Trokendi XR

Extended-Release Capsules
25 mg/ 50 mg/ 100 mg/ 200 mg

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1 INDICATIONS AND USAGE

1.1 Monotherapy Epilepsy

TROKENDI XR® is indicated in patients 6 years of age and older as initial monotherapy for partial onset or primary generalized tonic-clonic seizures [*see Clinical Studies (14.2)*].

1.2 Adjunctive Therapy Epilepsy

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

1.3 Migraine

TROKENDI XR® is indicated for the prophylaxis of migraine headache in adult patients [*see Clinical Studies (14.4)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosing in Monotherapy Epilepsy

When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve monotherapy with topiramate, consideration should be given to the effects this may have on seizure control. Unless safety concerns require an abrupt withdrawal of the concomitant AED, a gradual discontinuation at the rate of approximately one-third of the concomitant AED dose every 2 weeks is recommended [see *Warnings and Precautions (5.9)*].

When enzyme inducing drugs are withdrawn, topiramate levels will increase. A decrease in topiramate dosage may be required if clinically indicated.

Adults

Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2-week intervals by increments of 25 or 50 mg/day, administered orally once daily. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used. Dose and titration rate should be guided by clinical outcome.

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day and the maximum recommended daily dose is 500 mg. Some patients with refractory forms of epilepsy have tolerated topiramate monotherapy at doses of 1,000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

Pediatric Patients Ages 6 to 9 Years of Age

Treatment of children aged 6 to 9 years should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 0.5 to 1 mg/kg/day, administered orally once daily. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used. Dose and dose titration rate should be guided by clinical outcome.

The recommended initial target dose range for topiramate monotherapy in children aged two years and above is 3 to 6 mg/kg/day. Children with recently diagnosed partial onset seizures have received doses of up to 500 mg/day.

2.2 Dosing in Adjunctive Therapy Epilepsy

Adults

The recommended total daily dose of TROKENDI XR® as adjunctive therapy in adults should begin at 25 to 50 mg nightly for one week. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25 to 50 mg/day and taken orally once daily. Dose titration should be guided by clinical outcome. Some patients may achieve efficacy with once-a-day dosing.

In clinical trials as adjunctive therapy, 200 mg was effective and was the lowest dosage studied. This is therefore considered the minimum effective dose. The usual daily dose is 200 to 400 mg orally once daily. Individual patients have received doses as high as 1600 mg/day.

These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease [see *Warnings and Precautions (5.13)*].

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 orally once daily. Begin titration at 25 mg once daily (or 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-or 2-week intervals by increments of 1 mg/kg/day to 3 mg/kg/day (administered orally once daily) to achieve optimal clinical response. Dose titration should be guided by clinical outcome. The total daily dose should not exceed 400 mg/day.

Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

2.3 Dosing in Migraine Prophylaxis

Adults

The recommended total daily dose of TROKENDI XR® as treatment for prophylaxis of migraine headache in adult patients is 100 mg once daily. Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. Dose and titration rate should be guided by clinical outcome.

Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, 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 (8.5, 8.6), 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)]*.

2.7 Administration Instructions

TROKENDI XR® can be taken without regard to meals.
Swallow capsule whole and intact. Do not sprinkle on food, chew, or crush.

3 DOSAGE FORMS AND STRENGTHS

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

- 25 mg: Size 2 capsules, light green opaque body/yellow opaque cap (printed "SPN" on the cap, "25" on the body)
- 50 mg: Size 0 capsules, light green opaque body/orange opaque cap (printed "SPN" on the cap, "50" on the body)
- 100 mg: Size 00 capsules, green opaque body/blue opaque cap (printed "SPN" on the cap, "100" on the body)
- 200 mg: Size 00 capsules, pink opaque body/blue opaque cap (printed "SPN" on the cap, "200" on the body)

4 CONTRAINDICATIONS

TROKENDI XR® is contraindicated in patients:

- Hypersensitivity to any component of this product.
- With recent alcohol use (i.e., within 6 hours prior to and 6 hours after TROKENDI XR® use) [*see Warnings and Precautions (5.5)*]

5 WARNINGS AND PRECAUTIONS

5.1 Acute Myopia and Secondary Angle Closure Glaucoma

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

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

5.2 Visual Field Defects

Visual field defects (independent of elevated intraocular pressure) have been reported in clinical trials and in postmarketing experience in patients receiving topiramate. In clinical trials, most of these events were reversible

after topiramate discontinuation. If visual problems occur at any time during treatment with TROKENDI XR®, consideration should be given to discontinuing the drug.

