 2 to 4 times greater than expected in a similar, untreated population. In the general population, the incidence of stone formation among topiramate-treated patients was 0.4%, compared to 0.1% in a similar, untreated population. In pediatric patients, the incidence of kidney stones was 1.5% in patients taking topiramate at 100 mg/day, 0.9% in patients taking topiramate at 50 mg/day, and 0.6% in patients taking placebo.

The concomitant use of topiramate with any other drug that may cause hypothermia is not recommended.

5.11 Hypothermia with Concomitant Valproic Acid (VPA)

Hypothermia, defined as an unintentional drop in body core temperature to <35°C (95°F), has been reported in association with topiramate use with concomitant valproic acid (VPA) both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse reaction in patients using concomitant topiramate and valproate can occur after starting topiramate treatment or after increasing the daily dose of topiramate (see Drug Interactions (7.1)). Consideration should be given to stopping topiramate or valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, syncope, coma, and unconsciousness. Cold exposure may exacerbate hypothermia in susceptible persons.

5.12 Overdose

The acute oral LD₅₀ of topiramate in mice and rats is greater than 1000 mg/kg. Topiramate is rapidly absorbed after oral administration, with peak plasma concentrations occurring in 2 to 3 hours. The elimination half-life of topiramate is approximately 12 hours. Topiramate is highly bound to plasma proteins (approximately 95%) and is extensively metabolized. Topiramate is an inducer of hepatic enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4).

Topiramate is excreted in both its parent form and as metabolites, mainly in the urine. The major plasma metabolites are the 5-epimer of topiramate, 1-aminophenyl-2-propylamine (1-APPA), and 3-pyrrolidinomethyl-2-propylamine (3-PMMA). 1-APPA and 3-PMMA are active, central nervous system (CNS) metabolites. Topiramate is also a weak inhibitor of CYP2C19.

The pharmacokinetics of topiramate are dose proportional and not altered by renal or hepatic impairment. However, topiramate accumulation is increased in patients with hepatic impairment. There is no evidence that topiramate accumulation is increased in patients with mild to moderate renal impairment. There is no information on the pharmacokinetics of topiramate in patients with severe renal impairment or dialysis patients.

Topiramate is not a substrate for P-glycoprotein or breast cancer resistance protein (BCRP). Topiramate is not a substrate for CYP1A2, CYP2C9, CYP2C19, CYP3A4, and CYP3A5.

Topiramate is not an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP3A4, and CYP3A5.

6. Adverse Reactions

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

Acute Nephropathy and Secondary Angle Closure (see Warnings and Precautions (5.14))

Visual Field Defects (see Warnings and Precautions (5.12))

Oligodendroitis and Hypothermia (see Warnings and Precautions (5.1))

Metabolic Acidosis (see Warnings and Precautions (5.4))

Suicidal Behavior and Ideation (see Warnings and Precautions (5.5))

Cognitive Neuropsychiatric Adverse Reactions (see Warnings and Precautions (5.6))

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

Sudden Unexpected Death in Epilepsy (SUDEP) (see Warnings and Precautions (5.8))

Hypermnemonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use) (see Warnings and Precautions (5.9))

Kidney Stones (see Warnings and Precautions (5.10))

Hypothermia with Concomitant Valproic Acid (VPA) Use (see Warnings and Precautions (5.11))
6.1 Clinical Trials Experience

Monotherapy Epilepsy

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

Increased Risk for Bleeding

Topiramate treatment is associated with an increased risk for bleeding. In a pooled analysis of placebo-controlled studies of approved and unapproved indications, bleeding was more frequently reported as an adverse event for topiramate tablets than for placebo (4.6% versus 2.6% of adult patients, and 6.0% versus 3.8% of pediatric patients). Difficulty with memory (see Warnings and Precautions (5.13)), anemia, thrombocytopenia, and bleeding occurred more frequently with topiramate tablets and placebo was 0.3% versus 0.2% for adult patients, and 6.4% versus 0.0% for pediatric patients.

Adverse bleeding reactions reported with topiramate tablets ranged from mild epistaxis, ecchymosis, and increased menstrual bleeding to life-threatening hemorrhages. In patients with various bleeding events, conditions that increased the risk for bleeding were identified. The conditions included but were not limited to patients with serious bleeding events, conditions that increased the risk for bleeding (e.g., von Willebrand disease, anticoagulants, antiplatelet agents, other anticoagulants), or other anticoagulants.

Adjunctive Therapy Epilepsy

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 occurring in at least 2% of adult and pediatric patients treated with topiramate tablets.

