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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TROKENDI XR safely and effectively. See full prescribing information for TROKENDI XR.

TROKENDI XR (topiramate) extended-release capsules, for oral use
Initial U.S. Approval: 1996

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1, 1.3)	4/2017
Dosage and Administration (2.1, 2.3)	4/2017
Warnings and Precautions (5.4, 5.7, 5.10, 5.11)	4/2017

----------INDICATIONS AND USAGE----------

TROKENDI XR® is indicated for:

- Monotherapy epilepsy: initial monotherapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures (1.1)
- Adjunctive therapy epilepsy: adjunctive therapy in patients 6 years of age and older with partial onset, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome (LGS) (1.2)
- Migraine: Prophylaxis of migraine headache in adults and adolescents 12 years of age and older (1.3)

----------DOSAGE AND ADMINISTRATION----------

	Initial Dose	Titration	Recommended Dose
Monotherapy: Partial Onset or Primary Generalized Tonic-Clonic Seizures			
Adults and pediatric patients 10 years and older (2.1)	50 mg orally once daily	Increase dose weekly by increments of 50 mg for first 4 weeks then 100 mg for weeks 5 to 6	400 mg once daily
Pediatric patients 6 to less than 10 (2.1)	25 mg/day nightly for the first week	Titrate over 5 to 7 weeks	Daily doses based on weight (Table 1)
Adjunctive Therapy			
Adults with partial onset seizures or LGS (2.2)	25 mg to 50 mg orally once daily	Increase dose weekly by increments of 25 mg to 50 mg to achieve an effective dose	200 mg to 400 mg once daily
Adults with primary generalized tonic-clonic seizures (2.2)	25 mg to 50 mg orally once daily	Increase dose weekly to an effective dose by increments of 25 mg to 50 mg	400 mg once daily
Pediatric patients 6 years and older with partial onset seizures, primary generalized tonic-clonic seizures, or LGS (2.2)	25 mg once at nighttime (based on a range of 1 mg/kg to 3 mg/kg once daily) for first week	Increase dosage at 1- or 2-week intervals by increments of 1 mg/kg to 3 mg/kg Dose titration should be guided by clinical outcome	5 mg/kg to 9 mg/kg once daily
Migraine			
Prophylaxis of migraine headache (2.3)	25mg once daily administered for first week	Increase dosage weekly by 25mg increments to achieve desired clinical outcome	100 mg once daily

Swallow capsule whole and intact. Do not sprinkle on food, chew, or crush (2.10)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release capsules: 25 mg, 50 mg, 100 mg, and 200 mg (3)

----------CONTRAINDICATIONS----------

- With recent alcohol use, ie, within 6 hours prior to and 6 hours after TROKENDI XR® use (4), (5.5)
- In patients with metabolic acidosis taking concomitant metformin (4), (5.4)

----------WARNINGS AND PRECAUTIONS----------

- Acute myopia and secondary angle closure glaucoma: Untreated elevated intraocular pressure can lead to permanent visual loss. Discontinue TROKENDI XR® if it occurs (5.1)
- Visual field defects: These have been reported independent of elevated intraocular pressure. Consider discontinuation of TROKENDI XR (5.2)
- Oligohydrosis and hyperthermia: Monitor decreased sweating and increased body temperature, especially in pediatric patients (5.3)
- Metabolic acidosis: Measure baseline and periodic measurement of serum bicarbonate. Consider dose reduction or discontinuation of TROKENDI XR® if clinically appropriate (5.4)
- Suicidal behavior and ideation: Antiepileptic drugs increase the risk of suicidal behavior or ideation (5.6)
- Cognitive/neuropsychiatric: TROKENDI XR® may cause cognitive dysfunction. Use caution when operating machinery including automobiles. Depression and mood problems may occur (5.7)
- Fetal toxicity: Topiramate use during pregnancy can cause cleft lip and/or palate and increases the risk of being small for gestational age (5.8)
- Withdrawal of AEDs: Withdrawal of TROKENDI XR® should be done gradually (5.9)
- Hyperammonemia and encephalopathy: Patients with inborn errors of metabolism or reduced mitochondrial activity may have an increased risk of hyperammonemia. Measure ammonia if encephalopathic symptoms occur (5.10)
- Kidney stones: Avoid use with other carbonic anhydrase inhibitors, other drugs causing metabolic acidosis, or in patients on a ketogenic diet (5.11)
- Hypothermia: Reported with concomitant valproic acid use (5.12)

----------ADVERSE REACTIONS----------

The most common (≥ 10% more frequent than placebo or low-dose topiramate in monotherapy and adjunctive therapy) adverse reactions in adult and pediatric patients were paresthesia, anorexia, weight decrease, speech disorders/related speech problems, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, abnormal vision, difficulty with memory, difficulty with concentration/attention, and fever (6.1).
The most common (≥5% more frequent than placebo) adverse reactions at recommended dosing in adult and adolescent controlled migraine clinical trials were paresthesia , anorexia, weight decrease, difficulty with memory, taste perversion, upper respiratory tract infections, abdominal pain, diarrhea, hypoesthesia, and nausea (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Supernus Pharmaceuticals at 1-866-398-0833 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Oral contraceptives: Decreased contraceptive efficacy and increased breakthrough bleeding, especially at doses greater than 200 mg per day (7.2)
- Phenytoin or carbamazepine: Concomitant administration with topiramate decreased plasma concentrations of topiramate (7.3)
- Lithium: Monitor lithium levels when co-administered with high-dose topiramate (7.7)

----------USE IN SPECIFIC POPULATIONS----------

- Renal Impairment: (creatinine clearance less than 70 mL/min/1.73m^2), one-half of the adult dose is recommended (8.7)
- Patients undergoing hemodialysis: Topiramate is cleared by hemodialysis. Dosage adjustment is necessary to avoid rapid drops in topiramate plasma concentration during hemodialysis (8.8)
- Pediatric Use: Because the capsule must be swallowed whole, and may not be sprinkled on food, crushed, or chewed, TROKENDI XR® is recommended only for children ages 6 years and older (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 4/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy Epilepsy

TROKENDI XR® extended-release capsules are indicated in patients 6 years of age and older as initial monotherapy for partial onset or primary generalized tonic-clonic seizures. Safety and effectiveness in patients who were converted to monotherapy from a previous regimen of other anticonvulsant drugs have not been established in controlled trials [*see Clinical Studies (14.2)*].

1.2 Adjunctive Therapy Epilepsy

TROKENDI XR® extended-release capsules are indicated as adjunctive therapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome [*see Clinical Studies (14.3, 14.4, 14.5)*].

1.3 Migraine

TROKENDI XR® capsules are indicated for the prophylaxis of migraine headache in adults and adolescents 12 years of age and older [*see Clinical Studies (14.6)*]. The usefulness of TROKENDI XR® in the acute treatment of migraine headache has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing in Monotherapy Epilepsy

Adults and Pediatric Patients 10 Years and Older with Partial Onset or Primary Generalized Tonic-Clonic Seizures

The recommended dose for topiramate monotherapy in adults and in pediatric patients 10 years of age and older is 400 mg orally once daily. Titrate TROKENDI XR® according to the following schedule:

Week 1	50 mg once daily
Week 2	100 mg once daily
Week 3	150 mg once daily
Week 4	200 mg once daily
Week 5	300 mg once daily
Week 6	400 mg once daily

Pediatric Patients Ages 6 to less than 10 Years

Dosing of topiramate as initial monotherapy in pediatric patients 6 to less than 10 years of age with partial onset or primary generalized tonic-clonic seizures was based on a pharmacometric bridging approach *[see Clinical Studies (14.1)]*.

Dosing in patients 6 to less than 10 years is based on weight. During the titration period, the initial dose of TROKENDI XR® should be 25 mg/day administered nightly for the first week. Based upon tolerability, the dosage can be increased to 50 mg/day in the second week. Dosage can be increased by 25-50 mg/day each subsequent week as tolerated. Titration to the minimum maintenance dose should be attempted over 5-7 weeks of the total titration period. Based upon tolerability and clinical response, additional titration to a higher dose (up to the maximum maintenance dose) can be attempted at 25-50 mg/day weekly increments. The total daily dose should not exceed the maximum maintenance dose for each range of body weight (Table 1).

Table 1: Monotherapy Target Total Daily Maintenance Dosing for Patients 6 to less than 10 Years

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Weight (kg)	Total Daily Dose (mg/day) Minimum Maintenance Dose	Total Daily Dose (mg/day) Maximum Maintenance Dose
Up to 11	150	250
12 - 22	200	300
23 - 31	200	350
32 - 38	250	350
Greater than 38	250	400

2.2 Dosing in Adjunctive Therapy Epilepsy

Adults 17 Years of Age and Over with Partial Onset Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome

The recommended total daily dose of TROKENDI XR® as adjunctive therapy in adults with partial onset seizures or Lennox-Gastaut Syndrome is 200 mg to 400 mg orally once daily and with primary generalized tonic-clonic seizures is 400 mg orally once daily.

Initiate therapy at 25 mg to 50 mg once daily followed by titration to an effective dose in increments of 25 mg to 50 mg every week. Daily topiramate doses above 1600 mg have not been studied.

In the study of primary generalized tonic-clonic seizures using topiramate, the assigned dose was reached at the end of 8 weeks [*see Clinical Studies (14.4)*].

Pediatric Patients 6 to 16 Years of Age - Partial Onset Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome

The recommended total daily dose of TROKENDI XR® as adjunctive therapy for pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 mg/kg to 9 mg/kg orally once daily. Begin titration at 25 mg once daily (based on a range of 1 mg/kg/day to 3 mg/kg/day) given nightly for the first week. Subsequently, increase the dosage at 1- or 2-week intervals by increments of 1 mg/kg to 3 mg/kg to achieve optimal clinical response. Dose titration should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.

In the study of primary generalized tonic-clonic seizures, the assigned dose of 6 mg/kg once daily was reached at the end of 8 weeks [*see Clinical Studies (14.4)*].

2.3 Dosing in Migraine

The recommended total daily dose of TROKENDI XR® as treatment for prophylaxis of migraine headache in adults and adolescents 12 years of age and older is 100 mg once daily. The recommended titration rate for TROKENDI XR® for migraine prophylaxis to 100 mg once daily is:

Migraine Prophylaxis Titration Schedule for Adults and Adolescents 12 Years of Age and Older

Week 1: 25mg once daily
Week 2: 50mg once daily
Week 3: 75mg once daily
Week 4: 100mg once daily

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

2.4 Administration with Alcohol

Alcohol use should be completely avoided within 6 hours prior to and 6 hours after TROKENDI XR® administration [see *Warnings and Precautions (5.5)*].

2.5 Dose Modifications in Patients with Renal Impairment

In patients with renal impairment (creatinine clearance less than 70 mL/min/1.73 m^2), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Prior to dosing, obtain an estimated GFR measurement in patients at high risk for renal insufficiency (e.g., older patients, or those with diabetes mellitus, hypertension, or autoimmune disease).

2.6 Dosage Modifications in Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than in patients with normal renal function. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an antiseizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account the:

- duration of dialysis period
- clearance rate of the dialysis system being used
- effective renal clearance of topiramate in the patient being dialyzed

2.7 Laboratory Testing Prior to Treatment Initiation

Measurement of baseline and periodic serum bicarbonate during TROKENDI XR® treatment is recommended [*see Warnings and Precautions (5.4)*].

2.8 Dosing Modifications in Patients Taking Phenytoin and/or Carbamazepine

The co-administration of TROKENDI XR® with phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TROKENDI XR® may require adjustment of the dose of TROKENDI XR®.

2.9 Monitoring for Therapeutic Blood Levels

It is not necessary to monitor topiramate plasma concentrations to optimize TROKENDI XR® therapy.

2.10 Administration Instructions

TROKENDI XR® can be taken without regard to meals.

Swallow capsule whole and intact. Do not sprinkle on food, chew, or crush.

3 DOSAGE FORMS AND STRENGTHS

TROKENDI XR® (topiramate) extended-release capsules are available in the following strengths and colors:

25 mg: Size 2 capsules, light green opaque body/yellow opaque cap (printed “SPN” on the cap, “25” on the body)

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50 mg: Size 0 capsules, light green opaque body/orange opaque cap (printed “SPN” on the cap, “50” on the body)
100 mg: Size 00 capsules, green opaque body/blue opaque cap (printed “SPN” on the cap, “100” on the body)
200 mg: Size 00 capsules, pink opaque body/blue opaque cap (printed “SPN” on the cap, “200” on the body)

4 CONTRAINDICATIONS

TROKENDI XR® is contraindicated in patients:

- With recent alcohol use (i.e., within 6 hours prior to and 6 hours after TROKENDI XR® use) [*see Warnings and Precautions (5.5)*]
- With metabolic acidosis who are taking concomitant metformin [*see Warnings and Precautions (5.4) and Drug Interactions (7.6)*]

5 WARNINGS AND PRECAUTIONS

5.1 Acute Myopia and Secondary Angle Closure Glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TROKENDI XR® as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of TROKENDI XR®, may be helpful.

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

5.2 Visual Field Defects

Visual field defects (independent of elevated intraocular pressure) have been reported in clinical trials and in postmarketing experience in patients receiving topiramate. In clinical trials, most of these events were reversible after topiramate discontinuation. If visual problems occur at any time during treatment with TROKENDI XR, consideration should be given to discontinuing the drug.

5.3 Oligohydrosis and Hyperthermia

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

The majority of the reports have been in pediatric patients. Patients, especially pediatric patients, treated with TROKENDI XR® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TROKENDI XR® is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity *[see Drug Interactions (7.5)]*.

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5.4 Metabolic Acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate, and can be expected with treatment with TROKENDI XR®. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild to moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet or specific drugs) may be additive to the bicarbonate lowering effects of topiramate.

Manifestations of Metabolic Acidosis

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in long-term, placebo-controlled trials. Long-term, open-label treatment of infants/toddlers, with intractable partial epilepsy, for up to 1 year, showed reductions from baseline in Z SCORES for length, weight, and head circumference compared to age and sex-matched normative data, although these patients with epilepsy are likely to have different growth rates than normal infants. Reductions in Z SCORES for length and weight were correlated to the degree of acidosis [*see Pediatric Use (8.4)*]. Topiramate treatment that causes metabolic acidosis during pregnancy can possibly produce adverse effects on the fetus and might also cause metabolic acidosis in the neonate from possible transfer of topiramate to the fetus [*see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)*].

Epilepsy

Adult Patients

In adults, the incidence of persistent decreases in serum bicarbonate (levels of less than 20 mEq/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg per day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg per day. The incidence of persistent decreases in serum bicarbonate in adult patients (≥16 years of age) in the epilepsy controlled clinical trial for monotherapy was 14% for 50 mg per day and 25% for 400 mg per day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value less than 17 mEq/L and greater than 5 mEq/L decrease from pretreatment) in the adjunctive therapy trials was 3% for 400 mg per day, and 0% for placebo and in the monotherapy trial was 1% for 50 mg per day and 6% for 400 mg per day. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg per day.