5.3 Oligohydrosis and Hyperthermia

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

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

5.4 Metabolic Acidosis

TROKENDI XR® can cause hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis). This metabolic acidosis is caused by renal bicarbonate loss due carbonic anhydrase inhibition by TROKENDI XR. TROKENDI XR® -induced metabolic acidosis can occur at any time during treatment. Bicarbonate decrements are usually mild to moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet or specific drugs) may be additive to the bicarbonate lowering effects of TROKENDI XR®.

Metabolic acidosis was commonly observed in adult and pediatric patients treated with immediate-release topiramate in clinical trials. The incidence of decreased serum bicarbonate in pediatric trials for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures was as high as 67% for immediate-release topiramate (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5mEq/L decrease from pretreatment) in these trials was up to 11%, compared to ≤2% for placebo.

Manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates, which may decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in long-term, placebo-controlled trials. Long-term, open-label treatment of pediatric patients 1 to 24 months old with intractable partial epilepsy, for up to 1 year, showed reductions from baseline in length, weight, and head circumference compared to age and sex-matched normative data, although these patients with epilepsy are likely to have different growth rates than normal 1 to 24 month old pediatrics. Reductions in length and weight were correlated to the degree of acidosis [*see Use in Specific Populations (8.4)*]. TROKENDI XR® treatment that causes metabolic acidosis during pregnancy can possibly produce adverse effects on the fetus and might also cause metabolic acidosis in the neonate from possible transfer of topiramate to the fetus [*see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)*].

Measurement of Serum Bicarbonate in Epilepsy and Migraine Patients

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

5.5 Interaction with Alcohol

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

5.6 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs) increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED, including TROKENDI XR® for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

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

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

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

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

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

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

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

5.7 Cognitive/Neuropsychiatric Adverse Reactions

Immediate-release topiramate can cause, and therefore 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 dose-related adverse reactions began in the titration or in the maintenance phase, and in some patients these events began during titration and persisted into the maintenance phase.

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

In the 6-month migraine prophylaxis controlled trials of immediate release topiramate using a slower titration regimen (25mg per day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reactions was 19% for topiramate 50 mg per day, 22% for 100 mg per day (the recommended dose), 28% for 200 mg per day and 10% for placebo. Cognitive adverse reactions most commonly developed during titration and sometimes persisted after completion of titration.

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (e.g., depression, mood) were dose-related for both the adjunctive epilepsy and migraine populations 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 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 (adjunctive 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 frequently reported neuropsychiatric reactions in pediatric epilepsy patients during adjunctive therapy double-blind studies were somnolence and fatigue. The most frequently reported cognitive/neuropsychiatric reactions in pediatric epilepsy patients in the 50 mg/day and 400 mg/day groups during the monotherapy double-blind study were headache, dizziness, anorexia, and somnolence.

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

The risk for cognitive/neuropsychiatric adverse reactions was dose-dependent, and was greatest at the highest dose (200 mg). This risk for cognitive/neuropsychiatric adverse reactions was also greater in younger patients (6 to 11 years of age) than in older patients (12 to 17 years of age). The most common cognitive/neuropsychiatric adverse reaction in these trials was difficulty with concentration/attention. Cognitive adverse reactions most commonly developed during titration and sometimes persisted for various durations after completion of titration. The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to adolescents (12 to 17 years of age) to assess the effects of topiramate on cognitive function at baseline at the end of the Study 3 *[see Clinical Studies (14.4)]*. Mean change from baseline in certain CANTAB tests suggests that topiramate treatment may result in psychomotor slowing and decreased verbal fluency.