The incidence of adverse reactions in the clinical trials of another drug, and may not.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Pediatric (≥ 12 Years) N=77</th>
<th>Adult (≥ 16 Years) N=159</th>
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</thead>
<tbody>
<tr>
<td>N (N=74)</td>
<td>N (N=45)</td>
<td>N (N=40)</td>
</tr>
<tr>
<td>Body System</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>General Disorders</td>
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<tr>
<td>Arithesia</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Fever</td>
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<td>2</td>
</tr>
<tr>
<td>Leg pain</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Central &amp; Peripheral Nervous System Disorders</td>
<td></td>
<td></td>
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<tr>
<td>Migraine</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Oedema</td>
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<td>14</td>
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<td>Hypertonia</td>
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<td>5</td>
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<tr>
<td>Hypersensitivity</td>
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<td>5</td>
</tr>
<tr>
<td>Muscle contractile myotonia</td>
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<td>4</td>
</tr>
<tr>
<td>Nervosness</td>
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<td>13</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Gastrointestinal System Disorders</td>
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<td>Diarrhea</td>
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<td>Gastroesophageal reflux</td>
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<td>Dry mouth</td>
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<td>Liver and Biliary System Disorders</td>
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<td>Gastrointestinal disorders</td>
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<td>Metabolic and Nutritional Disorders</td>
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<tr>
<td>Angina</td>
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<td>Anxiety</td>
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<td>Depression</td>
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<tr>
<td>Difficulty with concentration/attention</td>
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<td>5</td>
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<tr>
<td>Anxiety</td>
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</tr>
<tr>
<td>Mood problems</td>
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<tr>
<td>Personality disorder/behavior problems</td>
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<td>3</td>
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<td>Psychomotor slowing</td>
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<td>Gastrointestinal disorders</td>
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<td>15</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Reproduction Disorders, Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermenstrual bleeding</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Reproduction Disorders, Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermenstrual bleeding</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Reproduction Disorders, All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermenstrual bleeding</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Infection site</td>
<td>1</td>
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</tr>
<tr>
<td>Respiratory System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis site</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis sinusitis</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Skin and Appendages Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosacea</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Paronychia</td>
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<td>4</td>
</tr>
<tr>
<td>Vascular (extracranial) Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Vascular (extracranial) Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

The data described in the following sections were obtained using topiramate tablets.
Incidence in EPILEPSY CONTROLLED CLINICAL TRIALS – ADJUNCTIVE THERAPY – PARTIAL ONSET SEIZURES, PRIMARY GENERALIZED TONIC-CLONIC SEIZURES, AND LENNOX-GASTAUT SYNDROME

Table 5: Incidence of Treatment-emergent adverse reactions occurring in at least 1% of adults treated with 200 to 400 mg/day of topiramate in controlled clinical trials discontinued 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, difficulty with memory, confusion, abnormal vision, difficulty with concentration/attention, and asthenia. The incidence of these adverse reactions in patients treated with topiramate were numerically more common at this dose than in patients treated with placebo. In general, most patients who experienced adverse reactions during the first four to eight weeks of these trials no longer experienced them by their last visit. Table 6 shows the incidence of treatment-emergent adverse reactions occurring in at least 1% of pediatric patients treated with 200 to 1,000 mg/day of topiramate in controlled clinical trials. Approximately 11% of the 310 pediatric patients who received topiramate tablets at dosages of 300 to 600 mg/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, anxiety, dizziness, difficulty with memory, confusion, abnormal vision, difficulty with concentration/attention, and asthenia. The incidence of these adverse reactions in patients treated with topiramate were numerically more common at this dose than in patients treated with placebo. In general, most patients who experienced adverse reactions during the first four to eight weeks of these trials no longer experienced them by their last visit. Table 6 shows the incidence of treatment-emergent adverse reactions occurring in at least 1% of pediatric patients treated with 200 to 1,000 mg/day of topiramate in controlled clinical trials. Approximately 28% of the 1757 adults with epilepsy who received topiramate tablets at dosages of 200 to 1,000 mg/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, anxiety, dizziness, difficulty with memory, confusion, abnormal vision, difficulty with concentration/attention, and asthenia. The incidence of these adverse reactions in patients treated with topiramate were numerically more common at this dose than in patients treated with placebo. In general, most patients who experienced adverse reactions during the first four to eight weeks of these trials no longer experienced them by their last visit. Table 6 shows the incidence of treatment-emergent adverse reactions occurring in at least 1% of pediatric patients treated with 200 to 1,000 mg/day of topiramate in controlled clinical trials.
Incidence of Treatment-Emergent Adverse Reactions in Study 119

Table 7: Incidence of Treatment-Emergent Adverse Reactions in Study 119

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Topiramate Tablets %</th>
<th>Placebo %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Ataxia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Oral hypoesthesia</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Seborrhea</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Skin disorder</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other Systemic</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Topiramate Tablets %</td>
<td>Placebo %</td>
</tr>
<tr>
<td>1 mg/day</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2 mg/day</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>3 mg/day</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>4 mg/day</td>
<td>12</td>
<td>18</td>
</tr>
</tbody>
</table>

Adverse reactions reported by at least 1% of patients in the topiramate tablets 200–400 mg/day group were:

- Headache
- Nervousness
- Fatigue
- Hypersensitivity
- Sleep disturbances

Patients receiving 3 mg/day topiramate tablets were more likely to report these adverse reactions than patients in the placebo group.

Table 8: Incidence (%) of Treatment-Emergent Adverse Reactions in Study 119

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Topiramate Tablets Dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 92)</td>
</tr>
<tr>
<td>Jitter</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
</tr>
<tr>
<td>Nervousness</td>
<td>1</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>0</td>
</tr>
<tr>
<td>Ataxia</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>1</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1</td>
</tr>
<tr>
<td>Oral hypoesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>1</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>1</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1</td>
</tr>
<tr>
<td>Acne</td>
<td>1</td>
</tr>
<tr>
<td>Seborrhea</td>
<td>1</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>1</td>
</tr>
<tr>
<td>Skin disorder</td>
<td>1</td>
</tr>
<tr>
<td>Other Systemic</td>
<td>1</td>
</tr>
</tbody>
</table>

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

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

The most commonly observed adverse reactions associated with the use of topiramate tablets that were seen at an incidence higher (≥ 5%) than in the placebo group were:

- Nausea
- Flatulence
- Gastroenteritis
- Oral hypoesthesia
- Sleep disturbances

Patients receiving 3 mg/day topiramate tablets were more likely to report these adverse reactions than patients in the placebo group.