Pediatric Patients (2 Years to 16 Years of Age)

Although TROKENDI XR® is not approved for use in patients below the age of 6, the incidence of persistent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures in patients age 2 years to 16 years was 67% for topiramate (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of markedly abnormally low serum bicarbonate (i.e., absolute value less than 17 mEq/L and greater than 5 mEq/L decrease from pretreatment) in these trials was 11% for topiramate and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

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In pediatric patients (6 years to 15 years of age), the incidence of persistent decreases in serum bicarbonate in the epilepsy controlled clinical trial for monotherapy performed with topiramate was 9% for 50 mg per day and 25% for 400 mg per day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value less than 17 mEq/L and greater than 5 mEq/L decrease from pretreatment) in this trial was 1% for 50 mg per day and 6% for 400 mg per day.

Pediatric Patients (Under 2 Years of Age)
Although TROKENDI XR® is not approved for use in patients less than 6 years of age, a study of topiramate as adjunctive use in patients under 2 years of age with partial onset seizures revealed that topiramate produced a metabolic acidosis that is notably greater in magnitude than that observed in controlled trials in older children and adults. The mean treatment difference (25 mg/kg/day topiramate-placebo) was -5.9 mEq/L for bicarbonate. The incidence of metabolic acidosis (defined by a serum bicarbonate less than 20 mEq/L) was 0% for placebo, 30% for 5 mg/kg/day, 50% for 15 mg/kg/day, and 45% for 25 mg/kg/day. The incidence of markedly abnormal changes (i.e., less than 17 mEq/L and greater than 5 mEq/L decrease from baseline of greater than or equal to 20 mEq/L) was 0% for placebo, 4% for 5 mg/kg/day, 5% for 15 mg/kg/day, and 5% for 25 mg/kg/day [*see Use in Specific Populations(8.4)*].

Migraine
Adult Patients
The incidence of persistent decreases in serum bicarbonate in placebo-controlled trials with immediate-release topiramate in adults for the prophylaxis of migraine was 44% for 200 mg per day, 39% for 100 mg per day, 23% for 50 mg per day, and 7% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e. absolute value less than 17mEq/L, and greater than 5mEq/L decrease from pretreatment) in these trials was 11% for 200 mg per day, 9% for 100 mg per day, 2% for 50 mg per day, and less than 1% for placebo.

Adolescent Patients
In pooled, double-blind migraine prophylaxis studies in adolescent patients (12 to 17 years of age), the incidence of persistent decreases in serum bicarbonate was 77% for 200 mg/day, 27% for 100 mg/day, 30% for 50 mg/day, and 9% for placebo. The incidence of markedly low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) was 6% for 100 mg/day, 2% for 50 mg/day, and 2% for placebo. This bicarbonate criterion was not met by any patients in the 200 mg/day group, which had a low number of subjects (n=13).

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

5.5 Interaction with Alcohol

In vitro data show that, in the presence of alcohol, the pattern of topiramate release from TROKENDI XR® capsules is significantly altered. As a result, plasma levels of topiramate with TROKENDI XR® may be markedly higher soon after dosing and subtherapeutic later in the day. Therefore, alcohol use should be completely avoided within 6 hours prior to and 6 hours after TROKENDI XR® administration.

5.6 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs) increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED, including TROKENDI XR® for any indication should be

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monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

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

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

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

Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1,000 Patients	Drug Patients with Events per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

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

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

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

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5.7 Cognitive/Neuropsychiatric Adverse Reactions

Adverse reactions most often associated with the use of topiramate, and therefore expected to be associated with the use of TROKENDI XR®, were related to the central nervous system and were observed in both the epilepsy and migraine populations. In adults, the most frequent of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties), 2) Psychiatric/behavioral disturbances (e.g.,depression or mood problems), and 3) Somnolence or fatigue.

Adult Patients

Cognitive Related Dysfunction

The majority of cognitive-related adverse reactions were mild to moderate in severity, and they frequently occurred in isolation. Rapid titration rate and higher initial dose were associated with higher incidences of these reactions. Many of these reactions contributed to withdrawal from treatment [*see Adverse Reactions (6.1)*].

In the adjunctive epilepsy controlled trials conducted with topiramate (using rapid titration such as 100 mg per day to 200 mg per day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reactions was 42% for 200 mg per day, 41% for 400 mg per day, 52% for 600 mg per day, 56% for 800 and 1,000 mg per day, and 14% for placebo. These dose-related adverse reactions began with a similar frequency in the titration or in the maintenance phase, although in some patients the events began during titration and persisted into the maintenance phase. Some patients who experienced one or more cognitive-related adverse reactions in the titration phase had a dose-related recurrence of these reactions in the maintenance phase.

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

In the 6-month migraine prophylaxis controlled trials of immediate release topiramate using a slower titration regimen (25mg per day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reactions was 19% for topiramate 50 mg per day, 22% for 100 mg per day (the recommended dose), 28% for 200 mg per day and 10% for placebo. These dose-related adverse reactions typically began in the titration phase and often persisted into the maintenance phase, but infrequently began in the maintenance phase. Some patients experienced a recurrence of one or more of these cognitive adverse reactions and this recurrence was typically in the titration phase. A relatively small proportion of topiramate-treated patients experienced more than one concurrent cognitive adverse reaction. The most common cognitive adverse reactions occurring together included difficulty with memory along with difficulty with concentration/attention, difficulty with memory along with language problems, and difficulty with concentration/attention along with language problems. Rarely, topiramate-treated patients experienced three concurrent cognitive reactions.

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (depression or mood) were dose-related for both the epilepsy and migraine populations treated with topiramate *[see Warnings and Precautions (5.6) and Adverse Reactions (6.1)]*.

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 somnolence did not differ substantially between 200 mg per day and 1,000 mg per day, but the incidence of fatigue was dose-related and increased at dosages above 400 mg per day. For the monotherapy epilepsy population in the 50 mg per day and 400 mg per day groups, the incidence of somnolence was dose-related (9% for the 50 mg per day group and

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15% for the 400 mg per day group) and the incidence of fatigue was comparable in both treatment groups (14% each). For the migraine population, somnolence and fatigue were dose-related and more common in the titration phase.

Additional nonspecific CNS events commonly observed with topiramate in the adjunctive epilepsy population include dizziness or ataxia.

Pediatric Patients

Epilepsy

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

No patients discontinued treatment due to any adverse reactions in the adjunctive epilepsy double-blind trials. In the monotherapy epilepsy double-blind trial conducted with immediate-release topiramate product, 1 pediatric patient (2%) in the 50 mg per day group and 7 pediatric patients (12%) in the 400 mg per day group discontinued treatment due to any adverse reactions. The most common adverse reaction associated with discontinuation of therapy was difficulty with concentration/attention; all occurred in the 400 mg per day group.

Migraine

The incidence of cognitive adverse reactions was increased in topiramate-treated patients (7%) versus placebo (4%) in pooled, double-blind placebo-controlled studies in which adolescent patients (12 to 17 years) were randomized to placebo or one of several fixed daily doses of immediate release topiramate (50 mg, 100 mg, 200 mg).

The incidence of cognitive adverse reactions was also increased in a placebo-controlled study of pediatric patients (6 to 16 years) treated with 2 to 3 mg/kg/day of immediate release topiramate (10%) versus placebo treatment (2%). TROKENDI XR is not approved for prophylaxis of migraine in pediatric patients under 12 years of age.

The risk for cognitive adverse reactions was dose-dependent, and was particularly evident at the 200 mg dose. This risk for cognitive adverse reactions was also greater in younger patients (6 to 11 years) than in older patients (12 to 17 years). The most common cognitive adverse reaction in these trials was difficulty with concentration/attention. Cognitive adverse reactions most commonly developed in the titration period and sometimes persisted into the maintenance period. These adverse reactions typically occurred in isolation as single type of cognitive adverse reaction. Cognitive adverse reactions that led to study discontinuation occurred in one patient (difficultly with concentration/attention and language problems). The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to adolescents (12 to 17 years) to assess the effects of topiramate on cognitive function at baseline at the end of the Study 3 *[see Clinical Studies (14.6)]*. Mean change from baseline in certain CANTAB tests suggests that topiramate treatment may result in psychomotor slowing and decreased verbal fluency.

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5.8 Fetal Toxicity

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

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

5.9 Withdrawal of Antiepileptic Drugs

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

5.10 Hyperammonemia and Encephalopathy

Hyperammonemia/Encephalopathy Without Concomitant Valproic Acid (VPA)

Topiramate treatment has produced hyperammonemia (in some instances dose-related) in a clinical investigational program in adolescent patients (12 to 17 years) who were treated with topiramate for migraine prophylaxis. The incidence of hyperammonemia (above the upper limit of normal reference) at any time in the trial was 9% for placebo, 14% for 50 mg, and 26% for 100 mg topiramate daily. In some patients, hyperammonemia was observed at the end of the trial at the final visit. The incidence of markedly increased hyperammonemia (at least 50% or higher above upper limit of normal) at any time in the trial in adolescent patients was also increased at 100 mg/day (9%) compared to 50 mg topiramate (0%) or placebo (3%). During this trial, markedly increased ammonia levels returned to normal in all but one patient (in whom the ammonia level fell to high instead of markedly abnormal).

Topiramate treatment has produced hyperammonemia in a clinical investigational program in very young pediatric patients (1 month to 24 months) who were treated with adjunctive topiramate for partial onset epilepsy (8% for placebo, 10% for 5 mg/kg/day, 0% for 15 mg/kg/day, 9% for 25 mg/kg/day). TROKENDI XR® is not approved as adjunctive treatment of partial onset seizures in pediatric patients less than 6 years old. In some patients, ammonia was markedly increased (greater than or equal to 50% above upper limit of normal). The hyperammonemia associated with topiramate treatment occurred with and without encephalopathy in placebo-controlled trials, and in an open-label, extension trial of infants with refractory epilepsy. Dose-related hyperammonemia was also observed in the extension trial in pediatric patients up to 2 years old. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting.

Hyperammonemia with and without encephalopathy has also been observed in postmarketing reports in patients who were taking topiramate without concomitant valproic acid (VPA).

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Hyperammonemia/Encephalopathy With Concomitant Valproic Acid (VPA)
Concomitant administration of topiramate and valproic acid (VPA) has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone based upon postmarketing reports. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse reaction is not due to a pharmacokinetic interaction.

Although TROKENDI XR® is not indicated for use in infants/toddlers (1 month to 24 months), topiramate with concomitant VPA clearly produced a dose-related increase in the incidence of hyperammonemia (above the upper limit of normal, 0% for placebo, 12% for 5 mg/kg/day, 7% for 15 mg/kg/day, 17% for 25 mg/kg/day) in an investigational program using topiramate. Markedly increased, dose-related hyperammonemia (0% for placebo and 5 mg/kg/day, 7% for 15 mg/kg/day, and 8% for 25 mg/kg/day) also occurred in these infants/toddlers. Dose-related hyperammonemia was similarly observed in a long-term, extension trial utilizing topiramate in these very young, pediatric patients [*see Use in Specific Populations (8.4)*].

Hyperammonemia with and without encephalopathy has also been observed in postmarketing reports in patients taking topiramate with valproic acid (VPA).

The hyperammonemia associated with topiramate treatment appears to be more common when used concomitantly with VPA.

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

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

5.11 Kidney Stones

A total of 32/2086 (1.5%) of adults exposed to topiramate during its adjunctive epilepsy therapy development reported the occurrence of kidney stones, an incidence about 2 to 4 times greater than expected in a similar, untreated population. In the double-blind monotherapy epilepsy study, a total of 4/319 (1.3%) of adults exposed to topiramate reported the occurrence of kidney stones. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men. Kidney stones have also been reported in pediatric patients taking topiramate for epilepsy or migraine. During long-term (up to 1 year) topiramate treatment in an open-label extension study of 284 pediatric patients 1 month to 24 months old with epilepsy, 7% developed kidney or bladder stones that were diagnosed clinically or by sonogram. TROKENDI XR® is not approved for pediatric patients less than 6 years old [*see Use in Specific Populations (8.4)*].

Kidney stones have also been reported in pediatric patients taking topiramate for migraine prophylaxis. For the double-blind migraine prophylaxis studies, one adverse event (renal calculus) occurred in a topiramate-treated subject in the age 12 to 17 years group. The overall experience with open-label, long-term, topiramate treatment for migraine prophylaxis is limited in pediatric patients.

TROKENDI XR® would be expected to have the same effect as topiramate on the formation of kidney stones. An explanation for the association of topiramate and kidney stones may lay in the fact that topiramate is a

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

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

5.12 Hypothermia with Concomitant Valproic Acid Use

Hypothermia, defined as an unintentional drop in body core temperature to less than 35ºC (95ºF) has been reported in association with topiramate use with concomitant valproic acid (VPA) both in the presence 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 (7.5)*]. Consideration should be given to stopping topiramate or valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

5.13 Paresthesia

Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of topiramate. Paresthesia was more frequently reported in the monotherapy epilepsy and migraine prophylaxis trials conducted with topiramate than in the adjunctive therapy epilepsy trials conducted with the same product. In the majority of instances, paresthesia did not lead to treatment discontinuation.

5.14 Interaction with Other CNS Depressants

Topiramate is a CNS depressant. Concomitant administration of topiramate with other CNS depressant drugs can result in significant CNS depression. Patients should be watched carefully when TROKENDI XR® is co-administered with other CNS depressant drugs.

6 ADVERSE REACTIONS

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

- Acute Myopia and Secondary Angle Closure Glaucoma [*see Warnings and Precautions (5.1)*]
- Visual Field Defects [*see Warnings and Precautions 5.2]*
- Oligohydrosis and Hyperthermia [*see Warnings and Precautions (5.3)*]
- Metabolic Acidosis [*see Warnings and Precautions (5.4)*]
- Suicidal Behavior and Ideation [*see Warnings and Precautions (5.6)*]
- Cognitive/Neuropsychiatric Adverse Reactions [*see Warnings and Precautions (5.7)*]
- Fetal Toxicity [*see Warnings and Precautions (5.8)* and *Use in Specific Populations (8.1)]*]
- Withdrawal of Antiepileptic Drugs [*see Warnings and Precautions (5.9)*]
- Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid Use [*see Warnings and Precautions (5.10)*]
- Kidney Stones [*see Warnings and Precautions (5.11)*]
- Hypothermia with Concomitant Valproic Acid Use [*see Warnings and Precautions (5.12)*]
- Paresthesia [*see Warnings and Precautions (5.13)*]

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The data described in the following sections were obtained using immediate-release topiramate tablets in studies of patients with epilepsy. TROKENDI XR® has not been studied in a randomized, placebo-controlled Phase III clinical study in the epilepsy patient population. However, it is expected that TROKENDI XR® would produce a similar adverse reaction profile as immediate-release topiramate.

