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)
Dose and Administration (2.1, 2.3)
Warnings and Precautions (5.7, 5.10, 5.11)

INDICATIONS AND USAGE

TROKENDI XR® is indicated for:

• Epilepsy: initial monotherapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures (1.1); 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)

• Prophylaxis of migraine in patients 12 years of age and older with partial onset, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome (LGS) (1.1)

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

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

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

Swallow capsule whole and intact. Do not sprinkle on food, chew, or crush (2.7)

WARNINGS AND PRECAUTIONS

Acute myopia and secondary angle closure glaucoma: can lead to permanent visual loss; discontinue TROKENDI XR® as soon as possible (5.1)

• Visual field defects: consider discontinuation of TROKENDI XR® (5.2)

• Oligohydrosis and hyperthermia: monitor decreasing sweating and increased body temperature, especially in pediatric patients (5.3)

• Metabolic acidosis: baseline and periodic measurement of serum bicarbonate is recommended. Consider dose reduction or discontinuation of 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 use caution when operating machinery including cars; depression and mood problems may occur (5.7)

• Fetal toxicity: use during pregnancy can cause cleft lip and/or palate and being small for gestational age (5.8)

• Withdrawal of AEDs: withdraw TROKENDI XR® gradually (5.9)

• Hyperammonemia/encephalopathy: 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 has been reported with and without hyperammonemia during topiramate treatment with concomitant valproic acid use (5.12)

ADVERSE REACTIONS

Epilepsy: Most common (≥10% more frequent than placebo or low-dose topiramate in monotherapy and adjunctive therapy) adverse reactions in adult and pediatric patients were paresthesia, anorexia, weight loss, speech disorders/related speech problems, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, abnormal vision, and fever (6.1).

Migraine: Most common (≥25% more frequent than placebo) adverse reactions in adult and pediatric patients were paresthesia, anorexia, weight loss, speech disorders/related speech problems, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, abnormal vision, and fever (6.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2018

FULL PRESCRIBING INFORMATION: CONTENTS

1 INDICATIONS AND USAGE

1.1 Monotherapy Epilepsy
1.2 Adjunctive Therapy Epilepsy
1.3 Migraine

2 DOSAGE AND ADMINISTRATION

2.1 Dosing in Monotherapy Epilepsy
2.2 Dosing in Adjunctive Therapy Epilepsy
2.3 Dosing in Migraine Prophylaxis
2.4 Administration with Alcohol
2.5 Dose Modifications in Patients with Renal Impairment
2.6 Dosage Modifications in Patients Undergoing Hemodialysis
2.7 Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

• Acute myopia and secondary angle closure glaucoma: can lead to permanent visual loss; discontinue TROKENDI XR® as soon as possible (5.1)

5 WARNINGS AND PRECAUTIONS

5.1 Acute Myopia and Secondary Angle Closure Glaucoma
5.2 Visual Field Defects
5.3 Oligohydrosis and Hyperthermia
5.4 Metabolic Acidosis
5.5 Interaction with Alcohol
5.6 Suicidal Behavior and Ideation
5.7 Cognitive/Neuropsychiatric Adverse Reactions
5.8 Fetal Toxicity
5.9 Withdrawal of Antiepileptic Drugs
5.10 Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid Use)
5.11 Kidney Stones
5.12 Hypothermia with Concomitant Valproic Acid Use

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Alcohol
7.2 Antiepileptic Drugs

7.3 Other Carbonic Anhydrase Inhibitors
7.4 CNS Depressants
7.5 Oral Contraceptives
7.6 Hydrochlorothiazide (HCTZ)
7.7 Pioglitazone
7.8 Lithium
7.9 Amitriptyline

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Patients Undergoing Hemodialysis

9 OVERDOSE

10 DESCRIPTION

11 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Relative Bioavailability of TROKENDI XR® Compared to Immediate-Release Topiramate

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

14 CLINICAL STUDIES

14.1 Bridging Study to Demonstrate Pharmacokinetic Equivalence between Extended-Release and Immediate-Release Topiramate Formulations
14.2 Monotherapy Epilepsy
14.3 Adjunctive Therapy Epilepsy
14.4 Migraine Prophylaxis

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed
1.2 Adjunctive Therapy Epilepsy
TROKENDI XR® is indicated as adjunctive therapy in patients 6 years of age and older with partial on set or primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome [see Clinical Studies (14.3)].

1.3 Migraine
TROKENDI XR® is indicated for patients 12 years and older for the prophylaxis of migraine headache [see Clinical Studies (14.4)].

2. DOSEAGE AND ADMINISTRATION

2.1 Dosing in Monotherapy Epilepsy
Adults and Pediatric Patients 10 Years of Age 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 6 | 400 mg once daily |
| Week 5 | 300 mg once daily |
| Week 4 | 200 mg once daily |
| Week 3 | 150 mg once daily |
| Week 2 | 100 mg once daily |
| Week 1 | 50 mg once daily |

Pediatric Patients Ages 6 to 9 Years of Age
Dosing in patients 6 to 9 years of age is based on weight. During the titration period, the initial dose of TROKENDI XR® is 25 mg/day nightly for the first week. Based on tolerability, the dosage can be increased to 50 mg/day in the second week. Dosage can be increased by 25 mg to 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 on tolerability and clinical response, additional titration (up to a higher dose) (up to the maximum maintenance dose) can be attempted at 25 mg to 50 mg/day weekly increments. The total daily dose should not exceed the maximum maintenance dose for each range of body weight (see Table 1).