Table 9: Incidence (%) of Treatment-Emergent Adverse Reactions From Placebo-Controlled, Add-On Trials in Adults With Partial Onset Seizures

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=92)</th>
<th>Topiramate Tablets (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jitter</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ataxia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0</td>
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</tr>
<tr>
<td>Gastroenteritis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Oral hypoesthesia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
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</tr>
<tr>
<td>Urinary incontinence</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Seborrhea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mucocutaneous</td>
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<td>1</td>
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<tr>
<td>Skin disorder</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other Systemic</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Adverse reactions reported by at least 2% of patients in the topiramate tablets 200–400 mg/day group were:

- Nausea
- Flatulence
- Gastroenteritis
- Oral hypoesthesia
- Sleep disturbances

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

Table 10: Incidence (% of Dose-Related Adverse Reactions From Placebo-Controlled, Add-On Trials in Adults With Partial Onset Seizures

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=101)</th>
<th>Topiramate Tablets (N=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jitter</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Nervousness</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Ataxia</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
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</tr>
<tr>
<td>Tinnitus</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Flatulence</td>
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<td>14</td>
</tr>
<tr>
<td>Gastroenteritis</td>
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<td>14</td>
</tr>
<tr>
<td>Oral hypoesthesia</td>
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<td>14</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Urinary tract infection</td>
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<td>14</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Acne</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Seborrhea</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Skin disorder</td>
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<td>14</td>
</tr>
<tr>
<td>Other Systemic</td>
<td>1</td>
<td>14</td>
</tr>
</tbody>
</table>

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

Table 11: Incidence (%) of Adverse Reactions in Placebo-Controlled, Add-On Trials in Adults With Partial Onset Seizures

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=92)</th>
<th>Topiramate Tablets (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jitter</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ataxia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
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<td>1</td>
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<tr>
<td>Gastroenteritis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Oral hypoesthesia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hematuria</td>
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<td>1</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Seborrhea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Skin disorder</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other Systemic</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Adverse reactions reported by at least 1% of patients in the topiramate tablets 200–400 mg/day group and more common than in the placebo group are listed in this table.
| Heart Rate and Rhythm Disorders | 0 | 1 |
| Metabolic and Nutritional Disorders | 1 | 0 |
| Hypoglycaemia | 2 | 1 |
| Hyperglycaemia | 1 | 2 |
| Weight decrease | 0 | 1 |
| Weight increase | 0 | 1 |
| Patient, Bleeding, & Clotting Disorders | 4 | 0 |
| Uterine bleeding | 1 | 6 |
| Hæmorrhage | 1 | 4 |
| Prothrombin increased | 0 | 1 |
| Thrombocytopenia | 0 | 1 |
| Psychiatric Disorders | 0 | 1 |
| Agitation | 26 | 15 |
| Anxiety | 24 | 17 |
| Nervousness | 14 | 9 |
| Personality disorder (behaviour problems) | 6 | 4 |
| Difficulties with concentration/attention | 10 | 2 |
| Aggression reaction | 9 | 4 |
| Inattention | 7 | 8 |
| Difficulty with memory | 0 | 0 |
| Confusion | 2 | 4 |
| Psychomotor slowing | 2 | 4 |
| Appetite increased | 0 | 1 |
| Neuropsychoses disorders | 0 | 1 |
| Reproductive Disorders, Female | 2 | 0 |
| Leukorrhoea | 0 | 2 |
| Resistance Mechanism Disorders | 3 | 7 |
| Skin and Appendages Disorders | 1 | 5 |
| Nausea | 0 | 1 |
| Diarrhoea | 0 | 1 |
| Dermatitis | 0 | 1 |
| Hyperkalaemia | 1 | 2 |
| Skin discoloration | 1 | 2 |
| Sepsis | 0 | 1 |
| Skin discoloration | 0 | 1 |
| Skin disorder | 0 | 1 |
| Urinary System Disorders | 2 | 4 |
| Gastrointestinal disorder | 2 | 4 |
| Vulvar disorders | 0 | 1 |
| Vomiting | 1 | 2 |
| Weight increase | 1 | 2 |
| Dizziness | 1 | 2 |
| Dizziness | 1 | 2 |
| Diarrhoea | 0 | 1 |
| Male | 0 | 1 |
| Malignant | 0 | 1 |
|乌头 Cell and RBS Disorders | 0 | 1 |

Other Adverse Reactions Observed During All Epilepsy Clinical Trial

Topiramate tablets have been administered to 2246 adults and 427 pediatric patients with epilepsy during all clinical studies, only some of which were placebo-controlled. During these trials, the proportions of patients experiencing an adverse reaction were determined by classifying all adverse reactions that occurred during the study and can be included in more than one adverse reaction category.

Other Adverse Reactions Observed During All Epilepsy Clinical Trials

- Patients in these add-on/adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to topiramate tablets or placebo.
- Patients represent the percentage of patients reporting a given adverse reaction. Patients may have experienced a reaction of the type cited on at least one occasion while receiving topiramate tablets post-approval.
- Other adverse experiences have not been listed above and data are insufficient to determine the clinical significance of 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)).