6.1 Clinical Trials Experience

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

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 than for placebo (4.5% versus 3.0% in adult patients, and 4.4% versus 2.3% in pediatric patients). In this analysis, the incidence of serious bleeding events for topiramate and placebo was 0.3% versus 0.2% for adult patients, and 0.4% versus 0% for pediatric patients.

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

Clinical Trials Experience in Epilepsy

Adverse Reactions Observed in Monotherapy Trial for Epilepsy

Adult Patients 16 Years of Age and Older

The adverse reactions in the controlled trial (Study 1) that occurred most commonly in adults in the 400 mg per day group and at an incidence higher (≥ 5%) than in the 50 mg per day group were paresthesia, weight decrease, somnolence, anorexia, and difficulty with memory (see Table 3) [*see Clinical Studies (14.2)*].

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

Pediatric Patients 6 Years to Less Than 16 Years of Age

The adverse reactions in the controlled trial (Study 1) that occurred most commonly in pediatric patients in the 400 mg per day topiramate group and at an incidence higher (≥ 5%) than in the 50 mg per day group were fever, weight decrease, paresthesia, mood problems, cognitive problems, infection, and flushing (see Table 4) [*see Clinical Studies (14.2)*].

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

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Table 3: Incidence (%) of Adverse Reaction in the Monotherapy Epilepsy Trial in Adults[a] Where Incidence Was at Least 2% in the 400 mg/day Immediate-Release Topiramate Group and Greater Than the Rate in the 50 mg/day Immediate-Release Topiramate Group

	Immediate-release topiramate Dosage (mg/day)	
Body System/	**50**	**400**
Adverse Reaction	**(N=160)**	**(N=159)**
Body as a Whole-General Disorders		
Asthenia	4	6
Leg Pain	2	3
Chest Pain	1	2
Central & Peripheral Nervous System Disorders		
Paresthesia	21	40
Dizziness	13	14
Hypoesthesia	4	5
Ataxia	3	4
Hypertonia	0	3
Gastro-intestinal System Disorders		
Diarrhea	5	6
Constipation	1	4
Gastritis	0	3
Dry Mouth	1	3
Gastroesophageal Reflux	1	2
Liver and Biliary System Disorders		
Gamma-GT Increased	1	3
Metabolic and Nutritional Disorders		
Weight Decrease	6	16
Psychiatric Disorders		
Somnolence	9	15
Anorexia	4	14
Difficulty with Memory NOS	5	10
Insomnia	8	9
Depression	7	9
Difficulty with Concentration/Attention	7	8
Anxiety	4	6
Psychomotor Slowing	3	5
Mood Problems	2	5
Confusion	3	4
Cognitive Problem NOS	1	4
Libido Decreased	0	3
Reproductive Disorders, Female		
Vaginal Hemorrhage	0	3
Red Blood Cell Disorders		
Anemia	1	2
Resistance Mechanism Disorders		
Infection Viral	6	8
Infection	2	3
Respiratory System Disorders		

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Bronchitis	3	4
Rhinitis	2	4
Dyspnea	1	2
Skin and Appendages Disorders		
Rash	1	4
Pruritus	1	4
Acne	2	3
Special Senses Other, Disorders		
Taste Perversion	3	5
Urinary System Disorders		
Cystitis	1	3
Renal Calculus	0	3
Urinary Tract Infection	1	2
Dysuria	0	2
Micturition Frequency	0	2

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

Table 4: Incidence (%) of Adverse Reactions in the Monotherapy Epilepsy Trial in Pediatric Patients (Ages 6 to Less Than 16 Years)[a] Where Incidence Was at Least 2% in the 400 mg/day Immediate-Release Topiramate Group and Greater than the Rate in the 50 mg/day Immediate-Release Topiramate Group

	Immediate-release topiramate Dosage (mg/day)	
Body System/	**50**	**400**
Adverse Reaction	**(N=74)**	**(N=77)**
Body as a Whole-General Disorders		
Fever	1	12
Asthenia	0	3
Central & Peripheral Nervous System Disorders		
Paresthesia	3	12
Muscle Contractions Involuntary	0	3
Vertigo	0	3
Gastro-Intestinal System Disorders		
Diarrhea	8	9
Metabolic and Nutritional Disorders		
Weight Decrease	7	17
Platelet, Bleeding & Clotting Disorders		
Epistaxis	0	4
Psychiatric Disorders		
Difficulty with Concentration/Attention	7	10
Mood Problems	1	8
Cognitive Problems	1	6
Difficulty with Memory	1	3
Confusion	0	3
Depression	0	3

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	Immediate-release topiramate Dosage (mg/day)	
Body System/	**50**	**400**
Adverse Reaction	**(N=74)**	**(N=77)**
Personality Disorder (Behavior Problems)	0	3
Red Blood Cell Disorders		
Anemia	1	3
Reproductive Disorders, Female[b]		
Intermenstrual Bleeding	0	3
Resistance Mechanism Disorders		
Infection	3	8
Infection Viral	3	6
Respiratory System Disorders		
Upper Respiratory Tract Infection	16	18
Rhinitis	5	6
Bronchitis	1	5
Sinusitis	1	4
Skin and Appendages Disorders		
Rash	3	4
Alopecia	1	4
Urinary System Disorders		
Urinary Incontinence	1	3
Micturition Frequency	0	3
Vascular (Extracardiac) Disorders		
Flushing	0	5

[a]Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category
[b] N with Reproductive Disorders, Female-Incidence calculated relative to the number of females; Pediatric TPM 50 mg n=40; Pediatric TPM 400 mg n=33

Adverse Reactions Observed in Adjunctive Therapy Epilepsy Trials

The most commonly observed adverse reactions associated with the use of topiramate at dosages of 200 to 400 mg per day in controlled trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome that were seen at greater frequency in topiramate-treated patients and did not appear to be dose-related were: somnolence, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia and diplopia [see Table 5] [*see Clinical Studies (14.3, 14.4, and 14.5)*]. The most common dose-related adverse reactions at dosages of 200 mg to 1,000 mg per day were: fatigue, nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, anxiety, mood problems, and weight decrease [*see Table 7*].

Adverse reactions associated with the use of topiramate at dosages of 5 mg/kg/day to 9 mg/kg/day in controlled trials in pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome that were seen at greater frequency in topiramate-treated patients were: fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease [*see Table 8*].

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

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

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

Table 5 lists adverse reactions that occurred in at least 1% of adults treated with 200 to 400 mg per day topiramate in controlled trials that were numerically more common at this dose than in the patients treated with placebo. In general, most patients who experienced adverse reactions during the first eight weeks of these trials no longer experienced them by their last visit. Table 8 lists adverse reactions that occurred in at least 1% of pediatric patients treated with 5 mg/kg to 9 mg/kg topiramate in controlled trials that were numerically more common than in patients treated with placebo.

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

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

Table 5: Incidence (%) of Adverse Reactions in Placebo-Controlled, Adjunctive Epilepsy Trials in Adults [a,b,c]

	Topiramate Dosage (mg per day)		
Body System/ Adverse Reaction[c]	**Placebo (N=291)**	**200-400 (N=183)**	**600-1,000 (N=414)**
Body as a Whole-General Disorders			
Fatigue	13	15	30
Asthenia	1	6	3
Back pain	4	5	3
Chest pain	3	4	2
Influenza-like symptoms	2	3	4
Leg pain	2	2	4
Hot flushes	1	2	1
Allergy	1	2	3
Edema	1	2	1

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	Topiramate Dosage (mg per day)		
Body System/ Adverse Reaction[c]	**Placebo (N=291)**	**200-400 (N=183)**	**600-1,000 (N=414)**
Body odor	0	1	0
Rigors	0	1	<1
Central & Peripheral Nervous System Disorders			
Dizziness	15	25	32
Ataxia	7	16	14
Speech disorders/Related speech problems	2	13	11
Paresthesia	4	11	19
Nystagmus	7	10	11
Tremor	6	9	9
Language problems	1	6	10
Coordination abnormal	2	4	4
Hypoesthesia	1	2	1
Gait abnormal	1	3	2
Muscle contractions involuntary	1	2	2
Stupor	0	2	1
Vertigo	1	1	2
Gastro-intestinal System Disorders			
Nausea	8	10	12
Dyspepsia	6	7	6
Abdominal pain	4	6	7
Constipation	2	4	3
Gastroenteritis	1	2	1
Dry mouth	1	2	4
Gingivitis	<1	1	1
GI disorder	<1	1	0
Hearing and Vestibular Disorders			
Hearing decreased	1	2	1
Metabolic and Nutritional Disorders			
Weight decrease	3	9	13
Musculoskeletal System Disorders			
Myalgia	1	2	2
Skeletal pain	0	1	0
Platelet, Bleeding & Clotting Disorders			
Epistaxis	1	2	1
Psychiatric Disorders			
Somnolence	12	29	28
Nervousness	6	16	19
Psychomotor slowing	2	13	21
Difficulty with memory	3	12	14
Anorexia	4	10	12
Confusion	5	11	14
Depression	5	5	13
Difficulty with concentration/attention	2	6	14
Mood problems	2	4	9
Agitation	2	3	3
Aggressive reaction	2	3	3
Emotional liability	1	3	3
Cognitive problems	1	3	3
Libido decreased	1	2	<1
Apathy	1	1	3
Depersonalization	1	1	2

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	Topiramate Dosage (mg per day)		
Body System/ Adverse Reaction[c]	**Placebo (N=291)**	**200-400 (N=183)**	**600-1,000 (N=414)**
Reproductive Disorders, Female			
Breast pain	2	4	0
Amenorrhea	1	2	2
Menorrhagia	0	2	1
Menstrual disorder	1	2	1
Reproductive Disorders, Male			
Prostatic disorder	<1	2	0
Resistance Mechanism Disorders			
Infection	1	2	1
Infection viral	1	2	<1
Moniliasis	<1	1	0
Respiratory System Disorders			
Pharyngitis	2	6	3
Rhinitis	6	7	6
Sinusitis	4	5	6
Dyspnea	1	1	2
Skin and Appendages Disorders			
Skin disorder	<1	2	1
Sweating increased	<1	1	<1
Rash, erythematous	<1	1	<1
Special Senses Other, Disorders			
Taste perversion	0	2	4
Urinary System Disorders			
Hematuria	1	2	<1
Urinary tract infection	1	2	3
Micturition frequency	1	1	2
Urinary incontinence	<1	2	1
Urine abnormal	0	1	<1
Vision Disorders			
Vision abnormal	2	13	10
Diplopia	5	10	10
White Cell and RES Disorders			
Leukopenia	1	2	1

[a]Patients in these adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to topiramate or placebo
[b]Values represent the percentage of patients reporting a given reaction. Patient may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category.
[c]Adverse reactions reported by at least 1% of patients in the topiramate 200 mg to 400 mg per day group and more common than in the placebo group

Adverse Reactions Observed in Adjunctive Therapy Trial in Adults with Partial Onset Seizures (Study 7)

Study 7 was a randomized, double-blind, adjunctive, placebo-controlled, parallel group study with 3 treatment arms: 1) placebo; 2) topiramate 200 mg per day with a 25 mg per day starting dose, increased by 25 mg per day each week for 8 weeks until the 200 mg per day maintenance dose was reached; and 3) topiramate 200 mg per day with a 50 mg per day starting dose, increased by 50 mg per day each week for 4 weeks until the 200 mg per day maintenance dose was reached. All patients were maintained on concomitant carbamazepine with or without another concomitant antiepileptic drug.

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The incidence of adverse reactions (Table 6) did not differ significantly between the 2 topiramate regimens. Because the frequencies of adverse reactions reported in this study were markedly lower than those reported in the previous epilepsy studies, they cannot be directly compared with data obtained in other studies.

Table 6: Incidence (%) of Adverse Reactions in Placebo Controlled, Adjunctive Trial in Adults with Partial Onset Seizures (Study 7) [a,b,c]

		Topiramate Dosage (mg per day)
Body System/	**Placebo**	**200**
Adverse Reaction[c]	**(N=92)**	**(N=171)**
Body as a Whole-General Disorders		
Fatigue	4	9
Chest pain	1	2
Cardiovascular Disorders, General		
Hypertension	0	2
Central & Peripheral Nervous System Disorders		
Paresthesia	2	9
Dizziness	4	7
Tremor	2	3
Hypoesthesia	0	2
Leg cramps	0	2
Language problems	0	2
Gastro-intestinal System Disorders		
Abdominal pain	3	5
Constipation	0	4
Diarrhea	1	2
Dyspepsia	0	2
Dry mouth	0	2
Hearing and Vestibular Disorders		
Tinnitus	0	2
Metabolic and Nutritional Disorders		
Weight decrease	4	8
Psychiatric Disorders		
Somnolence	9	15
Anorexia	7	9
Nervousness	2	9
Difficulty with concentration/attention	0	5
Insomnia	3	4
Difficulty with memory	1	2
Aggressive reaction	0	2
Respiratory System Disorders		
Rhinitis	0	4
Urinary System Disorders		
Cystitis	0	2
Vision Disorder		
Diplopia	0	2
Vision abnormal	0	2

[a]Patients in these adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to topiramate or placebo

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[b]Values represent the percentage of patients reporting a given adverse reaction. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category
[c]Adverse reactions reported by at least 2% of patients in the topiramate 200 mg per day group and more common than in the placebo group

Table 7: Incidence (%) of Dose-Related Adverse Reactions From Placebo-Controlled, Adjunctive Trials in Adults With Partial Onset Seizures (Studies 2 through 7)[a]

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

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

Table 8: Incidence (%) of Adverse Reaction in Placebo-Controlled, Adjunctive Epilepsy Trial in Pediatric Patients (Ages 2 Years to 16 Years)[a,b,c] (Study 8)

Body System/	**Placebo**	**Topiramate**
Adverse Reaction	**(N=101)**	**(N=98)**
Body as a Whole-General Disorders		
Fatigue	5	16
Injury	13	14
Allergic reaction	1	2
Back pain	0	1
Pallor	0	1
Cardiovascular Disorders, General		
Hypertension	0	1
Central & Peripheral Nervous System Disorders		
Gait abnormal	5	8
Ataxia	2	6
Hyperkinesia	4	5
Dizziness	2	4
Speech disorders/Related speech problems	2	4
Hyporeflexia	0	2
Convulsions grand mal	0	1
Fecal incontinence	0	1
Paresthesia	0	1
Gastro-Intestinal System Disorders		
Nausea	5	6
Saliva increased	4	6