Table 1: Monotherapy Target Total Daily Maintenance Dosing for Patients 6 to 9 Years of Age

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Minimum Maintenance Dose</th>
<th>Maximum Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 11</td>
<td>150</td>
<td>250</td>
</tr>
<tr>
<td>12 - 22</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>23 - 31</td>
<td>200</td>
<td>350</td>
</tr>
<tr>
<td>32 - 38</td>
<td>250</td>
<td>350</td>
</tr>
<tr>
<td>Greater than 38</td>
<td>250</td>
<td>400</td>
</tr>
</tbody>
</table>

2.2 Dosing in Adjunctive Therapy Epilepsy
Adults (17 Years of Age and Over)
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. Titration in increments of 25 mg/day every week may delay the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in adults with partial onset seizures.

Pediatric Patients 6 to 16 Years of Age
The recommended total daily dose of TROKENDI XR® as adjunctive therapy for patients 6 to 16 years of age 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 oral once daily. Begin titration at 25 mg once daily and less, 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 1-2 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. The total daily dose should not exceed 400 mg/day.

2.3 Dosing in Migraine Prophylaxis
The recommended total daily dose of TROKENDI XR® treatment for prophylaxis of migraines headache in patients 12 years of age and older is 100 mg once daily. Titrate TROKENDI XR® for migraine prophylaxis according to the following schedule:

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

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 m²), one-half of the usual adult dose of TROKENDI XR is recommended [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

2.6 Dosage Modifications in Patients Undergoing Hemodialysis
To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of TROKENDI XR may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].
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 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 expected relative risk (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 analysis. The increase in 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

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

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for all 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 appear during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.7 Cognitive/Neuropsychiatric Adverse Reactions

In clinical trials using immediate-release topiramate, the most frequently reported adverse reaction expected to be caused by TROKENDI XR®, cognitive/neuropsychiatric adverse reactions. The most frequent of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g., depression or mood problems); and 3) Somnolence or fatigue.

Adult Patients

Cognitive-Related Dysfunction

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

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

In the monotherapy epilepsy clinical trial conducted with immediate-release topiramate, the proportion of patients who experienced 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 cognitive adverse reactions was one-third (6% for 200 mg, 12% for 300 mg, 22% for 400 mg per day, 22% for 100 mg per day (the recommended dose), 28% for 200 mg per day and 10% for placebo. Cognitive adverse reactions most commonly developed during titration and sometimes persisted after completion of titration.

Psychiatric/Behavioral Disturbance

Cognitive/behavioral disturbances (e.g., depression, mood) were dose-related for both the adjunctive epilepsy and migraine populations treated with topiramate [see Warnings and Precautions (5.6)].

Somnolence/Fatigue

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

Pediatric Patients

In pediatric epilepsy trials (additive and monotherapy) conducted with topiramate, the incidence of cognitive/neuropsychiatric adverse reactions in pediatric patients was generally lower than that observed in adults. These reactions included psychomotor slowing, difficulty with concentration/attention, speech disorders/related speech problems and language problems. The most common cognitive/neuropsychiatric adverse reaction in these trials was difficulty with concentration/attention (see Clinical Studies (14.4)). Medications that prolong the half-life of topiramate should be used with caution; there is evidence that topiramate has a negative impact on neuropsychological function.

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

5.8 Fetal Toxicity

Topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk. This drug is known to 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. When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring [see Use in Specific Populations (8.1)].

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 precipitation of seizures [see Drug Interactions (7.2)]. Topiramate should not be abruptly withdrawn because this may result in increased seizure frequency [see Drug Interactions (7.2)]. Topiramate treatment should not be withdrawn until another antiepileptic drug is in place, and then the switch should be done gradually.

The incidence of hyperammonemia in pediatric patients 12 to 17 years of age in migraine prophylaxis trials was 26% in patients taking topiramate monotherapy at 100 mg/day, and 14% in patients taking topiramate at 50 mg/day, compared to 9% in patients taking placebo. There were no new cases of hyperammonemia beyond 16 years of age.

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

In some patients, hyperammonemia can be asymptomatic. Monitoring for Hyperammonemia

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, topiramate or TROKENDI XR® treatment or an interaction of concomitant topiramate-based products and valproic acid may lead to increased ammonia levels.

5.11 Kidney Stones

Topiramate increases the risk of kidney stones. During adjunctive epilepsy trials, the risk for kidney stones in immediate-release topiramate-treated adults was 1.5%, an incidence about 2 to 4 times higher than reported in placebo treated patients. This increased risk of kidney stone formation by reducing urinary citrate excretion and by increasing urinary pH [see Warnings and Precautions (5.6)].

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. To date, postmarketing cases of hyperammonemia with or without encephalopathy have been reported in pediatric patients receiving topiramate with or without valproic acid in patients who previously tolerated either drug alone [see Drug Interactions (7.2)].

Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy and/or vomiting. In most cases, hyperammonemia is associated with a metabolic acidosis.

The incidence of hyperammonemia in pediatric patients 12 to 17 years of age in migraine prophylaxis trials was 26% in patients taking topiramate monotherapy at 100 mg/day, and 14% in patients taking topiramate at 50 mg/day, compared to 9% in patients taking placebo. There were no new cases of hyperammonemia beyond 16 years of age.

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

In some patients, hyperammonia can be asymptomatic. Monitoring for Hyperammonemia

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, topiramate or TROKENDI XR® treatment or an interaction of concomitant topiramate-based products and valproic acid may lead to increased ammonia levels.