5.8 Fetal Toxicity

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

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

5.9 Withdrawal of Antiepileptic Drugs

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

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

Topiramate treatment can cause hyperammonemia with or without encephalopathy *[see Adverse Reactions (6.2)]*. The risk for hyperammonemia with topiramate appears dose-related. Hyperammonemia has been reported more

frequently when topiramate is used concomitantly with valproic acid. Postmarketing cases of hyperammonemia with or without encephalopathy have been reported with topiramate and valproic acid in patients who previously tolerated either drug alone *[see Drug Interactions (7.2)]*.

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, hyperammonemic encephalopathy abated with discontinuation of treatment.

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 product and valproic acid treatment may exacerbate existing defects or unmask deficiencies in susceptible persons.

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

5.11 Kidney Stones

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 greater than expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate-treated patients was higher in men. Kidney stones have also been reported in pediatric patients taking topiramate for epilepsy or migraine. During long-term (up to 1 year) topiramate treatment in an open-label extension study of 284 pediatric patients 1-24 months old with epilepsy, 7% developed kidney or bladder stones. TROKENDI XR® would be expected to have the same effect as immediate-release topiramate on the formation of kidney stones. TROKENDI XR® is not approved for treatment of epilepsy in pediatric patients less than 6 years old [*see Use in Specific Populations (8.4)*].

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

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

5.12 Hypothermia with Concomitant Valproic Acid Use

Hypothermia, defined as a drop in body core temperature to < 35°C (95°F), has been reported in association with topiramate use with concomitant valproic acid (VPA) both in conjunction with 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 or valproate in patients who develop hypothermia,

which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

5.13 Renal Impairment

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with moderate or severe renal impairment may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function.

As with all patients, the titration schedule should be guided by clinical outcome (i.e., seizure control, avoidance of side effects) with the knowledge that subjects with known renal impairment may require a longer time to reach steady-state at each dose [see *Dosage and Administration (2.5), Clinical Pharmacology (12.3)*].

5.14 Serious Skin Reactions

Serious skin reactions (Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)) have been reported in patients receiving topiramate [see Adverse Reactions]. The majority of cases have occurred in patients concurrently taking other medications that are known to be associated with SJS and TEN. There have also been several cases in patients receiving monotherapy. It is recommended that patients be informed about the signs of serious skin reactions. If SJS or TEN are suspected, use of topiramate should be discontinued.

5.15 Hepatic Impairment

In hepatically-impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased [see *Clinical Pharmacology (12.3)*].

5.16 Hydration

Oligohidrosis (decreased sweating) and anhidrosis have been reported in association with the use of topiramate. Decreased sweating and hyperthermia (rise in body temperature) may occur especially in young children exposed to high ambient temperatures [see *Adverse Reactions*].

Adequate hydration while using topiramate is very important. Hydration can reduce the risk of nephrolithiasis [see *Warnings and Precautions (5.11)*]. Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse events [see *Adverse Reactions*].

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)*]
- Interaction with Alcohol[see *Warnings and Precautions (5.5)*]
- Suicidal Behavior and Ideation [*see Warnings and Precautions (5.6)*]
- Cognitive/Neuropsychiatric Adverse Reactions [*see Warnings and Precautions (5.7)*]
- Fetal Toxicity [see *Warnings and Precautions (5.8)*]
- Withdrawal of Antiepileptic Drugs [*see Warnings and Precautions (5.9)*]

- Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid Use) [*see Warnings and Precautions (5.10)*]
- Kidney Stones [*see Warnings and Precautions (5.11)*]
- Hypothermia with Concomitant Valproic Acid Use [*see Warnings and Precautions (5.12)*]
- Renal Impairment [see *Warnings and Precautions (5.13)*]
- Serious Skin Reactions [see *Warnings and Precautions (5.14)*]
- Hepatic Impairment [see *Warnings and Precautions (5.15)*]
- Hydration [see *Warnings and Precautions (5.16)*]

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

Adverse reactions reported in ≥1% of immediate-release topiramate-treated adult patients in double-blind, controlled monotherapy epilepsy trials are shown in Table 2. Adverse reactions that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included paresthesia, weight decreased, fatigue, anorexia, depression, memory impairment, anxiety, diarrhea, asthenia, dysguesia, and hypoesthesia.