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Body System/ Adverse Reaction	Placebo (N=101)	Topiramate (N=98)
Constipation	4	5
Gastroenteritis	2	3
Dysphagia	0	1
Flatulence	0	1
Gastroesophageal reflux	0	1
Glossitis	0	1
Gum hyperplasia	0	1
Heart Rate and Rhythm Disorders		
Bradycardia	0	1
Metabolic and Nutritional Disorders		
Weight decrease	1	9
Thirst	1	2
Hypoglycemia	0	1
Weight increase	0	1
Platelet, Bleeding & Clotting Disorders		
Purpura	4	8
Epistaxis	1	4
Hematoma	0	1
Prothrombin increased	0	1
Thrombocytopenia	0	1
Psychiatric Disorders		
Somnolence	16	26
Anorexia	15	24
Nervousness	7	14
Personality disorder (Behavior Problems)	9	11
Difficulty with concentration/attention	2	10
Aggressive reaction	4	9
Insomnia	7	8
Difficulty with memory	0	5
Confusion	3	4
Psychomotor slowing	2	3
Appetite increased	0	1
Neurosis	0	1
Reproductive Disorders, Female		
Leukorrhea	0	2
Resistance Mechanism Disorders		
Infection viral	3	7
Respiratory System Disorders		
Pneumonia	1	5
Respiratory disorder	0	1
Skin and Appendages Disorders		
Skin Disorder	2	3
Alopecia	1	2

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Body System/ Adverse Reaction	Placebo (N=101)	Topiramate (N=98)
Dermatitis	0	2
Hypertrichosis	1	2
Rash erythematous	0	2
Eczema	0	1
Seborrhea	0	1
Skin discoloration	0	1
Urinary System Disorders		
Urinary incontinence	2	4
Nocturia	0	1
Vision Disorders		
Eye abnormality	1	2
Vision abnormal	1	2
Diplopia	0	1
Lacrimation abnormal	0	1
Myopia	0	1
White Cell and RES Disorders		
Leukopenia	0	2

[a]Patients in these adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to topiramate or placebo
[b]Values represent the percentage of patients reporting a given adverse reaction. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category
[c] Reactions that occurred in at least 1% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients

Clinical Trial Experience in Migraine

Adult Patients

In the four multicenter, randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials (which included 35 adolescent patients age 12 to 15 years) conducted with immediate-release topiramate, most of the adverse reactions were mild or moderate in severity. Most adverse reactions occurred more frequently during the titration period than during the maintenance period.

The most common (≥5% more frequent than placebo) adverse reactions associated with the use of the 100 mg topiramate dose in controlled, migraine clinical trials of predominantly adults were paresthesia, anorexia, weight decrease, taste perversion, diarrhea, difficulty with memory, hypoesthesia, and nausea. Table 9 includes those adverse reactions reported for patients in the placebo-controlled trials where the incidence in any immediate-release topiramate group was at least 2% and was greater than that for placebo patients.

Table 9: Incidence (%) of Adverse Reactions in Placebo-Controlled, Migraine Trials Where Incidence Was ≥ 2% in Any Immediate-release Topiramate Group and Greater than the Rate in Placebo Patients[*ab]

Body System/	Placebo	Topiramate dosage (mg per day)		
		50	100	200
Adverse Reaction	(N=445) %	(N=235) %	(N=386) %	(N=514) %
Body as a Whole-General Disorders				
Fatigue	11	14	15	19
Injury	7	9	6	6
Asthenia	1	Less than 1	2	2

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Body System/	Placebo	Topiramate dosage (mg per day)		
		50	100	200
Adverse Reaction	(N=445) %	(N=235) %	(N=386) %	(N=514) %
Fever	1	1	1	2
Influenza-like symptoms	Less than 1	Less than 1	Less than 1	2
Allergy	Less than 1	2	Less than 1	Less than 1
Central & Peripheral Nervous System Disorders				
Paresthesia	6	35	51	49
Dizziness	10	8	9	12
Hypoaesthesia	2	6	7	8
Language problems	2	7	6	7
Involuntary muscle contractions	1	2	2	4
Ataxia	Less than 1	1	2	1
Speech disorders/Related speech problems	Less than 1	1	Less than 1	2
Gastro-Intestinal System Disorders				
Nausea	8	9	13	14
Diarrhea	4	9	11	11
Abdominal pain	5	6	6	7
Dyspepsia	3	4	5	3
Dry mouth	2	2	3	5
Vomiting	2	1	2	3
Gastroenteritis	1	3	3	2
Hearing and Vestibular Disorders				
Tinnitus	1	Less than 1	1	2
Metabolic and Nutritional Disorders				
Weight decrease	1	6	9	11
Thirst	Less than 1	2	2	1
Musculoskeletal System Disorders				
Arthralgia	2	7	3	1
Neoplasms				
Neoplasm	Less than 1	2	Less than 1	Less than 1
Psychiatric Disorders				
Anorexia	6	9	15	14
Somnolence	5	8	7	10
Difficulty with memory	2	7	7	11
Difficulty with concentration/attention	2	3	6	10
Insomnia	5	6	7	6
Anxiety	3	4	5	6
Mood Problems	2	3	6	5
Depression	4	3	4	6
Nervousness	2	4	4	4
Confusion	2	2	3	4
Psychomotor slowing	1	3	2	4
Libido decreased	1	1	1	2
Aggravated depression	1	1	2	2
Agitation	1	2	2	1
Cognitive problems	1	Less than 1	2	2

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Body System/	Placebo	Topiramate dosage (mg per day)		
		50	100	200
Adverse Reaction	(N=445) %	(N=235) %	(N=386) %	(N=514) %
Reproductive Disorders, Female				
Menstrual disorder	2	3	2	2
Reproductive Disorders, Male				
Ejaculation premature	0	3	0	0
Resistance Mechanism Disorders				
Viral Infection	3	4	4	3
Otitis media	Less than 1	2	1	1
Respiratory System Disorders				
Upper respiratory tract infection	12	13	14	12
Sinusitis	6	10	6	8
Pharyngitis	4	5	6	2
Coughing	2	2	4	3
Bronchitis	2	3	3	3
Dyspnea	2	1	3	2
Rhinitis	1	1	2	2
Skin and Appendages Disorders				
Pruritis	2	4	2	2
Special Sense Other, Disorders				
Taste perversion	1	15	8	12
Taste loss	Less than 1	1	1	2
Urinary System Disorders				
Urinary tract infection	2	4	2	4
Renal calculus	0	0	1	2
Vision Disorders				
Vision abnormal	Less than 1	1	2	3
Blurred vision	2	4	2	4
Conjunctivitis	1	1	2	1

[*] Includes 35 adolescent patients age 12 to 15 years
[a] Values represent the percentage of patients reporting a given reaction. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category.
[b] Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for more than 50% of reactions coded as vision abnormal, a preferred term

Of the 1135 patients exposed to immediate-release topiramate in the placebo-controlled studies, 25% discontinued due to adverse reactions, compared to 10% of the 445 placebo patients. The adverse reactions associated with discontinuing therapy in patients in these studies included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%) and dizziness (2%).

Patients treated in these studies experienced mean percent reductions in body weight that were dose-dependent. This change was not seen in the placebo group. Mean changes of 0%, -2%, -3%, and -4% were seen for the placebo group, immediate-release topiramate 50 mg, 100 mg, and 200 mg groups, respectively.

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Table 10 shows adverse reactions that were dose-dependent. Several central nervous system adverse reactions, including some that represented cognitive dysfunction, were dose-related. The most common dose-related adverse reactions (treatment difference ≥5% for the 100 mg dose) were: paresthesia, nausea, anorexia, difficulty with memory, diarrhea, weight decrease, and hypoesthesia.

Table 10: Incidence (%) of Dose-Related Adverse Reactions From Placebo-Controlled, Migraine Trials[a]

Body System/	Placebo	Topiramate dosage (mg per day)		
		50	100	200
Adverse Reaction	(N=445) %	(N=235) %	(N=386) %	(N=514) %
Paresthesia	6	35	51	49
Fatigue	11	14	15	19
Nausea	8	9	13	14
Anorexia	6	9	15	14
Dizziness	10	8	9	12
Weight decrease	1	6	9	11
Difficulty with memory	2	7	7	11
Diarrhea	4	9	11	11
Difficulty with concentration/attention	2	3	6	10
Somnolence	5	8	7	10
Hypoaesthesia	2	6	7	8
Anxiety	3	4	5	6
Depression	4	3	4	6
Mood problems	2	3	6	5
Dry mouth	2	2	3	5
Confusion	2	2	3	4
Involuntary muscle contractions	1	2	2	4
Abnormal vision	Less than 1	1	2	3
Renal calculus	0	0	1	2

* Includes 35 adolescent patients age 12 to <16 years

[a] The incidence of adverse reactions in the 200mg per day group was greater than or equal to 2% than the incidence in both the placebo group and the 50 mg per day group

Adolescents 12 to 17 Years of Age

In five randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials, most of the adverse reactions with immediate-release topiramate were mild or moderate in severity. Most adverse reactions occurred more frequently during the titration period than during the maintenance period. Among adverse reactions with onset during titration, approximately half persisted into the maintenance period.

In four, fixed-dose, double-blind migraine prophylaxis clinical trials in immediate-release topiramate treated adolescent patients, the most commonly observed adverse reactions associated with the use of 100 mg of immediate-release topiramate that were seen at an incidence higher (≥5%) than in the placebo group were: paresthesia, upper respiratory tract infection, anorexia, and abdominal pain (see Table 11). Table 11 shows adverse reactions from the adolescent pivotal trial (Study 3) demonstrating the efficacy of immediate-release topiramate in which there were 103 adolescent patients who were treated with placebo or 50 mg or 100 mg of immediate-release topiramate, and three predominantly adult trials in which there were 49 adolescent patients (12 to 17 years) who were treated with placebo or 50 mg, 100 mg or 200 mg of immediate-release topiramate *[see Clinical Studies (14.6)]*. Table 11 also shows adverse reactions in adolescents in the controlled migraine trials when the incidence in an immediate-release topiramate dose group was at least 5% or higher than the incidence of placebo. Many adverse reactions shown in Table 11 indicated a dose-dependent relationship.

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Table 11: Incidence (%) of Adverse Reactions in at Least 5% or Greater than the Placebo Incidence of Adolescents (12 – 17 Years) in any Immediate-Release Topiramate Group in Pooled Double-Blind Migraine Prophylaxis Studies[ab]

	Immediate-Release Topiramate Dosage			
Body System/ Adverse Reaction	**Placebo (N=45) %**	**50 mg/day (N=46) %**	**100 mg/day (N=48) %**	**200 mg/day (N=13) %**
Body as a Whole – General Disorders				
Allergy	0	0	4	8
Fatigue	7	7	8	15
Fever	2	4	6	0
Leg pain	0	2	2	8
Central & Peripheral Nervous System Disorders				
Dizziness	4	4	6	0
Headache	2	2	4	8
Language problems	2	0	0	15
Muscle contractions involuntary	0	0	0	8
Paresthesia	7	20	19	38
Endocrine Disorders				
Hyperthyroidism	0	0	0	8
Gastrointestinal System Disorders				
Abdominal pain	9	7	15	15
Diarrhea	0	2	2	8
Nausea	4	4	8	0
Metabolic and Nutritional Disorders				
Edema pharynx	0	0	0	8
Weight decrease	2	7	4	31
Platelet, Bleeding & Clotting Disorders				
Epistaxis	0	2	2	8
Psychiatric Disorders				
Anorexia	4	9	10	15
Anxiety	0	0	0	8
Difficulty with concentration/attention	0	0	2	15
Difficulty with memory	2	0	0	8
Insomnia	2	9	2	0
Mood problems	4	2	2	8
Psychomotor slowing	0	2	0	8
Somnolence	2	2	6	15
Resistance Mechanism Disorders				
Infection viral	4	4	8	15
Otitis media	0	0	0	8
Respiratory System Disorders				

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Coughing	0	7	2	0
Laryngitis	0	0	0	8
Rhinitis	2	7	6	8
Sinusitis	2	9	4	15
Upper respiratory tract infection	11	26	23	23
Skin and Appendages Disorders				
Rash erythematous	0	0	0	8
Special Senses Other, Disorders				
Taste perversion	2	2	6	8
Vision Disorders				
Conjunctivitis	4	7	4	0

[a]35 adolescent patients aged 12 to <16 years were also included in adverse reaction assessment for adults (Tables 9 and10)
[b] Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.

In the double-blind placebo-controlled studies, adverse reactions led to discontinuation of treatment in 8% of placebo patients compared with 6% of immediate-release topiramate-treated patients. Adverse reactions associated with discontinuing therapy that occurred in more than one immediate-release topiramate-treated patient were fatigue (1%), headache (1%), and somnolence (1%).

Laboratory Abnormalities

Topiramate decreases serum bicarbonate [*see Warnings and Precautions (5.4)*]

Topiramate treatment with or without concomitant valproic acid (VPA) can cause hyperammonemia with or without encephalopathy [*see Warnings and Precautions (5.10)*].

Immediate-release topiramate treatment was associated with changes in several clinical laboratory analytes in randomized, double-blind, placebo-controlled studies. Similar effects should be anticipated with use of TROKENDI XR®.

Epilepsy
Controlled trials of adjunctive topiramate treatment of adults for partial onset seizures showed an increased incidence of markedly decreased serum phosphorus (6% topiramate, 2% placebo), markedly increased serum alkaline phosphatase (3% topiramate, 1% placebo), and decreased serum potassium (0.4 % topiramate, 0.1 % placebo). The clinical significance of these abnormalities has not been clearly established.

Changes in several clinical laboratory results (increased creatinine, BUN, alkaline phosphatase, total protein, total eosinophil count and decreased potassium) have been observed in a clinical investigational program in very young (2 years and younger) pediatric patients who were treated with adjunctive topiramate for partial onset seizures [*see Use in Specific Populations (8.4)*].

Migraine
In pooled double-blind studies in pediatric patients (6 to 17 years), an increased risk for certain abnormalities (value outside normal reference range) in selected clinical laboratory analytes measured in blood has been observed during topiramate treatment of pediatric patients compared to placebo-treated patients. In some

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instances, abnormalities were also observed at the end of the trial at the final visit and the changes were considered markedly abnormal.

For patients 12 to 17 years, the following were noted to be abnormally increased more frequently with topiramate than with placebo: BUN, creatinine, uric acid, chloride *[see Warnings and Precautions (5.4)]*, ammonia *[see Warnings and Precautions (5.10)]*, total protein, and platelets. The following were abnormally decreased in some subjects: phosphorus, and bicarbonate *[see Warnings and Precautions (5.4)]*.