5.12 Hyperthermia with Concomitant Valproic Acid Use

Hyperthermia, defined as a drop in body core temperature to < 35ºC (95ºF), has been reported in patients treated with concomitant valproic acid (VPA) both in conjunction with 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 (7.2)]. Consideration should be given to stopping TROKENDI XR®.
TROKENDI XR or valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections of the labeling:
- Acute Myopia and Secondary Angle Closure Glaucoma [see Warnings and Precautions (5.1)]
- Visual Field Defects [see Warnings and Precautions (5.2)]
- 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)]
- Withdrawal of Antiepileptic Drugs [see Warnings and Precautions (5.8)]
- Hyperammonemia and Encephalopathy [With and Without Concomitant Valproic Acid Use] [see Warnings and Precautions (5.9)]
- Kidney Stones [see Warnings and Precautions (5.11)]
- Hypothermia with Concomitant Valproic Acid Use [see Warnings and Precautions (5.12)]

The data described in the following sections were obtained using immediate-release topiramate tablets. TROKENDI XR® has not been studied in a randomized, placebo-controlled Phase III clinical study; 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 practice.

Monotherapy Epilepsy

Adults 16 Years of Age and Older

The most common adverse reactions in the controlled trial (Study 1) that occurred in adults in the 400 mg/day topiramate group and at an incidence higher (≥ 10%) than in the 50 mg per day group were: paresthesia, weight loss, and anorexia (see Table 3). Approximately 21% of the 159 adult patients in the 400 mg/day group who received topiramate as monotherapy in Study 1 discontinued therapy due to adverse reactions. The most common (≥ 2% more frequent than low-dose 50 mg/day topiramate) adverse reactions causing discontinuation were difficulty with memory, fatigue, asthenia, insomnia, somnolence and paresthesia.

Pediatric Patients 6 Years to 15 Years of Age

The most common adverse reactions in the controlled trial (Study 1) that occurred in pediatric patients in the 400 mg/day topiramate group and at an incidence higher (≥ 10%) than in the 50 mg/day group were fever and weight loss (see Table 4). Approximately 14% of the 77 pediatric patients in the 400 mg/day group who received topiramate as monotherapy in the controlled clinical trial discontinued therapy due to adverse reactions. The most common (≥ 2% more frequent than low-dose 50 mg/day topiramate) adverse reactions resulting in discontinuation in this trial were difficulty with concentration/attention, fever, flushing, and confusion.

Tables 3 and 4 present the incidence of adverse reactions occurring in at least 3% of adult and pediatric patients treated with 400 mg/day immediate-release topiramate and occurring with greater incidence than 50 mg/day topiramate.

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

<table>
<thead>
<tr>
<th>Body System/</th>
<th>Immediate-release topiramate Dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole-General Disorders</td>
<td>50 400</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4 6</td>
</tr>
<tr>
<td>Leg pain</td>
<td>2 3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>21 40</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13 14</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>4 5</td>
</tr>
<tr>
<td>Ataxia</td>
<td>3 4</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>0 3</td>
</tr>
<tr>
<td>Gastro-intestinal System Disorders</td>
<td>1 3</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 4</td>
</tr>
<tr>
<td>Gastritis</td>
<td>0 3</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 3</td>
</tr>
<tr>
<td>Liver and Biliary System Disorders</td>
<td>1 3</td>
</tr>
<tr>
<td>Gamma-GT increased</td>
<td>1 3</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td>6 17</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>10 15</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>6 17</td>
</tr>
</tbody>
</table>

* 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 15 Years) Where Incidence Was at Least 3% in the 400 mg/day Immediate-Release Topiramate Group and Greater Than the Rate in the 50 mg/day Immediate-Release Topiramate Group

<table>
<thead>
<tr>
<th>Body System/</th>
<th>Immediate-release topiramate Dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole-General Disorders</td>
<td>50 400</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0 3</td>
</tr>
<tr>
<td>Central &amp; Peripheral Nervous System Disorders</td>
<td>4 3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3 12</td>
</tr>
<tr>
<td>Involuntary muscle contractions</td>
<td>0 3</td>
</tr>
<tr>
<td>Verrigo</td>
<td>0 3</td>
</tr>
<tr>
<td>Gastro-Intestinal System Disorders</td>
<td>2 8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 8</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td>7 17</td>
</tr>
</tbody>
</table>
Table 4: Incidence (%) of Adverse Reactions in the Monotherapy Epilepsy Trial in Pediatric Patients (Ages 6 to 15 Years) Where Incidence Was at Least 3% in the 400 mg/day Immediate-Release Topiramate Group and Greater than the Rate in the 50 mg/day Immediate-Release Topiramate Group (continued)

<table>
<thead>
<tr>
<th>Body System/ Adverse Reaction</th>
<th>Immediate-release topiramate Dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 (N=74)</td>
</tr>
<tr>
<td></td>
<td>400 (N=77)</td>
</tr>
</tbody>
</table>

Platelet, Bleeding & Clotting Disorders
- Epistaxis: 0%

Psychiatric Disorders
- Difficulty with concentration/attention: 7%
- Mood problems: 1%
- Cognitive problems: 1%
- Difficulty with memory: 1%
- Confusion: 0%
- Depression: 0%
- Personality disorder (behavior problems): 0%

Red Blood Cell Disorders
- Anemia: 1%

Reproductive Disorders, Female†
- Intermenstrual bleeding: 0%

Resistance Mechanism Disorders
- Infection: 3%
- Viral infection: 3%

Respiratory System Disorders
- Upper Respiratory Tract Infection: 16%
- Rhinitis: 5%
- Bronchitis: 1%
- Sinusitis: 1%