7.2 CNS Depressants

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

Topiramate can raise lithium levels when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for SGA compared to other infants (0.05 times the RHD on a mg/m² basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced in treatment with 100 mg/kg or greater.

7.4 Lithium

Some patients may experience a large increase in antipyrine concentration in the presence of topiramate and any adjustments in antipyrine 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

Topiramate should be used in pregnancy only if the potential benefit outweighs the potential risk. If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential for harm to a fetus (see Warnings and Precautions (5.7)).

8.2 Labor and Delivery

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in multiple animal species at clinically relevant doses. 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)).
and tolerance of topiramate oral liquid and sprinkle formulations as an adjunct to concurrent antiepileptic drug therapy in pediatric patients 6 to 16 years of age with refractory partial-onset seizures were assessed. After 10 days of double-blind treatment, topiramate (at fixed doses of 15, 30, and 60 mg/day) did not demonstrate efficacy compared with placebo in controlling seizures.

In general, the adverse reaction profile for topiramate in this population was similar to that of older pediatric patients, although results from the above controlled studies and an observational cohort study suggest some differences in the frequency and nature of adverse events.

5.2 Patients With Severe Impaired Renal Function

Topiramate is administered as a single dose. A dosage adjustment may not be necessary for elderly with renal impairment.

5.3 Patients With Impaired Hepatic Function

The effects of hepatic impairment on topiramate disposition have not been studied. A dosage adjustment is not recommended for patients with hepatic impairment (see Drug Interactions (14.3)).

5.4 Pediatric Use

The use of topiramate in children below the age of 2 years has not been established for the monotherapy treatment of epilepsy.

5.5 Migraine Prophylaxis in Pediatric Patients 12 to 17 Years of Age

Safety and effectiveness of topiramate in the prophylaxis of migraine was studied in 6 double-blind, randomized, placebo-controlled, parallel-group trials in a total of 239 pediatric patients, at doses of 50 to 200 mg/day, or 2 to 3 mg/kg/day. These comprised a fixed-dose study in 103 pediatric patients 12 to 17 years of age (see Clinical Studies (14.2)), a flexible-dose study in 62 patients who were titrated up to 200 mg/day (see Clinical Studies (14.2)), and 2 additional studies in 55 pediatric patients (see Clinical Studies (14.2)).

Topiramate was added to the treatment regimen of patients whose headache was inadequately controlled with their current prophylactic medication. After a stabilization period of at least 2 weeks, patients were randomized to placebo or to topiramate 30, 90, or 300 mg/kg/day. The mean duration of treatment was 26 weeks. Topiramate was well tolerated in the pediatric patients who received it for the treatment of migraine.

The most common adverse reactions observed in the pediatric patients treated with topiramate were: paresthesia, upper respiratory tract infection, anorexia, and abdominal pain. These adverse reactions normally occurred more frequently than placebo, and were generally mild to moderate in severity.

Difficulty with concentration/attention occurred in 3 topiramate-treated patients (5%). These reactions were also observed in a placebo-controlled trial in 157 pediatric patients (6 to 16 years of age) for 10 weeks in the pediatric trials (12 to 17 years of age) in which patients were randomized to placebo or a fixed daily dose of topiramate. The most common adverse reactions occurring with topiramate that were seen at an incidence 15% (the incidence of adverse reactions with placebo in the pediatric group was: paresthesia, upper respiratory tract infection, anorexia, and abdominal pain (see Adverse Reactions (6))).

5.6 Pre-Clinical Research

In juvenile primate studies (12 to 17 years of age) compared to placebo-treated pediatric patients, abnormally increased results were more frequent for creatinine, BUN, uric acid, cholesterol, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase. Abnormally decreased results were more frequent for potassium and sodium. In postmarketing experience, clinical laboratory results have more severely impaired renal function (see Warnings and Precautions (5.6)).

6.2 Nephropathy

The clearance of topiramate is reduced in patients with moderate (creatinine clearance 30 to 59 mL/min/1.73 m²) and severe (creatinine clearance <15 mL/min/1.73 m²) renal impairment. A dosage adjustment is recommended in patients with moderate or severe renal impairment (see Dosage and Administration (2.3)). Clinical Pharmacology (2.2)).

6.7 Patients Undergoing Hemodialysis

Topiramate is cleared in patients undergoing hemodialysis, which can result in a 1.4 to 2.0 times greater than in a normal individual. A dosage adjustment may be required (see Dosage and Administration (2.3)). Clinical Pharmacology (2.2)).

8.1 Women of Childbearing Potential

Topiramate is not known to cause fetal harm when administered to pregnant women. Topiramate is known to cause fetal harm when administered to pregnant women. Therefore, women of childbearing potential should be counseled regarding the relative risks and benefits of topiramate use during pregnancy, and alternative therapeutic options should be considered for these patients.
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 <30 mL/min/1.73m²). Reduced topiramate clearance resulted in slightly higher plasma and renal clearance of topiramate, topiramate plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life increased 13% in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. The mechanism underlying the decrease is not well understood.

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 60% 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 elimination half-life of topiramate 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 21% adsorb topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may be required.

Topiramate is cleared by hemodialysis. Using a high-efficiency, counterflow, single pass-dialysis hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20 to 30 mL/min for other drugs) is consistent with the amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may be required.