Table 2: Adverse Reactions in Adults in Double-Blind, Controlled, Monotherapy Epilepsy Studies (≥1% in any group)

	Immediate-Release Topiramate Dose				
System/Organ Class Adverse Reaction	**50 mg/day[a] (N=257) %**	**100 mg/day (N=171) %**	**200 mg/day (N=160) %**	**400 mg/day (N=153) %**	**500 mg/day[a] (N=113) %**
Blood and lymphatic system disorders	1.2	2.3	3.8	2.6	0.9
Anemia	0.8	0.6	0.6	2.0	0.9
Lymphadenopathy	0.4	1.2	1.9	0.7	0
Metabolism and nutrition disorders	5.8	10.5	13.8	16.3	12.4
Anorexia	3.5	5.3	10.0	12.4	8.0
Decreased appetite	2.3	4.7	3.8	2.6	2.7
Increased appetite	0.4	1.2	0	0.7	0
Psychiatric disorders	15.2	26.3	36.9	27.5	24.8
Bradyphrenia	2.3	2.9	6.3	4.6	7.1
Depression	4.3	8.2	13.1	8.5	6.2
Anxiety	3.9	4.7	5.6	6.5	5.3
Expressive language disorder	3.5	2.3	6.9	4.6	4.4
Mood altered	0.4	4.1	5.6	2.0	2.7
Aggression	1.2	3.5	1.9	0	1.8
Mood swings	1.6	3.5	1.3	2.0	1.8
Agitation	0	1.2	3.1	0.7	0.9
Anger	0	1.2	1.9	0.7	0.9

Depressed mood	0.8	1.2	1.3	2.6	0.9
Loss of libido	0	1.2	0	0	0.9
Dysphemia	0.8	0.6	1.9	0.7	0
Sleep disorder	0.8	1.8	1.3	0	0
Nervous system disorders	27.6	38.6	52.5	53.6	53.1
Paresthesia	18.7	28.1	38.1	40.5	35.4
Hypoesthesia	4.3	4.7	4.4	5.2	10.6
Dysgeusia	2.3	3.5	4.4	5.9	6.2
Coordination abnormal	1.9	2.3	3.1	0	5.3
Memory impairment	1.2	4.7	9.4	7.2	5.3
Mental impairment	0.8	1.8	1.9	2.0	5.3
Lethargy	1.2	5.8	5.6	2.0	3.5
Balance disorder	1.6	2.9	3.1	3.3	2.7
Cognitive disorder	0.4	1.2	1.9	2.0	2.7
Dysarthria	1.6	1.2	1.9	2.6	2.7
Burning sensation	0	0.6	0	0	1.8
Psychomotor skills impaired	0	0.6	0.6	2.0	0.9
Parosmia	0	1.8	0.6	0	0
Sedation	0	0.6	0.6	1.3	0
Visual field defect	0.4	0	0.6	1.3	0
Eye disorders	0	3.5	1.3	3.3	3.5
Diplopia	0	2.3	0.6	0.7	1.8
Dry eye	0	0	0	1.3	0
Ear and labyrinth disorders	1.6	1.8	2.5	2.6	1.8
Tinnitus	1.6	1.8	2.5	1.3	1.8
Ear pain	0	0.6	0	1.3	0
Cardiac disorders	0.8	0.6	1.9	0.7	4.4
Palpitations	0.8	0.6	1.9	0.7	3.5
Respiratory, thoracic and mediastinal disorders	1.2	2.3	3.8	3.3	0.9
Dyspnea	1.2	0.6	3.1	2.0	0.9
Rhinorrhea	0	1.8	0	1.3	0
Gastrointestinal disorders	10.1	15.2	18.8	17.6	27.4
Diarrhea	5.4	8.2	10.6	6.5	12.4
Dry mouth	0.4	2.9	0.6	2.6	6.2
Paresthesia oral	1.2	0	1.9	3.3	5.3
Abdominal pain	1.2	1.2	3.8	2.0	3.5
Abdominal discomfort	0.4	0	0.6	0.7	2.7
Stomach discomfort	0.4	0.6	0.6	0.7	2.7
Gastritis	0.8	0.6	1.3	2.6	1.8
Hypoesthesia oral	0.4	0.6	0.6	0	1.8
Gingival bleeding	0	1.8	0.6	1.3	0.9
Breath odour	0	0	1.3	0.7	0
Flatulence	0.4	1.2	0.6	0	0
Gastroesophageal reflux disease	0.4	0.6	0	2.0	0
Skin and subcutaneous tissue disorders	2.3	12.3	8.8	13.1	4.4
Alopecia	1.6	5.3	2.5	3.3	0.9
Hypoesthesia facial	0.4	0.6	0.6	2.0	0.9
Pruritus	0.4	1.2	1.9	3.3	0.9
Rash	0.4	7.6	3.1	3.9	0.9
Pruritus generalized	0	0	0	1.3	0
Musculoskeletal and connective tissue disorders	5.4	7.0	8.1	6.5	10.6
Arthralgia	1.9	3.5	3.1	2.0	4.4
Muscle spasms	2.7	2.3	3.8	3.3	2.7
Muscle twitching	0.4	0.6	0	1.3	1.8
Muscular weakness	0.8	0.6	0.6	0.7	1.8
Renal and urinary disorders	1.9	2.3	5.0	6.5	8.0
Pollakiuria	0.8	1.2	1.9	2.0	4.4
Dysuria	0.8	0	2.5	2.0	0.9