Skin and Appendages Disorders
- Rash: 3%
- Alopecia: 1%

Urinary System Disorders
- Urinary Incontinence: 1%
- Micturition Frequency: 0%

Vascular (Extracardiac) Disorders
- Flushing: 0%

* 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.
† 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

Table 5: Most Common Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Epilepsy Trials in Adults 1, 2

<table>
<thead>
<tr>
<th>Body System/ Adverse Reaction</th>
<th>Placebo (N=291)</th>
<th>Topiramate Dosage (mg/day) 200-400 (N=183)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
</tbody>
</table>

Body as a Whole-General Disorders
- Fatigue: 13%
- Asthenia: 1%
- Back pain: 4%
- Chest pain: 3%
- Influenza-like symptoms: 2%

Central & Peripheral Nervous System Disorders
- Dizziness: 15%
- Ataxia: 7%
- Speech disorders/Related speech problems: 2%
- Paresthesia: 4%
- Nystagmus: 7%
- Tremor: 6%
- Language problems: 1%
- Coordination abnormal: 2%
- Gait abnormal: 1%

Gastro-Intestinal System Disorders
- Nausea: 8%
- Dyspepsia: 6%
- Abdominal pain: 4%
- Constipation: 2%

Metabolic and Nutritional Disorders
- Weight loss: 3%

Psychiatric Disorders
- Somnolence: 12%
- Nervousness: 6%
- Psychomotor slowing: 2%
- Difficulty with memory: 3%
- Confusion: 5%
- Anorexia: 4%
- Mood problems: 2%
- Agitation: 2%
- Aggressive reaction: 2%
- Emotional liability: 1%
- Cognitive problems: 1%

Reproductive Disorders, Female
- Breast pain: 2%

Respiratory System Disorders
- Pharyngitis: 2%
- Rhinitis: 6%
- Sinusitis: 4%

Vision Disorders
- Diplopia: 5%

* 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.
† 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

In pooled controlled clinical trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, 183 patients received adjunctive therapy with immediate-release topiramate at dosages of 200 to 400 mg/day (recommended dosage range), and 291 patients received placebo. Patients in these trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to immediate-release topiramate or placebo. The most common adverse reactions in the controlled clinical trial that occurred in adult patients in the 200-400 mg/day topiramate group with an incidence higher (≥10%) than in the placebo group were: dizziness, speech disorders/related speech problems, somnolence, nervousness, psychomotor slowing, and vision abnormal (see Table 5) [see Clinical Studies (14.3)].

In controlled clinical trials in adults, 11% of patients receiving immediate-release 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 reactions 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.
Patients in these adjunctive trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to topiramate or placebo.

† 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.

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.

In the four multicenter, randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials which included 35 pediatric patients 12 to 15 years of age, most adverse reactions occurred more frequently during the titration period than during the maintenance period.

The most common adverse reactions with immediate-release topiramate 100mg in migraine prophylaxis clinical trials of predominantly adults that were seen at an incidence higher (>5%) than in the placebo group were: paresthesia, anorexia, weight loss, taste perversion, diarrhea, difficulty with memory, hypoesthesia, and nausea (see Table 7).

Table 7 includes those adverse reactions that occurred in the placebo-controlled trials where the incidence in any immediate-release topiramate group was at least 3% and was greater than that for placebo patients. The incidence of some adverse reactions (e.g., fatigue, dizziness, somnolence, difficulty with memory, difficulty with concentration/attention) was dose-related and greater at higher than recommended topiramate dosing (200 mg/day) compared to the incidence of these adverse reactions at the recommended dosing (100 mg/day).

### Table 6. Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Epilepsy Trial in Pediatric Patients 2 to 15 Years of Age

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Placebo (N=101) %</th>
<th>Topiramate (N=98) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Saliva increased</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gastro-Intestinal System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Platelet, Bleeding &amp; Clotting Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpura</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Anorexia</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Nervousness</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Personality disorder (Behavior Problems)</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Difficulty with memory/attention</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Aggressive reaction</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Difficulty with memory</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Confusion</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Psychomotor slowing</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Resistance Mechanism Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection viral</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Respiratory System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Skin and Appendages Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin Disorder</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Urinary System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

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

† 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.

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.

Migraine

In the four multicenter, randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials (which included 35 pediatric patients 12 to 15 years of age), most adverse reactions occurred more frequently during the titration period than during the maintenance period.
Table 7: Adverse Reactions in Pooled, Placebo-Controlled, Migraine Trials in Adults.\(^1\)\(^,\)\(^2\) (continued)

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Topiramate Dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=445)</td>
</tr>
<tr>
<td>Skin and Appendages Disorders</td>
<td>Pruritis</td>
</tr>
<tr>
<td></td>
<td>Taste paresthesia</td>
</tr>
<tr>
<td>Urinary System Disorders</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>Vision Disorders</td>
</tr>
</tbody>
</table>

* Includes 35 adolescent patients age 12 to 15 years
† 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.
‡ 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

Table 8: Adverse Reactions in Pooled Double-Blind Migraine Prophylaxis Studies in Pediatric Patients 12 to 17 Years of Age\(^1\) (continued)

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Placebo (N=45)</th>
<th>Immediate-release Topiramate Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=45)</td>
<td>Immediate-release Topiramate Dosage (N=54)</td>
</tr>
<tr>
<td></td>
<td>(N=45)</td>
<td>50 mg/day (N=46)</td>
</tr>
<tr>
<td>Body as a Whole – General Disorders</td>
<td>Fatigue</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>2</td>
</tr>
<tr>
<td>Central &amp; Peripheral Nervous System Disorders</td>
<td>Paresthesia</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal System Disorders</td>
<td>Abdominal pain</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>4</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td>Weight loss</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Anorexia</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>2</td>
</tr>
</tbody>
</table>

† 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%).