Renal Impairment

The clearance of topiramate was reduced by 43% in moderately renal impaired (creatinine clearance 30 to 60 mL/min/1.73m²) and by 54% in severely renal impaired (creatinine clearance <30 mL/min/1.73m²). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether the clearance can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment (creatinine clearance 30 to 69 mL/min/1.73m²). In patients with severe renal impairment (creatinine clearance <30 mL/min/1.73m²), it is unclear whether the clearance can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. Therefore, a supplemental dose may be required.

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 <30 mL/min/1.73m²). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether the clearance can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment (creatinine clearance 30 to 69 mL/min/1.73m²). In patients with severe renal impairment (creatinine clearance <30 mL/min/1.73m²), it is unclear whether the clearance can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. Therefore, a supplemental dose may be required.

Hepatic Impairment

In hepatitis-impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood.

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 <30 mL/min/1.73m²). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether the clearance can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment (creatinine clearance 30 to 69 mL/min/1.73m²). In patients with severe renal impairment (creatinine clearance <30 mL/min/1.73m²), it is unclear whether the clearance can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. Therefore, a supplemental dose may be required.

Warnings and Precautions

Topiramate overdose has resulted in severe metabolic acidosis.[32x31] Topiramate tablets and oral solution are available as 25 mg, 50 mg, and 100 mg circular tablets and 200 mg capsule shaped tablets for oral administration.

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 marketed in the United States as Topamax® tablets and Topamax® oral solution, 25 mg, 50 mg, and 100 mg. Topiramate tablets USP and oral solution are available as 25 mg, 50 mg, and 100 mg. 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, polyvinyl alcohol, 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.

Topiramate is designated chemically as 2,3:4,5-Di-O-isopropylidene-ß-D-fructopyranose 4-O-sulfate. Topiramate USP is a white crystalline powder with a bitter taste. Topiramate USP is most soluble in alkali solutions containing sodium hydroxide or sodium phosphate and forms a precipitate with sulfuric acid or acetic acid, dimethylsulfoxide and diethyl ether. The solubility in water is 6 mg/mL. Its saturated solution has a pH of 6.2. Topiramate has the molecular formula C14H21NO10 and a molecular weight of 336.36. Topiramate is designated chemically as 2,3:4,5-Di-O-isopropylidene-ß-D-fructopyranose 4-O-sulfate and has the following structural formula.
in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced. As recommended for all patients, dosage adjustment may be required in the elderly patient when impaired renal function (creatinine clearance rate ≤ 30 mL/min) is evident. It may be useful to monitor renal function in the elderly patient (see Dosage and Administration (6.0) and Warnings and Precautions (5.4)).

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

Pediatric Pharmacokinetics

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

Pediatric patients on anticonvulsant treatment exhibited a higher oral clearance (CL) of topiramate compared to patients on monotherapy, presumably because of increased clearance from concurrent enzyme-inducing antiepileptic drugs. In comparison, topiramate clearance per kg is greater in pediatric patients than in adults and in young pediatric patients compared to older pediatric patients. In the former, the plasma drug concentration for the same mg/kg/day dose would be lower in pediatric patients compared to adults and in younger pediatric patients compared to older pediatric patients. Clearance was independent of dose.

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

Drug-Drug Interactions

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical trials (see table). In patients with epilepsy, the effects of these interactions on mean plasma AUCs are summarized in Table 10.

In addition to the pharmacokinetic interaction described in the above table, concomitant administration of valproic acid and topiramate tablets has been associated with hyperammonemia, with or without encephalopathy and hypothermia (see Warnings and Precautions (5.10), (5.11) and Drug Interactions (7.1)).

CNS Depressants

Concomitant administration of topiramate and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate tablets to cause CNS depression, as well as other cognitive and/or neurophysiologic adverse effects, topiramate tablets should be used with extreme caution if used in combination with CNS depressant drugs (see Drug Interactions (7.1)).

Oral Contraceptives

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combined oral contraceptive product containing 1 mg norethindrone enantate (NET) plus 35 mcg ethinyl estradiol (EE), topiramate tablets, given in the absence of other medications at doses of 50 to 200 mg/day, was not associated with statistically significant changes in oral contraceptive efficacy. The metabolic pathways of both NET and EE are glucuronidated by cytochrome P450 enzymes. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (21%, 29%, and 40%, respectively) when given alone in the absence of the oral contraceptive therapy in patients taking valproic acid tablets. In this study, topiramate tablets (150 mg/day to 800 mg/day) did not significantly affect exposure to EE at valproic acid. Although there was a dose dependent decrease in EE exposure for doses between 200 and 800 mg/day, there was no significant difference in EE exposure for doses of 200 mg/day or greater with or without valproic acid. In a third study, there was a 15% decrease in oral contraceptive efficacy with concomitant administration of valproic acid and topiramate tablets. In addition, the possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination and contraceptive products with topiramate tablets. Patients taking estrogen-containing contraceptives should be advised to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding (see Drug Interactions (7.1)).

Biphosphonates

In a single-dose study, verum digoxin AUC was decreased by 11% with concomitant topiramate tablets. The clinical significance of this observation has not been established.

Hydrochlorothiazide

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of hydrochlorothiazide (HCTZ) (25 mg/day) and topiramate (96 mg q24h) when administered alone and concomitantly. The results of this study indicate that HCTZ Cmax,ss increased by 21% and AUC increased by 26% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose.