For patients 6 to 11 years, the following were noted to be abnormally increased more frequently with topiramate than with placebo: alkaline phosphatase, creatinine and eosinophils. Analytes abnormally decreased were: total white count and neutrophils. There was no testing for serum bicarbonate, chloride, ammonia, or phosphorus in these younger patients.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of topiramate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, maculopathy, pancreatitis, and pemphigus.

7 DRUG INTERACTIONS

7.1 Alcohol

Alcohol use is contraindicated within 6 hours prior to and 6 hours after TROKENDI XR® administration [*see Contraindications (4) and Warnings and Precautions (5.5)*].

7.2 Oral Contraceptives

Exposure to ethinyl estradiol was statistically significantly decreased when topiramate (at doses above 200 mg) was given as adjunctive therapy in patients taking valproic acid. However, norethindrone exposure was not significantly affected.

In another pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), topiramate, given in the absence of other medications at doses of 50 to 200 mg per day, was not associated with statistically significant changes in mean exposure to either component of the oral contraceptive.

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

7.3 Antiepileptic Drugs

Concomitant administration of phenytoin or carbamazepine with topiramate decreased plasma concentrations of topiramate [*see Clinical Pharmacology (12.3)*].

Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy. Concomitant administration of topiramate with valproic acid has also been associated with hypothermia (with and without hyperammonemia) in patients who have tolerated either drug

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alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported [*see Warnings and Precautions (5.10, 5.12) and Clinical Pharmacology (12.3)*].

Numerous AEDs are substrates of the CYP enzyme system. *In vitro* studies indicate that topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5 isozymes. *In vitro* studies indicate that immediate-release topiramate is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4. The same drug interactions can be expected with the use of TROKENDI XR®.

7.4 CNS Depressants

Topiramate is a CNS depressant. Concomitant administration of topiramate with other CNS depressant drugs or alcohol can result in significant CNS depression [*see Warnings and Precautions (5.14)*].

7.5 Other Carbonic Anhydrase Inhibitors

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

7.6 Metformin

Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated. The concomitant use of TROKENDI XR® and metformin is contraindicated in patients with metabolic acidosis [*see Clinical Pharmacology (12.3)*].

7.7 Lithium

In patients, there was an observed increase in systemic exposure of lithium following topiramate doses of up to 600 mg per day. Lithium levels should be monitored when co-administered with high-dose TROKENDI XR® [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have increased risk for cleft lip and/or cleft palate (oral clefts) and for being small for gestational age *[see Human Data]*.

In multiple animal species, topiramate demonstrated developmental toxicity, including teratogenicity, in the absence of maternal toxicity at clinically relevant doses *[see Animal Data]*.

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

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Clinical Considerations

Fetal/Neonatal Adverse reactions

Consider the benefits and risks of topiramate when prescribing this drug to women of childbearing potential, particularly when topiramate is considered for a condition not usually associated with permanent injury or death. Because of the risk of oral clefts to the fetus, which occur in the first trimester of pregnancy before many women know they are pregnant, all women of childbearing potential should be informed of the potential risk to the fetus from exposure to topiramate. Women who are planning a pregnancy should be counseled regarding the relative risks and benefits of topiramate use during pregnancy, and alternative therapeutic options should be considered for these patients.

Labor or Delivery

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

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

Data

Human Data

Data from the NAAED Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was 1.2% compared to a prevalence of 0.39% - 0.46% in infants exposed to other AEDs, and a prevalence of 0.12% in infants of mothers without epilepsy or treatment with other AEDs. For comparison, the Centers for Disease Control and Prevention (CDC) reviewed available data on oral clefts in the United States and found a similar background rate of 0.17%. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 9.6 (95% Confidence Interval=[CI] 4.0-23.0) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts of 3.2% among infants exposed to topiramate monotherapy. The observed rate of oral clefts was 16 times higher than the background rate in the UK, which is approximately 0.2%.

Data from the NAAED pregnancy registry and a population-based birth registry cohort indicate that exposure to topiramate in utero is associated with an increased risk of small for gestational age (SGA) newborns (birth weight <10th percentile). In the NAAED pregnancy registry, 18% of topiramate-exposed newborns were SGA compared to 7% of newborns exposed to a reference AED, and 5% of newborns of mothers without epilepsy and without AED exposure. In the Medical Birth Registry of Norway (MBRN), a population-based pregnancy registry, 25% of newborns in the topiramate monotherapy exposure group were SGA compared to 9 % in the comparison group who were unexposed to AEDs. The long-term consequences of the SGA findings are not known.

Animal Data

When topiramate (20, 100, and 500 mg/kg/day) was administered orally to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. Fetal body weights and skeletal ossification were reduced at the highest dose tested in conjunction with decreased maternal body weight gain. A no-effect dose for embryofetal developmental toxicity in mice was not

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identified. The lowest dose tested, which was associated with teratogenic effects, is less than the maximum recommended human dose (MRHD) for epilepsy (400 mg/day) or migraine (100 mg/day) on a body surface area (mg/m^2) basis.

In pregnant rats administered topiramate (20, 100, and 500 mg/kg/day or 0.2, 2.5, 30, and 400 mg/kg/day) orally during the period of organogenesis, the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased in fetuses at 400 or 500 mg/kg/day. Embryotoxicity (reduced fetal body weights, increased incidences of structural variations) was observed at doses as low as 20 mg/kg/day. Clinical signs of maternal toxicity were seen at 400 mg/kg/day and above, and maternal body weight gain was reduced at doses of 100 mg/kg/day or greater. The no-effect dose for embryofetal developmental toxicity in rats is less than the MRHD for epilepsy or migraine on a mg/m^2 basis.

In pregnant rabbits administered topiramate (20, 60, and 180 mg/kg/day or 10, 35, and 120 mg/kg/day) orally during organogenesis, embryofetal mortality was increased at 35 mg/kg/day and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg/day. Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg/day and above. The no-effect dose (20 mg/kg/day) for embryofetal developmental toxicity in rabbits is equivalent to the MRHD for epilepsy and approximately 4 times the MRHD for migraine on a mg/m^2 basis.

When topiramate (0.2, 4, 20, and 100 mg/kg/day or 2, 20, and 200 mg/kg/day) was administered orally to female rats during the latter part of gestation and throughout lactation, offspring exhibited decreased viability and delayed physical development at 200 mg/kg/day and reductions in pre-and/or postweaning body weight gain at 2 mg/kg/day and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg/day or greater.

In a rat embryo/fetal development study which included postnatal assessment of offspring, oral administration of topiramate (0.2, 2.5, 30, and 400 mg/kg/day) to pregnant animals during the period of organogenesis resulted in delayed physical development at 400 mg/kg/day and persistent reductions in body weight gain at 30 mg/kg/day and higher in the offspring. The no-effect dose (0.2 mg/kg/day) for pre- and postnatal developmental toxicity is less than the MRHD for epilepsy or migraine on a mg/m^2 basis.

8.2 Lactation

Risk Summary

Topiramate is excreted in human milk *[see Data]*. The effects of topiramate exposure in breastfed infants are unknown.

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

Data

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

8.3 Females and Males of Reproductive Potential

Contraception

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Women of childbearing potential who are not planning a pregnancy should use effective contraception because of the risks to the fetus of oral clefts and of being small for gestational age [*see Drug Interactions (7.2) and Use in Specific Populations (8.1)*].

8.4 Pediatric Use

Seizures in Pediatric Patients 6 Years of Age and Older

The safety and effectiveness of TROKENDI XR® for treatment of partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndromes in pediatric patients at least 6 years of age is based on controlled trials with immediate-release topiramate [*see Clinical Studies (14.2, 14.3, 14.4 and 14.5)*].

The adverse reactions in pediatric patients treated for partial onset seizure, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome are similar to those seen in adults [*see Warnings and Precautions (5) and Adverse Reactions (6)*].

These include, but are not limited to:

- oligohydrosis and hyperthermia [*see Warnings and Precautions (5.3)*]
- dose-related increased incidence of metabolic acidosis [*see Warnings and Precautions (5.4)*]
- dose-related increased incidence of hyperammonemia [*see Warnings and Precautions (5.10)*]

Not Recommended for Pediatric Patients Younger than 6 Years of Age

The safety and effectiveness of TROKENDI XR for treatment of partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndromes in pediatric patients younger than 6 years of age has not been established.

Because the capsule must be swallowed whole, and may not be sprinkled on food, crushed or chewed, TROKENDI XR® is recommended only for children age 6 or older.

The following pediatric use information for adjunctive treatment for partial onset epilepsy in infants and toddlers (1 to 24 months) is based on studies conducted with immediate-release topiramate, which failed to demonstrate efficacy.

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

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

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

Immediate-release topiramate resulted in an increased incidence of patients with increased creatinine (any topiramate dose 5%, placebo 0%), BUN (any topiramate dose 3%, placebo 0%), and protein (any topiramate dose 34%, placebo 6%), and an increased incidence of decreased potassium (any topiramate dose 7%, placebo 0%). This increased frequency of abnormal values was not dose related. Creatinine was the only analyte showing a noteworthy increased incidence (topiramate 25 mg/kg/day 5%, placebo 0%) of a markedly abnormal increase [*see Adverse Reactions (6.1*)]. The significance of these findings is uncertain.

Immediate-release topiramate treatment also produced a dose-related increase in the percentage of patients who had a shift from normal at baseline to high/increased (above the normal reference range) in total eosinophil count at the end of treatment. The incidence of these abnormal shifts was 6 % for placebo, 10% for 5 mg/kg/day, 9% for 15 mg/kg/day, 14% for 25 mg/kg/day, and 11% for any topiramate dose [*see Adverse Reactions (6.1)*]. There was a mean dose-related increase in alkaline phosphatase. The significance of these findings is uncertain.

Topiramate produced a dose-related increased incidence of hyperammonemia [*see Warnings and Precautions (5.10)*].

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

In open-label, uncontrolled experience, increasing impairment of adaptive behavior was documented in behavioral testing over time in this population. There was a suggestion that this effect was dose-related. However, because of the absence of an appropriate control group, it is not known if this decrement in function was treatment related or reflects the patient's underlying disease (e.g., patients who received higher doses may have more severe underlying disease) [*see Warnings and Precautions (5.7)*].

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

Other Pediatric Studies

Topiramate treatment produced a dose-related increased shift in serum creatinine from normal at baseline to an increased value at the end of 4 months treatment in adolescent patients (ages 12 years to 16 years) in a double-blind, placebo-controlled study [*see Adverse Reactions (6.1)*].

Migraine Prophylaxis in Adolescents 12 to 17 Years

Safety and effectiveness of topiramate in the prophylaxis of migraine was studied in 5 double-blind, randomized, placebo-controlled, parallel-group trials in a total of 219 pediatric patients, at doses of 50 mg/day to 200 mg/day, or 2 to 3 mg/kg/day. These comprised a fixed dose study in 103 adolescents age 12 to 17 years *[see Clinical Studies (14.6)]*, a flexible dose (2 to 3 mg/kg/day), placebo-controlled study in 157 pediatric patients age 6 to 16 years (including 67 adolescent patients age 12 to 16 years), and a total of 49 adolescents age

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12 to 17 years in 3 studies of migraine prophylaxis primarily in adults. Open-label extension phases of 3 studies enabled evaluation of long-term safety for up to 6 months after the end of the double-blind phase.

Efficacy of topiramate for migraine prophylaxis in adolescents is demonstrated for a 100 mg daily dose in Study 3 *[see Clinical Studies (14.6)]*. Efficacy of topiramate (2 to 3 mg/kg/day) for migraine prophylaxis was not demonstrated in a placebo-controlled trial of 157 pediatric patients (6 to 16 years) that included treatment of 67 adolescents (12 to 16 years) for 20 weeks.

In the adolescent trials (12 to 17 years) in which patients were randomized to placebo or a fixed daily dose of immediate-release topiramate, the most commonly observed adverse reactions associated with the use of immediate-release topiramate that were seen at an incidence higher (≥5%) than in the placebo group were: paresthesia, upper respiratory tract infection, anorexia, and abdominal pain *[see Adverse Reactions (6.1)]*.

The most common cognitive adverse reaction in pooled double-blind studies in adolescent patients age 12 to 17 years was difficulty with concentration/attention *[see Warnings and Precautions (5.7)]*.

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

In topiramate-treated adolescent patients (12 to 17 years) compared to placebo-treated patients, abnormally increased results were more frequent for creatinine, BUN, uric acid, chloride, ammonia, total protein, and platelets. Abnormally decreased results were observed with topiramate vs placebo treatment for phosphorus and bicarbonate *[see Warnings and Precautions(5.4 and Adverse Reactions (6.1))]*.

Notable changes (increases and decreases) from baseline in systolic blood pressure, diastolic blood pressure, and pulse that were observed occurred more commonly in adolescents treated with topiramate compared to adolescents treated with placebo *[see Clinical Pharmacology (12.2)]*.

Migraine Prophylaxis in Children 6-11 Years Old

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

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

The risk for cognitive adverse reactions was greater in younger patients (6 to 11 years) than in older patients (12 to 17 years) *[see Warnings and Precautions (5.7)]*.

For patients 6 to 11 years, the following were noted to be abnormally increased more frequently with topiramate than with placebo: alkaline phosphatase, creatinine, and eosinophils. Analytes abnormally decreased were: total white count and neutrophils *[see Adverse Reactions (6.1)]*.

Serum bicarbonate, chloride, phosphorus, and ammonia data were not collected for pediatric patients 6 to 11 years of age.

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Juvenile Animal Studies

When topiramate (30, 90, and 300 mg/kg/day) was administered orally to rats during the juvenile period of development (postnatal days 12 to 50), bone growth plate thickness was reduced in males at the highest dose tested. The higher of the doses not associated with effects on bone (90 mg/kg/day) is approximately 2 times the maximum recommended pediatric dose for epilepsy (9 mg/kg/day) on a body surface area (mg/m^2) basis.

8.5 Geriatric Use

Clinical studies of immediate-release topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment is necessary for elderly with creatinine clearance less than 70 mL/min/1.73 m^2. Estimate GFR should be measured prior to dosing [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)*].

8.6 Race and Gender Effects

Evaluation of effectiveness and safety of topiramate in clinical trials has shown no race- or gender-related effects.

8.7 Renal Impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30 to 69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance less than 30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance greater than 70 mL/min/1.73m^2). One-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)*].

8.8 Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account the duration of dialysis period, the clearance rate of the dialysis system being used, and the effective renal clearance of topiramate in the patient being dialyzed [*see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TROKENDI XR® (topiramate) extended-release capsule is not a controlled substance.

9.2 Abuse

The abuse and dependence potential of TROKENDI XR® has not been evaluated in human studies.