Increased Risk for Bleeding

Topiramate 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 reaction 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 minor mucosal 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).

Other Adverse Reactions Observed During Clinical Trials

Other adverse reactions seen during clinical trials were: abnormal coordination, eosinophilia, gingival bleeding, hematemia, hypotension, myalgia, myopia, postural hypotension, scotoma, suicide attempt, syncope, and visual field defect. Laboratory Test Abnormalities

Adult Patients

In addition to changes in serum bicarbonate (i.e., metabolic acidosis), sodium chloride and ammonia, immediate-release topiramate was associated with changes in several clinical laboratory analytes in randomized, double-blind, placebo-controlled studies (see Warnings and Precautions (5.4, 5.10)). Controlled trials of adjunctive topiramate treatment of adults for partial onset seizures showed an increased incidence of markedly decreased serum phosphorus (6% topiramate versus 2% placebo), markedly increased serum alkaline phosphatase (3% topiramate versus 1% placebo), and decreased serum potassium (0.4% topiramate versus 0.1% placebo).

Pediatric Patients

In pediatric patients (1-24 months) receiving adjunctive topiramate for partial onset seizures, there was an increased incidence for an increased result (relative to normal analyte reference range) associated with immediate-release topiramate (vs. placebo) for the following clinical laboratory analytes: creatinine, BUN, alkaline phosphatase, and total protein. The incidence was also increased for a decreased result for bicarbonate (i.e., metabolic acidosis), and potassium with immediate-release topiramate (vs. placebo) [see Use in Specific Populations (8.4)]. TROKENDI XR\(^*)\) is not indicated for partial onset seizures in pediatric patients less than 6 years of age.

In pediatric patients (ranging from 6-17 years old) receiving immediate-release topiramate for migraine prophylaxis, there was an increased incidence for an increased result (relative to normal analyte reference range) associated with immediate-release topiramate (vs. placebo) for the following clinical laboratory analytes: creatinine, BUN, uric acid, chlorine, ammonia, alkaline phosphatase, total protein, platelets, and eosinophils. The incidence was also increased for a decreased result for phosphorus, bicarbonate, total white blood count, and neutrophils [see Use in Specific Populations (8.4)]. TROKENDI XR\(^*)\) is not indicated for prophylaxis of migraine headache in pediatric patients less than 12 years of age.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of immediate-release 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.

Body as a Whole-General Disorders: oligohydrosis and hyperthermia [see Warnings and Precautions (5.3)], hyperammonemia, hyperammonemic encephalopathy [see Warnings and Precautions (5.10)], hypothermia with concomitant valproic acid [see Warnings and Precautions (5.12)].

Gastrointestinal System Disorders: hepatic failure (including fatalities), hepatitis, pancreatitis

Skin and Appendage Disorders: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), pemphigus

Urinary System Disorders: kidney stones [see Warnings and Precautions (5.11)]
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 Antiepileptic Drugs
Concomitant administration of valproic acid and topiramate has been associated with neurotoxicity and an increased risk of seizure exacerbation. When valproic acid and topiramate are used together, the dose of topiramate should be decreased (see Warnings and Precautions (5.2)).

7.3 Other Carbonic Anhydrase Inhibitors
Concomitant use of topiramate, a carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors (e.g., acetazolamide, dichlorphenamide, or azathioprine) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Patients 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)].

7.4 CNS Depressants
Concomitant administration of topiramate with other CNS depressant drugs or alcohol has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, the 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)].

7.5 Oral Contraceptives
The possibility of decreased contraceptive efficacy and increased breakthrough bleeding may occur 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 Use in Specific Populations (8.1)].

7.6 Hydrochlorothiazide (HCTZ)
Topiramate Cmax and AUC increased when HCTZ was added to immediate-release topiramate. The clinical significance of this change is unknown. The addition of HCTZ to TROKENDI XR® may require a decrease in the TROKENDI XR® dose [see Clinical Pharmacology (12.3)].

7.7 Pioglitazone
A decrease in the exposure of pioglitazone and its active metabolites were noted with the concurrent use of pioglitazone and immediate-release topiramate in a clinical trial. The clinical relevance of the decrease in pioglitazone exposure is unknown; however, 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 [see Clinical Pharmacology (12.3)].

7.8 Lithium
An increase in systemic exposure of lithium following topiramate doses of up to 600 mg/day can occur. Lithium levels should be monitored when co-administered with high-dose 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 TROKENDI XR® during pregnancy. Women 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 (SGA). Births with oral clefts were 16 times higher than the background rate in the UK (0.2%). Data from the NAAED pregnancy registry and a population-based birth registry cohort indicate that exposure to topiramate in utero is associated with an increased risk of small for gestational age (SGA) newborns (birth weight <10th percentile). In the NAAED pregnancy registry, 18% of topiramate-exposed newborns were SGA compared to 7% of newborns exposed to a reference AED. Evidence from 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 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/m²) 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 (primarily rib and vertebral malformations) was increased in the topiramate monotherapy group (58% at 400 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 30 mg/kg/day and above, and maternal body weight gain was reduced at doses of 100 mg/kg/day or greater. No evidence of embryopathology and/or developmental toxicity in rats is less than the MRHD for epilepsy or migraine on a mg/m² basis. In pregnant rabbits administered topiramate (20, 60, and 180 mg/kg/day or 10, 35, and 125 mg/kg/day) orally during organogenesis, embryofetal mortality was increased at 35 mg/kg/day and above. ECG changes (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg/day and above. The no-effect dose (20 mg/kg/day) for embryofetal developmental toxicity in rabbits is equivalent to the MRHD for epilepsy and approximately 4 times the MRHD for migraine on a mg/m² basis. 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/m² basis.