The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when topiramate was given alone. The systemic exposure of lithium (27% for Cmax,ss and 26% for AUC) following topiramate and lithium coadministration was also reduced by 13% and 15%, and Cmax,ss was reduced by 16% and 23%, respectively. The steady-state pharmacokinetics of lithium were unaffected by concomitant administration of hydrochlorothiazide.

Lithium

In patients, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure of lithium (27% for Cmax,ss and 26% for AUC) following topiramate dosing up to 800 mg/day. Lithium levels should be monitored when co-administered with high-dose topiramate tablets (see Drug Interactions (7.1)).

Hepatic Enzyme Inducers

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

Anticonvulsants

There was a 12% increase in AUC and Cmax,ss for amitriptyline (25 mg per day) in 18 normal subjects (9 males, 9 females) receiving 200 mg/day of topiramate. Some subjects may experience a larger increase in amitriptyline concentration in the presence of topiramate tablets. Changes in amitriptyline concentration may only be made according to the patient’s clinical response and not on the basis of plasma levels.

Sumatriptan

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

Risperidone

When administered concomitantly with topiramate tablets at escalating doses of 100, 200, and 400 mg/day, there was a reduction in risperidone systemic exposure (32% and 33% for steady-state AUC at the 250 and 400 mg/day doses of topiramate). No alterations of risperidone plasma levels were observed. Co-administration of topiramate 400 mg/day with risperidone resulted in a 14% increase in C\text{max}\_\text{risperidone} and a 12% increase in AUC\_\text{risperidone}. There were no clinically significant changes in the systemic exposure of risperidone plus 9-hydroxyrisperidone or of topiramate; therefore, this interaction is not likely to be of clinical significance.

Propranolol

Multiple dosing of topiramate (200 mg) in 24 healthy volunteers (12 male, 12 female) did not affect the pharmacokinetics of 1 mg subcutaneous dose of propranolol. Similarly, a 4 mg subcutaneous dose of propranolol did not affect the pharmacokinetics of a 200 mg daily dose of topiramate in the same study.

Zolfinamine

Multiple dosing of topiramate (150 mg) in healthy volunteers did not affect the pharmacokinetics of 1 mg subcutaneous dose of zolfinamine. Multiple dosing of topiramate (150 mg) for 2 weeks did not affect the pharmacokinetics of topiramate.

Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., ziramamide, acetazolamide, or dichlorphenamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if topiramate is used concomitantly with another carbonic anhydrase inhibitor, topiramate should be used with caution.

Drug/Laboratory Tests Interactions

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis Impairment of Fertility

Carcinogenesis

An increase in urinary bladder tumors was observed in mice given topiramate (50, 150, and 200 mg/kg) in a 18-month bioassay. The increased urinary bladder tumors were demonstrated in a repeat bioassay conducted in CD-1 mice. The incidence of urinary bladder tumors was associated with plasma concentrations of topiramate. In the third bioassay conducted in BalB/c mice, the urinary bladder tumors were not observed in the topiramate-treated groups (50, 150, and 200 mg/kg). No increases in the incidence of bladder tumors were observed in rats receiving topiramate (0, 5, 15, and 50 mg/kg) for 2 years or in hamsters receiving topiramate (0, 20, 60, and 200 mg/kg) for 2 years. In a 2-year carcinogenicity study in rats receiving topiramate (0, 20, 60, and 200 mg/kg) for 2 years, no increase in the incidence of any other tumors was noted in the topiramate-treated groups. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of topiramate-related genotoxicity was observed in the following tests: in vitro bacterial mutagenesis assays (Ames test), in vitro mammalian chromosome aberration assays, in vivo mouse lymphoma assay, or in vivo mouse micronucleus assay.

Impairment of Fertility

Topiramate did not demonstrate genotoxic potential when tested in a battery of animal fertility and reproducibility tests. Topiramate was not mutagenic in the Ames test or the mouse lymphoma assay. Topiramate did not demonstrate clastogenic activity in the mouse bone marrow chromosome aberration assay. Topiramate was not mutagenic in the mouse gene mutation test. No evidence of topiramate-related genotoxicity was observed in the following tests: in vitro bacterial mutagenesis assays (Ames test), in vitro mammalian chromosome aberration assays, in vivo mouse lymphoma assay, or in vivo mouse micronucleus assay.

Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., ziramamide, acetazolamide, or dichlorphenamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if topiramate is used concomitantly with another carbonic anhydrase inhibitor, topiramate should be used with caution.
Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate tablets or placebo. In each study, patients were stabilized on optimum dosages of their concurrent AEDs during baseline phase prior to 4, 8, or 12 weeks. Patients who experienced a prespecified minimum number of partial onset seizures, with or without secondary generalization, during the baseline phase (12 patients for 12-week baseline; 9 for 8-week baseline; or 3 for 4-week baseline) were randomized to each dose and the actual mean and median doses in the stabilization period are shown in Table 11.

Patients With Lennox-Gastaut Syndrome

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

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate tablets or placebo. Patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least six partial onset seizures, with or without secondary generalization, during the baseline phase were randomly assigned to placebo or topiramate tablets in addition to their other AEDs.

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

The primary measures of effectiveness were:

- The percent of patients who were minimally, much, or very much improved from baseline.
- Median % reduction and % responders for drop attacks, i.e., tonic or atonic seizures.
- % Responders to topiramate doses of 175, 225, or 400 mg/day based on patients' body weight to approximate a dosage of 175 mg to 200 mg/day increments every other week until the target dose of 125, 175, or 200 mg/day was reached, unless intolerance prevented increases.
- After titration, patients entered an 8-week stabilization period.