9.3 Dependence

TROKENDI XR® has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE

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

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

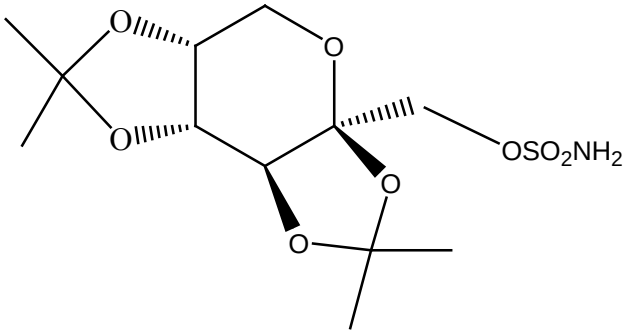
A patient who ingested a dose between 96 g and 110 g of topiramate was admitted to hospital with coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.

Similar signs, symptoms, and clinical consequences are expected to occur with overdosage of TROKENDI XR®. Therefore, in acute TROKENDI XR® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate *in vitro*. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body.

11 DESCRIPTION

Topiramate, USP, is a sulfamate-substituted monosaccharide. TROKENDI XR® (topiramate) extended-release capsules are available as 25 mg, 50 mg, 100 mg and 200 mg capsules for oral administration.

Topiramate is a white to off-white powder. Topiramate is freely soluble in polar organic solvents such as acetonitrile and acetone; and very slightly soluble to practically insoluble in non-polar organic solvents such as hexanes. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.4. Topiramate is designated chemically as 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate and has the following structural formula:



TROKENDI XR® (topiramate) is an extended-release capsule. TROKENDI XR® capsules contain the following inactive ingredients:

Sugar Spheres, NF
Hypromellose (Type 2910), USP
Mannitol, USP
Docusate Sodium, USP
Sodium Benzoate, NF
Ethylcellulose, NF
Oleic Acid, NF
Medium Chain Triglycerides, NF
Polyethylene Glycol, NF
Polyvinyl Alcohol, USP
Titanium Dioxide, USP
Talc, USP
Lecithin, NF
Xanthan Gum, NF

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The capsule shells contain gelatin, USP; Titanium Dioxide, USP; and Colorants.

The colorants are:

FD&C Blue #1 (all strength capsules)
Yellow Iron Oxide, USP (25 mg and 50 mg capsules)
FD&C Red #3 (50 mg, 100 mg and 200 mg capsules)
FD&C Yellow #6 (50 mg, 100 mg and 200 mg capsules)
Riboflavin, USP (25 mg capsules)

All capsule shells are imprinted with black print that contains shellac, NF, and black iron oxide, NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

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

12.3 Pharmacokinetics

Absorption and Distribution

Linear pharmacokinetics of topiramate from TROKENDI XR® were observed following a single oral dose over the range of 50 mg to 200 mg. At 25 mg, the pharmacokinetics of TROKENDI XR® is nonlinear possibly due to the binding of topiramate to carbonic anhydrase in red blood cells.

The peak plasma concentrations (C_{max}) of topiramate occurred at approximately 24 hours following a single 200 mg oral dose of TROKENDI XR®. At steady-state, the (AUC_{0-24}, C_{max}, and C_{min}) of topiramate from TROKENDI XR® administered once-daily and the immediate-release tablet administered twice-daily were shown to be bioequivalent. Fluctuation of topiramate plasma concentrations at steady-state for TROKENDI XR® administered once-daily was approximately 26% and 42% in healthy subjects and in epileptic patients,

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respectively, compared to approximately 40% and 51%, respectively, for immediate-release topiramate [see *Clinical Pharmacology (12.6)*].

Compared to the fasted state, high-fat meal increased the C_{max} of topiramate by 37% and shortened the T_{max} to approximately 8 hour following a single dose of TROKENDI XR®, while having no effect on the AUC. Modeling of the observed single dose fed data with simulation to steady state showed that the effect on C_{max} is significantly reduced following repeat administrations. TROKENDI XR® can be taken without regard to meals.

Topiramate is 15% to 41% bound to human plasma proteins over the blood concentration range of 0.5 mcg/mL to 250 mcg/mL. The fraction bound decreased as blood concentration increased.

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

Metabolism and Excretion

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 mL/min to 30 mL/min in adults following oral administration. The mean elimination half-life of topiramate was approximately 31 hours following repeat administration of TROKENDI XR®.

Specific Populations

Renal Impairment

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

Hemodialysis

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

Hepatic Impairment

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

Age, Gender and Race

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The pharmacokinetics of topiramate in elderly subjects (65 to 85 years of age, N=16) were evaluated in a controlled clinical study. The elderly subject population had reduced renal function (creatinine clearance [-20%]) compared to young adults. Following a single oral 100 mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1 to 2 hours. Reflecting the primary renal elimination of topiramate, topiramate plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced.

In a study of 13 healthy elderly subjects and 18 healthy young adults who received TROKENDI XR®, 30% higher mean C_{max} and 44% higher AUC values were observed in elderly compared to young subjects. Elderly subjects exhibited shorter median T_{max} at 16 hours versus 24 hours in young subjects. The apparent elimination half-life was similar across age groups. As recommended for all patients, dosage adjustment is indicated in elderly patients with a creatinine clearance rate less than 70 mL/min/1.73 m^2) [*see Dosage and Administration (2.5)*].

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

Pediatric Pharmacokinetics
Pharmacokinetics of immediate-release topiramate were evaluated in patients ages 2 years to less than 16 years. Patients received either no or a combination of other antiepileptic drugs. A population pharmacokinetic model was developed on the basis of pharmacokinetic data from relevant topiramate clinical studies. This dataset contained data from 1217 subjects including 258 pediatric patients aged 2 years to less than 16 years (95 pediatric patients less than 10 years of age). Pediatric patients on adjunctive treatment exhibited a higher oral clearance (L/h) of topiramate compared to patients on monotherapy, presumably because of increased clearance from concomitant enzyme-inducing antiepileptic drugs. In comparison, topiramate clearance per kg is greater in pediatric patients than in adults and in young pediatric patients (down to 2 years) than in older pediatric patients. Consequently, the plasma drug concentration for the same mg/kg/day dose would be lower in pediatric patients compared to adults and also in younger pediatric patients compared to older pediatric patients. Clearance was independent of dose.

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

Drug-Drug Interaction Studies

Antiepileptic Drugs
Potential interactions between immediate-release topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on mean plasma AUCs are summarized in Table 12. Interaction of TROKENDI XR® and standard AEDs is not expected to differ from the experience with immediate-release topiramate products.

In Table 12, the second column (AED concentration) describes what happened to the concentration of the AED listed in the first column when topiramate was added. The third column (topiramate concentration) describes how the co-administration of a drug listed in the first column modified the concentration of topiramate in experimental settings when topiramate was given alone.

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Table 12: Summary of AED Interactions with topiramate

AED Coadministered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase*	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide†	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400mg per day	13% decrease

* =Plasma concentration increased 25% in some patients, generally those on a twice a day dosing regimen of phenytoin
† =Is not administered but is an active metabolite of carbamazepine
NC=Less than 10% change in plasma concentration
AED=Antiepileptic drug
NE=Not evaluated
TPM=topiramate

In addition to the pharmacokinetic interaction described in the above table, concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy and hypothermia [*see Warnings and Precautions (5.10), (5.12) and Drug Interactions (7.5)*].

CNS Depressants or Alcohol
Concomitant administration of TROKENDI XR® and other CNS depressant drugs or alcohol has not been evaluated in clinical studies [*see Contraindications (4), Warnings and Precautions (5.5), (5.14), and Drug Interactions (7.1), (7.4)*].

Oral Contraceptives
In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), topiramate, given in the absence of other medications at doses of 50 to 200 mg per day, was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg per day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, topiramate (50 mg per day to 800 mg per day) did not significantly affect exposure to NET. Although there was a dose-dependent decrease in EE exposure for doses between 200 to 800 mg per day, there was no significant dose-dependent change in EE exposure for doses of 50 to 200 mg per day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TROKENDI XR®. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding [*see Drug Interactions (7.2)*].

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

Hydrochlorothiazide

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A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of hydrochlorothiazide (HCTZ) (25 mg every 24 hours) and topiramate (96 mg every 12 hours) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to TROKENDI XR® therapy may require an adjustment of the TROKENDI XR® dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin
Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated. TROKENDI XR® is expected to exhibit the same degree of metabolic acidosis as topiramate.

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin (500 mg every 12 hr) and topiramate in plasma when metformin was given alone and when metformin and topiramate (100 mg every 12 hr) were given simultaneously. The results of this study indicated that the mean metformin C_{max} and $AUC_{0\text{-}12h}$ increased by 17% and 25%, respectively, when topiramate was added. Topiramate did not affect metformin T_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is not known. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The clinical significance of the effect of metformin on topiramate or TROKENDI XR® pharmacokinetics is unclear [*see Drug Interactions (7.6)*].

Pioglitazone
A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the $AUC_{\tau,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known.

When TROKENDI XR® is added to pioglitazone therapy or pioglitazone is added to TROKENDI XR® therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

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

Lithium
In patients, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg per day; however, there was an observed increase in systemic exposure of lithium (27% for C_{max} and 26% for AUC) following topiramate doses up to 600 mg per day. Lithium levels should be monitored when co-administered with high-dose TROKENDI XR® [*see Drug Interactions (7.7)*].

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

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

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

Risperidone
When administered concomitantly with topiramate at escalating doses of 100, 250, and 400 mg per day, there was a reduction in risperidone systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg per day doses of topiramate). No alterations of 9-hydroxyrisperidone levels were observed. Coadministration of topiramate 400 mg per day with risperidone resulted in a 14% increase in C_{max} and a 12% increase in AUC_{12} of topiramate. There were no clinically significant changes in the systemic exposure of risperidone plus 9-hydroxyrisperidone or of topiramate; therefore, this interaction is not likely to be of clinical significance.

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

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

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

Venlafaxine
Multiple dosing of topiramate (150 mg per day) in healthy volunteers did not affect the pharmacokinetics of venlafaxine or O-desmethyl venlafaxine. Multiple dosing of venlafaxine (150 mg) did not affect the pharmacokinetics of topiramate.

Other Carbonic Anhydrase Inhibitors
Concomitant use of TROKENDI XR®, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if TROKENDI XR® is given concomitantly with another carbonic anhydrase inhibitor, the patient should be monitored for the appearance or worsening of metabolic acidosis [*see Drug Interactions (7.5)*].

Drug/Laboratory Tests Interactions
There are no known interactions of TROKENDI XR® with commonly used laboratory tests.

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12.6 Relative Bioavailability of TROKENDI XR® Compared to Immediate-Release Topiramate

Study in Healthy Normal Volunteers

TROKENDI XR® taken once a day provides steady state plasma levels comparable to immediate-release topiramate taken every 12 hours, when administered at the same total 200-mg daily dose. In a crossover study, 33 healthy subjects were titrated to a 200-mg dose of either TROKENDI XR® or immediate-release topiramate and were maintained at 200 mg per day for 10 days.

The 90% CI for the ratios of AUC_{0-24}, C_{max} and C_{min}, as well as partial AUC (the area under the concentration-time curve from time 0 to time p (post dose) for multiple time points were within the 80 to 125% bioequivalence limits, indicating no clinically significant difference between the two formulations. In addition, the 90% CI for the ratios of topiramate plasma concentration at each of multiple time points over 24 hours for the two formulations were within the 80 to 125% bioequivalence limits, except for the initial time points before 1.5 hour post-dose.

Study in Patients with Epilepsy

In a study in epilepsy patients treated with immediate-release topiramate alone or in combination with either enzyme-inducing or neutral AEDs who were switched to an equivalent daily dose of TROKENDI XR®, there was a 10% decrease in AUC_{0-24}, C_{max}, and C_{min} on the first day after the switch in all patients. At steady state, AUC_{0-24} and C_{max} were comparable to immediate-release topiramate in all patients. While patients treated with TROKENDI XR® alone or in combination with neutral AEDs showed comparable C_{min} at steady state, patients treated with enzyme-inducers showed a 10% decrease in C_{min}. This difference is likely not clinically significant and probably due to the small number of patients on enzyme-inducers.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg/day) in the diet for 21 months. An increase in the incidence of bladder tumors in males and females receiving 300 mg/kg was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. The higher of the doses not associated with an increase in tumors (75 mg/kg/day) is equivalent to the maximum recommended human dose (MRHD) for epilepsy and approximately 4 times the MRHD for migraine (100 mg) on a mg/m^2 basis. The relevance of this finding to human carcinogenic risk is uncertain.

No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg/day (approximately 3 times the MRHD for epilepsy and 12 times the MRHD for migraine on a mg/m^2 basis).

Mutagenesis

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

Impairment of Fertility

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No adverse effects on male or female fertility were observed in rats administered oral doses of up to 100 mg/kg/day (2.5 times the MRHD for epilepsy and 10 times the MRHD for migraine on a mg/m^2 basis) prior to and during mating and early pregnancy.

14 CLINICAL STUDIES

14.1 Bridging Study to Demonstrate Pharmacokinetic Equivalence between Extended-Release and Immediate-Release Topiramate Formulations

The basis for approval of the extended-release formulation (TROKENDI XR®) included the studies described below using an immediate-release formulation and the demonstration of the pharmacokinetic equivalence of TROKENDI XR® to immediate-release topiramate through the analysis of concentrations and cumulative AUCs at multiple time points [*see Clinical Pharmacology (12.6)*].

The clinical studies described in the following sections were conducted using immediate-release topiramate.

14.2 Monotherapy Treatment in Patients with Partial Onset or Primary Generalized Tonic-Clonic Seizures

Adults and Pediatric Patients 10 Years of Age and Older

The effectiveness of topiramate as initial monotherapy in adults and children 10 years of age and older with partial onset or primary generalized tonic-clonic seizures was established in a multicenter, randomized, double-blind, dose-controlled, parallel-group trial (Study 1).

Study 1 was conducted in 487 patients diagnosed with epilepsy (6 to 83 years of age) who had 1 or 2 well-documented seizures during the 3-month retrospective baseline phase who then entered the study and received topiramate 25 mg per day for 7 days in an open-label fashion. Forty-nine percent of subjects had no prior AED treatment and 17% had a diagnosis of epilepsy for greater than 24 months. Any AED therapy used for temporary or emergency purposes was discontinued prior to randomization. In the double-blind phase, 470 patients were randomized to titrate up to 50 mg per day or 400 mg per day of topiramate. If the target dose could not be achieved, patients were maintained on the maximum tolerated dose. Fifty-eight percent of patients achieved the maximal dose of 400 mg per day for greater than 2 weeks, and patients who did not tolerate 150 mg per day were discontinued.

The primary efficacy assessment was a between-group comparison of time to first seizure during the double-blind phase. Comparison of the Kaplan-Meier survival curves of time to first seizure favored the topiramate 400 mg per day group over the topiramate 50 mg per day group ($p=0.0002$, log rank test; Figure 1). The treatment effects with respect to time to first seizure were consistent across various patient subgroups defined by age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use.