8.2 Lactation
Risk Summary
Topiramate is excreted in human milk [see Data]. The effects of topiramate exposure in breastfed infants or on milk production 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 breastfed infants that were similar to or lower than maternal levels. These data were obtained from nonclinical studies. There are no adequate and well-controlled studies in pregnant women. The effects of topiramate on milk production have not been established. There is no evidence from controlled clinical studies in lactating women of the potential for topiramate to cause clinically significant problems when administered to breastfed infants. However, it is not known whether topiramate in the mother's milk could interfere with breast function or could have harmful effects on the nursing infant. The potential for topiramate to interfere with breast function or to have harmful effects on the nursing infant should be considered when topiramate is administered to a nursing woman.

8.3 Females and Males of Reproductive Potential
Contraception
Women of childbearing potential who are not planning a pregnancy should use effective contraception to prevent pregnancy and the potential for fetal implications of the use of topiramate during pregnancy. 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 fetus may have contraindicated the use of labor and delivery. [See Use in Specific Populations (8.1)].

TROKENDI XR 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 TROKENDI XR® should be monitored for metabolic acidosis because of transfer of topiramate to the fetus and possible occurrence of transient metabolic acidosis following birth.

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, in the treatment of primary generalized tonic-clonic seizures, and in Lennox-Gastaut syndrome in pediatric patients younger than 6 years of age is based on controlled trials with immediate-release topiramate [see Clinical Studies (14.1, 14.2)].

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:

• oligohydramnios and hydramnios [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 syndrome 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.

Vision disorders: acute myopia, secondary angle closure glaucoma [see Warnings and Precautions (5.1)]. maculopathy.
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-blind, placebo-controlled, single-dose study in 30 infants and toddlers (ages 3 months to 12 years), administration of 15 mg/kg/day (max 100 mg/day) topiramate as a single dose produced a dose-related incidence of hyperammonemia [see Warnings and Precautions (5.7)].

Efficacy of topiramate for migraine prophylaxis in pediatric patients 12 to 17 years of age is demonstrated for a 100 mg daily dose in Study 3. Topiramate treatment produced a dose-related increased incidence of hyperammonemia [see Warnings and Precautions (5.7)].

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 percent-age of patients who had a shift from normal at baseline to high/ increased (above the normal range) of one or more of the following analytes at any time during the double-blind phase. 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 (5.7)].

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 group (12 to 17 years of age) [see Clinical Studies (14.4)] with a flexible dose (2 to 3 mg/kg/day), placebo-controlled study in 157 pediatric patients 6 to 16 years of age (including 67 pediatric patients 12 to 16 years of age), and a total of 49 pediatric patients 12 to 17 years of age in 3 studies of migraine prophylaxis primarily in adults. Open-label extension phases of 3 studies enabled evaluation of long-term safety for up to 6 months after the end of the double-blind phase.

Efficacy of topiramate for migraine prophylaxis in pediatric patients 12 to 17 years of age is demonstrated for a 100 mg daily dose in Study 3 [see Clinical Studies (14.4)]. Efficacy of topiramate also has been demonstrated in a double-blind, placebo-controlled trial of 157 pediatric patients (6 to 16 years of age) that included treatment of 67 pediatric patients 12 to 16 years of age for 20 weeks. In the pediatric trials (12 to 17 years of age) in which patients were randomized to placebo or a free-dose follow-on of immediate-release topiramate, the proportion of patients with immediate-release topiramate that were seen at an incidence higher (≥2%) 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 pediatric patients 12 to 17 years of age was word-finding difficulty [see Warnings and Precautions (5.7)]. Markedly abnormal serum bicarbonate values indicative of metabolic acidosis were reported in topiramate-treated pediatric migraine patients [see Warnings and Precautions (5.4)]. In open-label-treatment studies of 5 mg/kg, 15 mg/kg, and 25 mg/kg (equal to 50 mg/kg) 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)].

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

Approximately 40% and 51%, respectively, for immediate-release topiramate [see Dosage and Administration] compared to approximately 26% and 42% in healthy young subjects. Elderly subjects exhibited shorter median T_{1/2} > 20 mm Hg, pulse increases or decreases ≥ 30 beats per minute. These changes were often dose-related, and were most frequently associated with the greatest treatment difference at the 200 mg dose level. Systematic collection of orthostatic vital signs has not been conducted. The significance of these various changes in vital signs has not been clearly established.

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 carboxy anhydride in red blood cells.

A study of 13 healthy elderly subjects and 18 healthy young adults who received 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 26% and 42% in elderly subjects and healthy young subjects, respectively, compared to approximately 40% and 51%, respectively, for immediate-release topiramate [see Clinical Pharmacology (12.6)].

Compared to the faster state, high-fat meal increased the C_{max} of topiramate by 27% and shortened the T_{1/2} to approximately 8 hours 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 cleared by 50% to 60% 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.

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.