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

<table>
<thead>
<tr>
<th>Protocol/Stabilization Placebo</th>
<th>Target Topiramate Dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol/Placebo</td>
<td>200 400 600 800 1,000 mg/day *</td>
</tr>
<tr>
<td>Placebo</td>
<td>-- -- -- -- --</td>
</tr>
<tr>
<td>Topiramate</td>
<td>200 400 600 800 1,000 mg/day</td>
</tr>
</tbody>
</table>

Comparisons with placebo:

Partial/Generalized Seizures

- in adults
- in pediatric patients

Median % Reduction

- in pediatric patients

% Responders

- in adults
- in pediatric patients

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

- **16.1 How Supplied**

**Topiramate tablets USP**

- **100 mg/day.**
- **200 mg/day.**

The mean migraine headache frequency rate at baseline was approximately 3.5 migraine headache(28) days and was similar across treatment groups. The change in the mean migraine headache frequency from baseline to the double-blind phase was -1.5, -2.1, and -2.2 in the topiramate 50, 100, and 200 mg/day groups, respectively, versus -0.8 in the placebo group (see Figure 2). The treatment differences between the topiramate groups and the placebo group were similar and statistically significant (p<0.001 for both comparisons).

In Study 11, a total of 468 patients (46 females, 42 males), ranging in age from 12 to 65 years, were randomized and provided efficacy data. Two hundred forty-six patients completed the entire 26-week double-blind phase. The median average daily dosages were 48 mg/day, 88 mg/day, and 132 mg/day in the target dose groups of topiramate 50, 100, and 200 mg/day, respectively.

The mean migraine headache frequency rate at baseline was approximately 3.5 migraine headache(28) days and was similar across treatment groups. The change in the mean migraine headache frequency from baseline to the double-blind phase was -1.4, -2.1, and -2.2 in the topiramate 50, 100, and 200 mg/day groups, respectively, versus -1.1 in the placebo group (see Figure 2). The differences between the topiramate 100 and 200 mg/day groups versus placebo were similar and statistically significant (p=0.008 and p<0.001, respectively).

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

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

**Figure 2: Reduction in 6-Week Migraine Headache Frequency**

(Studies 10 and 11 for Adults and Adolescents)

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo</th>
<th>Topiramate 50 mg/day</th>
<th>Topiramate 100 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.6</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Last 12 Weeks of Double-Blind Phase</td>
<td>2.3</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Percent Reduction (%)</td>
<td>44.4</td>
<td>44.4</td>
<td>72.2</td>
</tr>
</tbody>
</table>

*P-values for the dose groups were adjusted p-value according to the Hochberg multiple comparison procedure.*

### 14.3 Migraine Prophylaxis

Adult Patients

The results of 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials established the effectiveness of topiramate in the prophylactic treatment of migraine headache. The design of both trials (Study 10 was conducted in the U.S. and Study 12 was conducted in the U.S. and Canada) was identical, enrolling patients with a history of migraine, with or without aura, for at least 6 months, according to the International Headache Society criteria.

Pediatric Patients 12 to 17 Years of Age

The effectiveness of topiramate as prophylaxis for migraine headache in pediatric patients 12 to 17 years of age was established in a multicenter, randomized, double-blind, parallel-group trial. The study enrolled 103 patients (41 male, 62 female) 12 to 17 years of age with episodic migraine headaches with or without aura. Patient selection was based on IHS criteria (using proposed revisions to the 1988 IHS pediatric migraine criteria[IHS-A criteria].)

Patients who experienced 3 to 12 migraine attacks according to IHS criteria classified by patient reported diaries and a 4-week prospective baseline period were randomized to receive topiramate 50, 100, or 200 mg/day. The 2 parallel groups of patients were assigned based on subject’s weight to approximate a dosage of 6 mg/kg per day. Approximately 80% or more patients in each treatment group completed the study. The median average daily dosages were 45 and 79 mg/day in the target dose groups of topiramate 50, 100, and 200 mg/day, respectively.

Effectiveness of treatment was assessed by comparing each topiramate treatment group to placebo (ITT population). The percent reduction from baseline to the last 12 weeks of the double-blind phase in average monthly migraine attack rate (primary endpoint) was -1.4, -2.1, and -2.2 in the topiramate 50, 100, and 200 mg/day groups, respectively, versus -1.1 in the placebo group (see Figure 2). The differences between the topiramate 100 and 200 mg/day groups versus placebo were similar and statistically significant (p=0.008 and p<0.001, respectively).
one side and "C" on the other side and are available in
55700-227-30
55700-227-40
55700-227-40
55700-227-27
50 mg: Light orange colored, circular, blisters, film-coated tablets, debossed with "323"
on one side and "C" on the other side and are available in
100 mg: Orange colored, circular, blisters, film-coated tablets, debossed with "324"on one side and "C40" on the other side and are available in
200 mg: Pink colored, capsule shaped, blister, film-coated tablets, debossed with"325" on one side and "C41" on other side and are available in
PRINCIPAL DISPENSE in a light resistant container as defined in the USP. Use child-resistant closure (as required).

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

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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

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

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

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

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

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

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

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

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

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

17.11 Carcinogenesis, Mutagenesis, Impairment of Fertility
Instruct patient taking topiramate tablets should be told to seek immediate medical attention if they experience blurred vision, visual disturbances, or paranoid pain [see Warnings and Precautions (5.1)].