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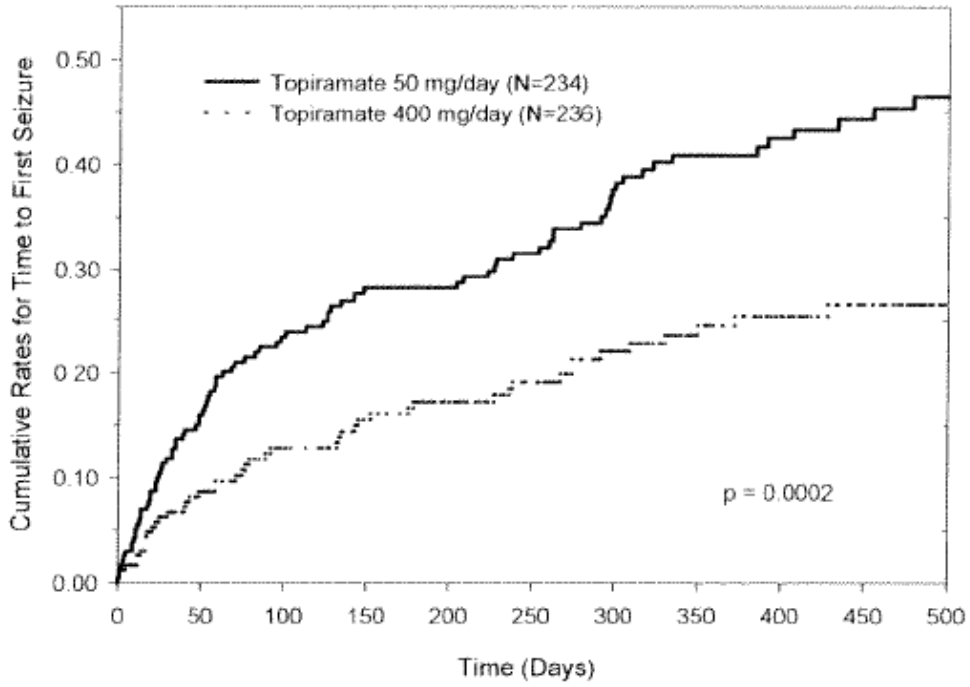

Figure 1: Kaplan-Meier Estimates of Cumulative Rates for Time to First Seizure in Study 1

Pediatric Patients 6 to Less than 10 Years of Age

The conclusion that topiramate is effective as initial monotherapy in pediatric patients 6 to less than 10 years of age with partial onset or primary generalized tonic-clonic seizures was based on a pharmacometric bridging approach using data from the controlled epilepsy trials conducted with immediate-release topiramate described in labeling. The approach consisted of first showing a similar exposure response relationship between pediatric patients down to 2 years of age and adults when immediate-release topiramate was given as adjunctive therapy *[see Use in Specific Populations (8.4)]*. Similarity of exposure-response was demonstrated in pediatric patients ages 6 to less than 16 years of age and adults when topiramate was given as initial monotherapy. Specific dosing in pediatric patients 6 to less than 10 years of age was derived from simulations utilizing plasma exposure ranges observed in pediatric and adult patients treated with immediate-release topiramate initial monotherapy*[see Dosage and Administration (2.1)]* .

14.3 Adjunctive Therapy in Patients with Partial Onset Seizures

Adult Patients with Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for adults with partial onset seizures was established in six multicenter, randomized, double-blind, placebo-controlled trials (Studies 2, 3, 4, 5, 6, and 7), two comparing several dosages of topiramate and placebo and four comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalized seizures.

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

Following randomization, patients began the double-blind phase of treatment. In five of the six studies, patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg per day

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increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. In Study 7, the 25 or 50 mg per day initial doses of topiramate were followed by respective weekly increments of 25 or 50 mg per day until the target dose of 200 mg per day was reached. After titration, patients entered a 4, 8 or 12-week stabilization period. The numbers of patients randomized to each dose, and the actual mean and median doses in the stabilization period are shown in Table 13.

Table 13: Immediate Release Topiramate Dose Summary During the Stabilization Periods of Each of Six Double-Blind, Placebo-Controlled, Adjunctive Trials in Adults with Partial Onset Seizures[a]

		Target Topiramate Dosage (mg per day)					
Study	**Stabilization Dose**	**Placebo[b]**	**200**	**400**	**600**	**800**	**1,000**
2	N	42	42	40	41	--	--
	Mean Dose	5.9	200	390	556	--	--
	Median Dose	6.0	200	400	600	--	--
3	N	44	--	--	40	45	40
	Mean Dose	9.7	--	--	544	739	796
	Median Dose	10.0	--	--	600	800	1,000
4	N	23	--	19	--	--	--
	Mean Dose	3.8	--	395	--	--	--
	Median Dose	4.0	--	400	--	--	--
5	N	30	--	--	28	--	--
	Mean Dose	5.7	--	--	522	--	--
	Median Dose	6.0	--	--	600	--	--
6	N	28	--	--	--	25	--
	Mean Dose	8.0	--	--	--	568	--
	Median Dose	8.0	--	--	--	600	--
7	N	90	157	--	--	--	--
	Mean Dose	8	200	--	--	--	--
	Median Dose	8	200	--	--	--	--

[a] Dose-response studies were not conducted for other indications or pediatric partial-onset seizures
[b] Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Study 4 (4 tablets/day); Studies 2 and 5 (6 tablets/day); Studies 6 and 7 (8 tablets/day); Study 3 (10 tablets/day)

Pediatric Patients Ages 2 to 16 Years with Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for pediatric patients ages 2 to 16 years with partial onset seizures was established in a multicenter, randomized, double-blind, placebo-controlled trial (Study 8), comparing topiramate and placebo in patients with a history of partial onset seizures, with or without secondarily generalized seizures.

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

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

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14.4 Adjunctive Therapy in Patients with Primary Generalized Tonic-Clonic Seizures

The effectiveness of topiramate as an adjunctive treatment for primary generalized tonic-clonic seizures in patients 2 years old and older was established in a multicenter, randomized, double-blind, placebo-controlled trial (Study 9), comparing a single dosage of topiramate and placebo.

Patients in Study 9 were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate or placebo. Patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least three primary generalized tonic-clonic seizures during the baseline phase were randomly assigned to placebo or topiramate in addition to their other AEDs.

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

14.5 Adjunctive Therapy in Patients with Lennox-Gastaut Syndrome

The effectiveness of topiramate as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome was established in a multicenter, randomized, double-blind, placebo-controlled trial comparing a single dosage of topiramate with placebo in patients 2 years of age and older (Study 10).

Patients in Study 10 were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate or placebo. Patients who were experiencing at least 60 seizures per month before study entry were stabilized on optimum dosages of their concomitant AEDs during a 4 week baseline phase. Following baseline, patients were randomly assigned to placebo or topiramate in addition to their other AEDs. Active drug was titrated beginning at 1 mg/kg/day for a week; the dose was then increased to 3 mg/kg/day for one week then to 6 mg/kg/day. After titration, patients entered an 8-week stabilization period. The primary measures of effectiveness were the percent reduction in drop attacks and a parental global rating of seizure severity.

In all adjunctive topiramate trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reductions in seizure rates and the responder rates (fraction of patients with at least a 50% reduction) by treatment group for each study are shown below in Table 14. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

Table 14: Efficacy Results in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

		Target Topiramate Dosage (mg per day)						
Study #	**#**	**Placebo**	**200**	**400**	**600**	**800**	**1,000**	**≈6mg/ kg/day***
Partial Onset Seizures Studies in Adults								
2	N	45	45	45	46	--	--	--
	Median % Reduction	11.6	27.2[a]	47.5[b]	44.7[c]	--	--	--
	% Responders	18	24	44[d]	46[d]	--	--	--
3	N	47	--	--	48	48	47	--
	Median % Reduction	1.7	--	--	40.8[c]	41.0[c]	36.0[c]	
	% Responders	9	--	--	40[c]	41[c]	36[d]	
4	N	24	--	23	--	--	--	--
	Median % Reduction	1.1	--	40.7[e]	--	--	--	--
	% Responders	8	--	35[d]	--	--	--	--
5	N	30	--	--	30	--	--	--

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	Median % Reduction	-12.2	--	--	46.4[f]	--	--	--
	% Responders	10	--	--	47[c]	--	--	--
6	N	28	--	--	--	28	--	--
	Median % Reduction	-20.6	--	--	--	24.3[c]	--	--
	% Responders	0	--	--	--	43[c]	--	--
7	N	91	168	--	--	--	--	--
	Median % Reduction	20.0	44.2[c]	--	--	--	--	--
	% Responders	24	45[c]					
Studies in Pediatric Patients								
8	N	45	--	--	--	--	--	41
	Median % Reduction	10.5	--	--	--	--	--	33.1[d]
	% Responders	20	--	--	--	--	--	39
Primary Generalized Tonic-Clonic[h]								
9	N	40	--	--	--	--	--	39
	Median % Reduction	9.0	--	--	--	--	--	56.7[d]
	% Responders	20	--	--	--	--	--	56[c]
Lennox-Gastaut Syndrome[i]								
10	N	49	--	--	--	--	--	46
	Median % Reduction	-5.1	--	--	--	--	--	14.8[d]
	% Responders	14						28[g]
	Improvement in Seizure Severity[j]	28						52d

Comparisons with placebo: [a]p=0.080; [b]p ≤ 0.010; [c]p ≤ 0.001; [d]p ≤ 0.050; [e]p=0.065; [f]p ≤0.005; [g]p=0.071;
[h]Median % reduction and % responders are reported for PGTC seizures;
[i]Median % reduction and % responders for drop attacks, i.e., tonic or atonic seizures
[j]Percentage of subjects who were minimally, much, or very much improved from baseline.

[*]For Studies 8 and 9, specified target dosages (less than 9.3 mg/kg/day) were assigned based on subject's weight to approximate a dosage of 6mg/kg per day; these dosages corresponded to mg per day dosages of 125 mg per day, 175 mg per day, 225 mg per day, and 400 mg per day

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

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

14.6 Migraine Prophylaxis

Adult Patients

The results of 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials conducted in US (Study 1) or the US and Canada (Study 2) established the effectiveness of immediate-release topiramate in the prophylactic treatment of migraine headache. The design of both trials was identical, enrolling patients with a history of migraine with or without aura, for at least 6 months, according to the International Headache Society (IHS) diagnostic criteria. Patients with a history of cluster headaches or basilar, opthalmoplegic, hemiplegic, or transformed migraine headaches were excluded from the trials. Patients were required to have completed up to a 2-week washout of any prior migraine preventative medications before starting the baseline phase.

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

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

In Study 1, a total of 469 patients (416 females, 53 males) ranging in age from 13 to 70 years, were randomized and provided efficacy data. Two hundred sixty-five patients completed the entire 26-week double-blind phase. The median average daily dosages were 48 mg per day, 88 mg per day, and 132 mg per day in the target dose groups of topiramate 50, 100 and 200 mg per day, respectively.

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

In Study 2, a total of 468 patients (406 females, 62 males) ranging in age from 12 to 65 years, were randomized and provided efficacy data. Two hundred fifty-five patients completed the entire 26-week double-blind phase. The median average daily dosages were 47 mg per day, 86 mg per day, and 150 mg per day in the target dose groups of immediate-release topiramate 50, 100, and 200 mg per day, respectively.

The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches per 28 days and was similar across treatment groups. The change in the mean 4-week migraine headache period frequency from baseline to the double-blind phase was -1.4, -2.1, and -2.4 in the immediate-release topiramate 50, 100, and 200 mg per day groups, respectively, versus -1.1 in the placebo group (see Figure 2). The differences between the immediate-release topiramate 100 and 200 mg per day groups versus placebo were similar and statistically significant (p equals 0.008 and p less than 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 immediate-release topiramate, daily dosages were decreased in weekly intervals by 25 to 50 mg per day.

Figure 2: Reduction in 4-Week Migraine Headache Frequency
(Studies 1 and 2 for Adults and Adolescents)

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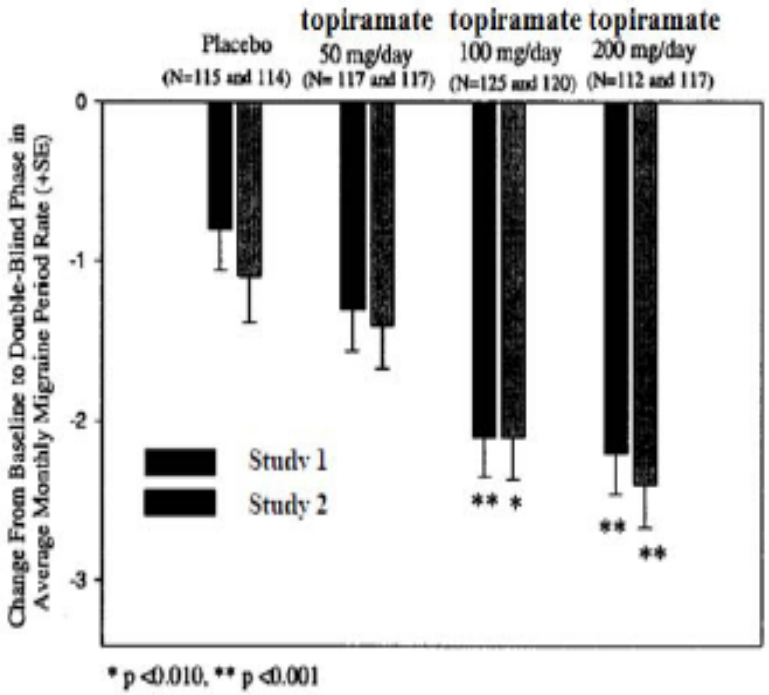

Adolescent Patients Age 12 to 17 Years

The effectiveness of immediate-release topiramate as prophylaxis for migraine headache in adolescents was established in a multicenter, randomized, double-blind, parallel-group trial (Study 3). The study enrolled 103 patients (40 male, 63 female) age 12 to 17 years with episodic migraine headaches with or without aura. Patient selection was based on IHS criteria for migraines (using proposed revisions to the 1988 IHS pediatric migraine criteria [IHS-R criteria]).

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

Effectiveness of treatment was assessed by comparing each immediate-release topiramate treatment group to placebo (ITT population) for the percent reduction from baseline to the last 12 weeks of the double-blind phase in the monthly migraine attack rate (primary endpoint). The percent reduction from baseline to the last 12 weeks of the double-blind phase in average monthly migraine attack rate is shown in Table 15. The 100 mg immediate-release topiramate dose produced a statistically significant treatment difference relative to placebo of 28% reduction from baseline in the monthly migraine attack rate.