In a study of 13 healthy elderly subjects and 18 healthy young adults who received TROKENDI XR®, absorption of topiramate was approximately 8 hour following a single dose of TROKENDI XR® and immediate-release tablets following administration. The mean elimination half-life of topiramate is approximately 2 hours when administered alone and 3 hours when administered in combination with other antiepileptic drugs.

Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ dosing. Serum hematologic changes were not observed following a single dose of topiramate. Serum lipids were not affected by topiramate treatment.

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.

Table: Summary of AED Interactions with topiramate

<table>
<thead>
<tr>
<th>AED Coadministered</th>
<th>AED Concentration</th>
<th>Topiramate Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>NC or 25% increase</td>
<td>48% decrease</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>CBZ epoxide†</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>11% decrease</td>
<td>14% decrease</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>NC at TPM doses up to 400 mg per day</td>
<td>13% decrease</td>
</tr>
</tbody>
</table>

NC = Less than 10% change in plasma concentration

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), immediate-release topiramate, given in the absence of other medications at doses of 50 to 200 mg/day, was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg 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, and there was no significant dose-dependent change in EE exposure for doses of 50 to 200 mg/day.

The clinical significance of the changes observed is not known [see Drug Interactions (7.3)].

Digoxin

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

A 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 24 hours) administered once-daily. The results of this study indicate that the C_{max} of topiramate increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results revealed decreases in serum potassium after topiramate dosing. Serum hematologic changes were not observed following a single dose of topiramate. Serum lipids were not affected by topiramate treatment.

Metformin

A drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin (500 mg every 12 hours) and topiramate (200 mg every 12 hours). The C_{max} and AUC_{0-12h} of metformin were given alone and when metformin and topiramate (100 mg every 12 hours) were coadministered. The results of this study indicated that the mean metformin C_{max} and AUC_{0-12h} increased by 17% and 25%, respectively, when topiramate was added. Topiramate did not affect neither the basal nor the capillary glucose level. The clinical significance of the effect of metformin on topiramate or TROKENDI XR® pharmacokinetics is unclear.

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 to <16 years of age. Patients received either no or a combination of other antiepileptic drugs. A population pharmacokinetic model was developed on the basis of pharmacokinetic data from 31 pediatric clinical studies. This dataset contained data from 1217 subjects including 258 pediatric patients age 2 years to <16 years of age (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 through non-anticonvulsant 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 of age) 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 young 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-Dose Interaction Studies

In vitro studies indicate that topiramate does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, or 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-drug interactions can be expected with the use of TROKENDI XR®.

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 9. Interaction of TROKENDI XR® and standard AEDs is not expected to differ from the experience with immediate-release topiramate products.
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 daily dose. In a double-blind, randomized, placebo-controlled study, patients received 100 mg per day of 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 the ratio of AUC (the area under the concentration-time curve from t = 0 to t = 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® or immediate-release topiramate, the conclusion that topiramate is effective as initial monotherapy in pediatric patients down to 2 years of age was based on a pediatric population study 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)].

Comparison of the Kaplan-Meier survival curves of time to first seizure favored the topiramate 400 mg/day group over the topiramate 50 mg/day group (Figure 1). The treatment effects were consistent across various patient subgroups defined by age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use.

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

Pediatric Patients 6 to 9 Years of Age

The conclusion that topiramate is effective as initial monotherapy in pediatric patients 6 to 9 years of age with partial onset or primary generalized tonic-clonic seizures was based on a pediatric population study 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)].

Specific dosing in pediatric patients 6 to 9 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 Use in Adjacency and Administration (2.1)].
patients entered an 8-week stabilization period. The primary measures of effectiveness were the intolerance prevented increases. After titration, patients entered an 8-week stabilization period. The dose was then increased to 3 mg/kg/day for one week then to 6 mg/kg/day. After titration, active drug beginning at 50 mg/day for four weeks; the dose was then increased by 50 mg to 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 numbers of patients randomized to each dose, and the actual mean and median doses in the stabilization period are shown in Table 10.

Table 11: Efficacy Results in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

### Target Topiramate Dosage (mg per day)

<table>
<thead>
<tr>
<th>Study</th>
<th>#</th>
<th>Placebo</th>
<th>200</th>
<th>400</th>
<th>600</th>
<th>800</th>
<th>1,000</th>
<th>&lt;6mg/kg/day</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>N</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>46</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Median % Reduction</td>
<td>12</td>
<td>27</td>
<td>41</td>
<td>45</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>% Responders</td>
<td>18</td>
<td>24</td>
<td>44</td>
<td>46</td>
<td>--</td>
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<td></td>
<td>N</td>
<td>47</td>
<td>--</td>
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<td>3</td>
<td>Median % Reduction</td>
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<td>--</td>
<td>41</td>
<td>41</td>
<td>36</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>% Responders</td>
<td>9</td>
<td>--</td>
<td>40</td>
<td>41</td>
<td>36</td>
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<td>--</td>
<td>41</td>
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<td></td>
<td>% Responders</td>
<td>8</td>
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<td>35</td>
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</tr>
<tr>
<td>5</td>
<td>Median % Reduction</td>
<td>12</td>
<td>--</td>
<td>46</td>
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</tr>
<tr>
<td></td>
<td>% Responders</td>
<td>10</td>
<td>--</td>
<td>47</td>
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<td></td>
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<td>28</td>
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</tr>
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<td>6</td>
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<tr>
<td></td>
<td>% Responders</td>
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<td>43</td>
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</tr>
<tr>
<td></td>
<td>N</td>
<td>91</td>
<td>168</td>
<td>40</td>
<td>40</td>
<td>40</td>
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<td>7</td>
<td>Median % Reduction</td>
<td>20</td>
<td>--</td>
<td>45</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>% Responders</td>
<td>24</td>
<td>--</td>
<td>56</td>
<td></td>
<td></td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Comparisons with placebo:

* For Studies 8 and 9, specified target dosages (~3.3 mg/kg/day) were assigned based on subject weight to approximate a dosage of 6mg/kg per day; these dosages corresponded to mg/day dosages of 125, 175, 225, and 400 mg/day

† p=0.080;
‡ p ≤ 0.010;
§ p ≤ 0.001;
¶ p ≤ 0.050;
ø p=0.065;
ø p≤0.005;

§ Studies included pediatric patients 2 years of age and older, an age group for which TROKENDI XR is not indicated [see Indications and Usage (1.2) and Use in Specific Populations (8.4)]

<table>
<thead>
<tr>
<th>Study</th>
<th>Target Topiramate Dosage (mg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Median % Reduction</td>
</tr>
<tr>
<td></td>
<td>% Responders</td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>Median % Reduction</td>
</tr>
<tr>
<td></td>
<td>% Responders</td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>Median % Reduction</td>
</tr>
<tr>
<td></td>
<td>% Responders</td>
</tr>
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<td>N</td>
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<td>5</td>
<td>Median % Reduction</td>
</tr>
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<td></td>
<td>% Responders</td>
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<td>N</td>
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<td>6</td>
<td>Median % Reduction</td>
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<tr>
<td></td>
<td>% Responders</td>
</tr>
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<td>N</td>
</tr>
<tr>
<td>7</td>
<td>Median % Reduction</td>
</tr>
<tr>
<td></td>
<td>% Responders</td>
</tr>
</tbody>
</table>

### Periods of Each of Six Double-Blind, Placebo-Controlled, Adjunctive Trials in Adults with Partial Onset Seizures

Table 10: 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Target Topiramate Dose (mg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Median % Reduction</td>
</tr>
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<td>% Responders</td>
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<td>Median % Reduction</td>
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<td>% Responders</td>
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<td>N</td>
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<td>Median % Reduction</td>
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<td>% Responders</td>
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<tr>
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<td>N</td>
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<td>5</td>
<td>Median % Reduction</td>
</tr>
<tr>
<td></td>
<td>% Responders</td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>Median % Reduction</td>
</tr>
<tr>
<td></td>
<td>% Responders</td>
</tr>
<tr>
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<tr>
<td>7</td>
<td>Median % Reduction</td>
</tr>
<tr>
<td></td>
<td>% Responders</td>
</tr>
</tbody>
</table>

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 11. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.
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 12. 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).

Table 12: 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)

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (N=33)</th>
<th>Immediate-Release Topiramate 50 mg/ day (N=35)</th>
<th>Immediate-Release Topiramate 100 mg/day (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.6</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Last 12 Weeks of Double-Blind Phase</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.3</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Percent Reduction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>44.4</td>
<td>44.6</td>
<td>72.2</td>
</tr>
<tr>
<td>P-value versus Placebo ‡</td>
<td>0.7975</td>
<td>0.0164</td>
<td></td>
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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 monty migraine attack rate during baseline period as a covariate.

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

‡ Indicates p-value is <0.05 (two-sided).

16 HOW SUPPLIED/STORAGE AND HANDLING

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

- 25 mg (light green opaque body/yellow opaque cap with black print “SPN” and “25”): • bottles of 30 count (NDC-17772-101-30) and 100 count (NDC-17772-101-01)
  - blister packs of 30-count (NDC-17772-101-15)
- 50 mg (light green opaque body/orange opaque cap with black print “SPN” and “50”): • bottles of 30 count (NDC-17722-102-30) and 100 count (NDC-17722-102-01)
  - blister packs of 30-count (NDC-17772-102-15)
- 100 mg (green opaque body/blue opaque cap with black print “SPN” and “100”): • bottles of 30 count (NDC-17772-103-30) and 100 count (NDC-17772-103-01)
  - blister packs of 30-count (NDC-17772-103-15)
- 200 mg (pink opaque body/lilac opaque cap with black print “SPN” and “200”): • bottles of 30 count (NDC-17772-104-30) and 100 count (NDC-17772-104-01)
  - blister packs of 30-count (NDC-17772-104-15)

16.2 Storage and Handling
TROKENDI XR® (topiramate) extended-release capsules should be stored in well-closed containers in a 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

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

Administer 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 (2.7)].

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

Advising patients taking TROKENDI XR® to seek immediate medical attention if they experience blurred vision, visual disturbances or periocular 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)].
Precautions (5.12)

should be specifically counseled on this potential adverse reaction. Professional and measure their body temperature. Patients taking concomitant valproic acid lead to alterations in mental status. If they note such changes, they should call their health care antiepileptic drugs during pregnancy. Hyperammonemia and Encephalopathy

Encourage pregnant women using topiramate to enroll in the North American Antiepileptic Drug TROKENDI XR

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Manufactured by: Catalent Pharma Solutions, Winchester, Kentucky 40391

Patients should be instructed to contact their physician if they develop unexplained lethargy, vomiting, or changes in mental status. 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.

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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.
- 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.
- 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. The long-term effects of this are not known. 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:
- 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.
- any other medicines you take.

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.

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?

- 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
- decreased feeling or sensitivity, especially in the skin

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

These are not all the possible side effects of 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.

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; t alc, 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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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

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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.