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

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

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

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

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

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

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

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

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

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

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

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

17.24 MEDICATION GUIDE
Topiramate (toe pir'a mate) Tablets, USP
What is the most important information I should know about topiramate tablets?
Topiramate tablets may cause decreased sweating and increased body temperature (fever). People, especially children, should be watched for signs of decreased sweating and fever, especially in hot temperatures. Some people may need to be hospitalized for this condition. Call your healthcare provider right away if you feel hot or have a high fever.

Topiramate tablets may cause acidosis (metabolic acidosis). If left untreated, metabolic acidosis can cause brittle or soft bones, growth problems in children, and growth (e.g., growth delay/retardation) in pediatric patients, and on the fetus [see Warnings and Precautions (5.4) and Use in Specific Populations (8.4)]

Topiramate tablets can increase the level of acid in your blood (metabolic acidosis). Sometimes people with metabolic acidosis will:
- feel tired
- not feel hungry (loss of appetite)
- feel changes in heartbeat
- have trouble thinking clearly

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

- Dizziness
- Effects on your vision
- Effects on your kidney function
- Effects on your mental health
- Effects on your thinking, behavior, or mood

Topiramate tablets can increase your chances of getting kidney stones. If you have kidney stones, avoid drinking alcohol while taking topiramate tablets. Topiramate and alcohol can make kidney stones worse. Your healthcare provider will tell you how to stop taking topiramate tablets safely if you need to stop taking it for any reason.

If you take too much topiramate tablets, call your healthcare provider or poison control center right away if you become pregnant while taking topiramate tablets, take your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The registry collects information about the safety of antiepileptic drugs during pregnancy.

What to know before taking topiramate tablets?

Topiramate tablets are a prescription medicine used:

- to treat certain types of seizures (partial-onset seizures and primary generalized tonic-clonic seizures) in adults and children 2 years and older.
- with other medicines to treat certain types of seizures (partial-onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children 2 years and older.

Topiramate tablets are not used to prevent migraine headaches in adults and adolescents 12 years and older.

How to take topiramate tablets?

- Take topiramate tablets exactly as prescribed.
- Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.
- Topiramate tablets should be swallowed whole. Do not chew or crush the tablets. They may leave a bitter taste.
- Store any medicine and food mixture for later use.
- If you take too much topiramate tablets, call your healthcare provider or poison control center right away if you miss one dose, take your usual dose of topiramate tablets, and stop the missed dose. Do not double your dose. If you have missed more than one dose, you should talk to your healthcare provider for advice.

What to avoid while taking topiramate tablets?

- Do not drink alcohol while taking topiramate tablets. Topiramate and alcohol can make kidney stones worse. Your healthcare provider will tell you how to stop drinking alcohol if you need to stop taking it for any reason.

- Do not do any activity that requires alertness, such as driving or operating heavy machinery, until you know how topiramate tablets affect you. Topiramate tablets can slow your thinking and motor skills, and may affect vision.

- Do not use nonprescription drugs or over-the-counter nonprescription medicine (drugs) unless you talk to your healthcare provider about using them.

- Do not drink alcohol while taking topiramate tablets. Topiramate and alcohol can make kidney stones worse. Your healthcare provider will tell you how to stop drinking alcohol if you need to stop taking it for any reason.

- Do not drive or operate heavy machinery while taking topiramate tablets. Your healthcare provider will tell you how to stop driving or operating heavy machinery if you need to stop taking it for any reason.

- Do not use nonprescription drugs or over-the-counter nonprescription medicine (drugs) unless you talk to your healthcare provider about using them.

- Do not drink alcohol while taking topiramate tablets. Topiramate and alcohol can make kidney stones worse. Your healthcare provider will tell you how to stop drinking alcohol if you need to stop taking it for any reason.

- Do not use nonprescription drugs or over-the-counter nonprescription medicine (drugs) unless you talk to your healthcare provider about using them.

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- Do not use nonprescription drugs or over-the-counter nonprescription medicine (drugs) unless you talk to your healthcare provider about using them.

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- Do not use nonprescription drugs or over-the-counter nonprescription medicine (drugs) unless you talk to your healthcare provider about using them.

- Do not drink alcohol while taking topiramate tablets. Topiramate and alcohol can make kidney stones worse. Your healthcare provider will tell you how to stop drinking alcohol if you need to stop taking it for any reason.

- Do not use nonprescription drugs or over-the-counter nonprescription medicine (drugs) unless you talk to your healthcare provider about using them.

- Do not drink alcohol while taking topiramate tablets. Topiramate and alcohol can make kidney stones worse. Your healthcare provider will tell you how to stop drinking alcohol if you need to stop taking it for any reason.

- Do not use nonprescription drugs or over-the-counter nonprescription medicine (drugs) unless you talk to your healthcare provider about using them.
- tingling of the arms and legs (paresthesia)
- not feeling hungry
- nausea
- a change in the way foods taste
- dizziness
- nervousness
- upper respiratory tract infection
- sleep problems
- weakness
- drowsiness
- sleeplessness/drowsiness
- slow reactions
- difficulty with memory
- pain in the abdomen
- fever
- decreased feeling or sensitivity, especially in the skin

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

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

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

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

Additional pediatric use information for patients ages 12 to 17 years is available. For more information, call 1-866-604-3268