The mean reduction from baseline to the last 12 weeks of the double-blind phase in average monthly attack rate, a key secondary efficacy endpoint in Study 3 (and the primary efficacy endpoint in Studies 1 and 2, of adults) was 3.0 for 100 mg immediate-release topiramate dose and 1.7 for placebo. This 1.3 treatment difference in mean reduction from baseline of monthly migraine rate was statistically significant (p=0.0087).

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Table 15: Percent Reduction from Baseline to the Last 12 Weeks of Double-Blind Phase in Average Monthly Attack Rate: Study 3 (Intent-to-Treat Analysis Set)

Category	Placebo (N=33)	Immediate-Release Topiramate 50 mg/day (N=35)	Immediate-Release Topiramate 100 mg/day (N=35)
Baseline			
Median	3.6	4.0	4.0
Last 12 Weeks of Double-Blind Phase			
Median	2.3	2.3	1.0
Percent Reduction (%)			
Median	44.4	44.6	72.2
P-value versus Placebo [a,b]		0.7975	0.0164[c]

[a] P-values (two-sided) for comparisons relative to placebo are generated by applying an ANCOVA model on ranks that includes subject's stratified age at baseline, treatment group, and analysis center as factors and monthly migraine attack rate during baseline period as a covariate.
[b] P-values for the dose groups are the adjusted p-value according to the Hochberg multiple comparison procedure.
[c] Indicates p-value is <0.05 (two-sided).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 TROKENDI XR® Capsules

TROKENDI XR® (topiramate) extended-release capsules are available as extended-release capsules in the following strengths and colors:

Bottles
25 mg (light green opaque body/yellow opaque cap) topiramate extended-release capsules (black print "SPN" and "25") – bottles of 30 count (NDC-17772-101-30) and 100 count (NDC-17772-101-01)

50 mg (light green opaque body/orange opaque cap) topiramate extended-release capsules (black print "SPN" and "50") – bottles of 30 count (NDC-17772-102-30) and 100 count (NDC-17772-102-01)

100 mg (green opaque body/blue opaque cap) topiramate extended-release capsules (black print "SPN" and "100") – bottles of 30 count (NDC-17772-103-30) and 100 count (NDC-17772-103-01)

200 mg (pink opaque body/blue opaque cap) topiramate extended-release capsules (black print "SPN" and "200") – bottles of 30 count (NDC-17772-104-30) and 100 count (NDC-17772-104-01)

Blister package
25 mg (light green opaque body/yellow opaque cap) topiramate extended-release capsules (black print "SPN" and "25") – blister packages of 30-count (NDC-17772-101-15)

50 mg (light green opaque body/orange opaque cap) topiramate extended-release capsules (black print "SPN" and "50") – blister packages of 30-count (NDC-17772-102-15)

100 mg (green opaque body/blue opaque cap) topiramate extended-release capsules (black print "SPN" and "100") – blister packages of 30-count (NDC-17772-103-15)

200 mg (pink opaque body/blue opaque cap) topiramate extended-release capsules (black print "SPN" and "200") – blister packages of 30-count (NDC-17772-104-15)

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16.2 Storage and Handling

TROKENDI XR® (topiramate) extended-release capsules should be stored in well closed containers at controlled room temperature [25°C (77°F); excursions 15°C-30°C (59°F-86°F)]. Protect from moisture and light.

17 PATIENT COUNSELING INFORMATION

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

Administration Instructions

Counsel patients to swallow TROKENDI XR® capsules whole and intact. TROKENDI XR® should not be sprinkled on food, chewed or crushed [*See Dosage and Administration (2.10)*].

Consumption of Alcohol

Advise patients to completely avoid consumption of alcohol at least 6 hours prior to and 6 hours after taking TROKENDI XR® [*see Warnings and Precautions (5.5)*].

Eye Disorders

Advise patients taking TROKENDI XR® to seek immediate medical attention if they experience blurred vision, visual disturbances or periorbital pain [*see Warnings and Precautions (5.1, 5.2)*].

Oligohydrosis and Hyperthermia

Counsel patients that TROKENDI XR®, especially pediatric patients, can cause decreased sweating and increased body temperature, especially in hot weather, and they should seek medical attention if this is noticed [*see Warnings and Precautions (5.3)*].

Metabolic Acidosis

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

Suicidal Behavior and Ideation

Counsel patients, their caregivers, and families that AEDs, including TROKENDI XR®, may increase the risk of suicidal thoughts and behavior and they should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior or the emergence of suicidal thoughts, behavior or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers [*see Warnings and Precautions (5.6)*].

Interference with Cognitive and Motor Performance

Warn patients about the potential for somnolence, dizziness, confusion, difficulty concentrating, visual effects and advise them not to drive or operate machinery until they have gained sufficient experience on TROKENDI XR® to gauge whether it adversely affects their mental performance, motor performance, and/or vision [*see Warnings and Precautions (5.7)*].

Advise patients that even when taking TROKENDI XR® or other anticonvulsants, some patients with epilepsy will continue to have unpredictable seizures. Therefore, counsel all patients taking TROKENDI XR® for

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epilepsy to exercise appropriate caution when engaging in any activities where loss of consciousness could result in serious danger to themselves or those around them (including swimming, driving a car, climbing in high places, etc.). Some patients with refractory epilepsy will need to avoid such activities altogether. Physicians should discuss the appropriate level of caution with their patients, before patients with epilepsy engage in such activities.

Fetal Toxicity

Counsel pregnant women and women of childbearing potential that use of topiramate during pregnancy can cause fetal harm, including an increased risk for cleft lip and/or cleft palate (oral clefts), which occur early in pregnancy before many women know they are pregnant. Also inform patients that infants exposed to topiramate monotherapy *in utero* may be small for their gestational age *[see Use in Specific Populations (8.1)]*. When appropriate, prescribers should counsel pregnant women and women of childbearing potential about alternative therapeutic options.

Advise women of childbearing potential who are not planning a pregnancy to use effective contraception while using topiramate, keeping in mind that there is a potential for decreased contraceptive efficacy when using estrogen-containing birth control with topiramate [*see Warnings and Precautions (5.8) and Drug Interactions (7.2)*].

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

Hyperammonemia and Encephalopathy

Warn patients about the possible development of hyperammonemia with or without encephalopathy. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. This hyperammonemia and encephalopathy can develop with topiramate treatment alone or with topiramate treatment with concomitant valproic acid (VPA). Patients should be instructed to contact their physician if they develop unexplained lethargy, vomiting, or changes in mental status [*see Warnings and Precautions (5.10)*].

Kidney Stones

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*)].

Hypothermia

Counsel patients that TROKENDI XR® can cause a reduction in body temperature, which can lead to alterations in mental status. If they note such changes, they should call their health care professional and measure their body temperature. Patients taking concomitant valproic acid should be specifically counseled on this potential adverse reaction [*see Warnings and Precautions (5.12)*].

Paresthesia

Counsel patients that they may experience tingling in the arms and legs. If this symptom occurs, they should consult with their physician [*see Warnings and Precautions (5.13)*].

Manufactured by: Catalent Pharma Solutions, Winchester, Kentucky 40391

Manufactured for: Supernus Pharmaceuticals, Inc., Rockville, Maryland 20850

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RA-TRO-Vx
Revised: Apr 2017

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MEDICATION GUIDE

TROKENDI XR (tro-KEN-dee eks ahr)
(topiramate) Extended-Release Capsules

What is the most important information I should know about Trokendi XR?

Take Trokendi XR® capsules whole. Do not sprinkle Trokendi XR® on food, or break, crush, dissolve, or chew Trokendi XR® capsules before swallowing. If you cannot swallow Trokendi XR® capsules whole, tell your healthcare provider. You may need a different medicine.

Do not drink alcohol within 6 hours prior to and 6 hours after Trokendi XR® administration.

Trokendi XR may cause eye problems. Serious eye problems include:

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

Trokendi XR 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. If a high fever, a fever that does not go away, or decreased sweating develops, call your healthcare provider right away.

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

- feel tired
- not feel hungry (loss of appetite)
- feel changes in heartbeat
- have trouble thinking clearly

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

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

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Do not stop Trokendi XR without first talking to a healthcare provider.

- Stopping Trokendi XR suddenly can cause serious problems.
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Trokendi XR can harm your unborn baby.

- If you take Trokendi XR during pregnancy, your baby has a higher risk for birth defects called cleft lip and cleft palate. These defects can begin early in pregnancy, even before you know you are pregnant.
- Cleft lip and cleft palate may happen even in children born to women who are not taking any medicines and do not have other risk factors.
- Also, if you take Trokendi XR during pregnancy, your baby may be smaller than expected at birth. The long-term effects of this are not known.
- There may be other medicines to treat your condition that have a lower chance of birth defects.
- All women of childbearing age should talk to their healthcare providers about using other possible treatments instead of Trokendi XR. If the decision is made to use Trokendi XR, you should use effective birth control (contraception) unless you are planning to become pregnant. You should talk to your doctor about the best kind of birth control to use while you are taking Trokendi XR.

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- Tell your healthcare provider right away if you become pregnant while taking Trokendi XR. You and your healthcare provider should decide if you will continue to take Trokendi XR while you are pregnant.
- If you take Trokendi XR during pregnancy, your baby may be smaller than expected at birth. Talk to your healthcare provider if you have questions about this risk during pregnancy.
- Metabolic acidosis may have harmful effects on your baby. Talk to your healthcare provider if Trokendi XR has caused metabolic acidosis during your pregnancy.
- Pregnancy Registry: If you become pregnant while taking Trokendi XR, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of Trokendi XR and other antiepileptic drugs during pregnancy.

What is Trokendi XR?

Trokendi XR is a prescription medicine used:

- to treat certain types of seizures (partial onset seizures and primary generalized tonic-clonic seizures) in people 6 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 6 years and older
- to prevent migraine headaches in adults and adolescents 12 years of age and older.

Before taking Trokendi XR , tell your healthcare provider about all of your medical conditions, including if you:

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

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially, tell your healthcare provider if you take:

- Metformin (such as Glucophage)
- Valproic acid (such as DEPAKENE or DEPAKOTE)
- any medicines that impair or decrease your thinking, concentration, or muscle coordination
- birth control pills. Trokendi XR may make your birth control pills less effective. Tell your healthcare provider if your menstrual bleeding changes while you are taking birth control pills and Trokendi XR.

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

How should I take Trokendi XR?

- Take Trokendi XR exactly as prescribed.
- Your healthcare provider may change your dose. **Do not** change your dose without talking to your healthcare provider.
- Take Trokendi XR capsules whole. **Do not** sprinkle Trokendi XR on food, or break, crush, dissolve, or chew Trokendi XR capsules before swallowing.
- Trokendi XR can be taken before, during, or after a meal. Drink plenty of fluids during the day. This may help prevent kidney stones while taking Trokendi XR.
- If you take too much Trokendi XR, call your healthcare provider right away or go to the nearest emergency room.
- Talk to your health care provider on what you should do if you miss a dose.
- Do not stop taking Trokendi XR without talking to your healthcare provider. Stopping Trokendi XR suddenly may cause serious problems. If you have epilepsy and you stop taking Trokendi XR suddenly, you may have seizures that do not stop. Your healthcare provider will tell you how to stop taking Trokendi XR slowly.
- Your healthcare provider may do blood tests while you take Trokendi XR.

What should I avoid while taking Trokendi XR?

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- Do not drink alcohol within 6 hours before or 6 hours after taking Trokendi XR capsules. Trokendi XR and alcohol can cause serious side effects such as severe sleepiness and dizziness and an increase in seizures.
- Do not drive a car or operate heavy machinery until you know how Trokendi XR affects you. Trokendi XR can slow your thinking and motor skills, and may affect vision.

What are the possible side effects of Trokendi XR?

Trokendi XR may cause serious side effects, including:

See "What is the most important information I should know about Trokendi XR?"

- **High blood ammonia levels.** High ammonia in the blood can affect your mental activities, slow your alertness, make you feel tired, or cause vomiting. This has happened when Trokendi XR is taken with a medicine called valproic acid (DEPAKENE and DEPAKOTE).
- **Kidney stones.** Drink plenty of fluids when taking Trokendi XR to decrease your chances of getting kidney stones.
- **Low body temperature.** Taking Trokendi XR when you are also taking valproic acid cause a drop in body temperature to less than 95ºF, feeling tired, confusion, or coma.
- **Effects on thinking and alertness.** Trokendi XR may affect how you think, and cause confusion, problems with concentration, attention, memory, or speech. Trokendi XR may cause depression or mood problems, tiredness, and sleepiness.
- **Dizziness or loss of muscle coordination.**

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

The most common side effects of Trokendi XR include:

- tingling of the arms and legs (paresthesia)
- not feeling hungry
- nausea
- weight loss
- abnormal vision
- a change in the way foods taste
- nervousness
- speech problems
- dizziness
- slow reactions
- upper respiratory tract infection
- fever
- tiredness
- sleepiness/drowsiness
- difficulty with memory
- diarrhea
- pain in abdomen

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 Trokendi XR.
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 Supernus Pharmaceuticals, Inc. at 1-866-398-0833.

How should I store Trokendi XR?

- Store Trokendi XR tablets at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep Trokendi XR in a tightly closed container.
- Keep Trokendi XR dry and away from moisture and light.
- **Keep Trokendi XR and all medicines out of the reach of children.**

General information about the safe and effective use of Trokendi XR.

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

You can ask your pharmacist or healthcare provider for information about Trokendi XR that is written for health professionals.

What are the ingredients in Trokendi XR?

Active ingredient: topiramate

Inactive ingredients: Sugar spheres, NF; hypromellose (Type 2910), USP; mannitol, USP; docusate sodium, USP; sodium benzoate, NF; ethylcellulose, NF; oleic acid, NF; medium chain triglycerides, NF; polyethylene glycol, NF; polyvinyl alcohol, USP; titanium dioxide, USP; talc, USP; lecithin, NF; xanthan gum, NF.

Capsule shells: Gelatin, USP; titanium dioxide, USP; colorants.

Colorants:

FD&C Blue #1 (all strength capsules)

Yellow iron oxide, USP (25 mg and 50 mg capsules)

FD&C red #3 (50 mg, 100 mg and 200 mg capsules)

FD&C yellow #6 (50 mg, 100 mg and 200 mg capsules)

Riboflavin, USP (25 mg capsules)

All capsule shells are imprinted with black print that contains shellac, NF, and black iron oxide, NF.

Manufactured by: Catalent Pharma Solutions, Winchester, KY USA 40391
Manufactured for: Supernus Pharmaceuticals, Inc. Rockville, MD USA 20850
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RA-TRO-MGVX
For more information, go to www.trokendixr.com or call 1-866-398-0833.
This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 4/2017