Nephrolithiasis	0	0.6	0	2.6	0.9
Micturition urgency	0	0.6	1.3	0	0
Reproductive system and breast disorders	0.8	1.2	1.3	1.3	1.8
Erectile dysfunction	0.8	0.6	0.6	1.3	1.8
General disorders and administration site conditions	20.6	32.2	31.3	22.2	23.0
Fatigue	15.2	21.6	21.9	14.4	18.6
Irritability	3.1	7.6	6.9	3.3	5.3
Asthenia	3.5	4.7	5.0	5.9	2.7
Peripheral coldness	0	1.2	0.6	0	2.7
Thirst	0.8	1.8	0.6	0.7	0
Investigations	7.0	10.5	13.1	17.0	17.7
Weight decreased	7.0	10.5	13.1	17.0	17.7

[a] Immediate Release Topiramate Dose 50 mg/day and TPM 500 mg/day groups also include subjects from Study TOPMAT-EPMN-104 whose baseline weight were no more than 50 kg and were randomized to receive Immediate Release Topiramate Dose 25 mg/day and 200 mg/day, respectively.

Pediatric patients

Adverse reactions reported in ≥2% of immediate-release topiramate-treated pediatric patients (6 to 16 years of age) in double-blind, controlled monotherapy epilepsy trials are shown in Table 3. Adverse reactions that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included weight decreased, paresthesia, diarrhea, disturbance in attention, pyrexia, and alopecia.

Table 3: Adverse Reactions in Children Age 6-16 Years Old in Double-Blind, Controlled, Monotherapy Epilepsy Studies (≥2% in any topiramate group)

	Immediate-Release Topiramate Dose				
System/Organ Class Adverse Reaction	**50 mg/day[a] (N=102) %**	**100 mg/day (N=38) %**	**200 mg/day (N=39) %**	**400 mg/day (N=83) %**	**500 mg/day[a] (N=14) %**
Immune system disorders	0	0	0	1.2	7.1
Hypersensitivity	0	0	0	1.2	7.1
Metabolism and nutrition disorders	2.9	7.9	2.6	7.2	14.3
Acidosis hyperchloraemic	0	0	0	0	7.1
Decreased appetite	2.9	5.3	2.6	6.0	7.1
Hypokalaemia	0	2.6	0	0	0
Psychiatric disorders	7.8	28.9	20.5	18.1	14.3
Aggression	1.0	2.6	5.1	1.2	7.1
Insomnia	3.9	2.6	5.1	1.2	7.1
Bradyphrenia	1.0	10.5	0	4.8	0
Confusional state	0	0	2.6	2.4	0
Crying	0	2.6	0	1.2	0
Depression	0	2.6	7.7	2.4	0
Expressive language disorder	0	0	2.6	2.4	0
Initial insomnia	0	2.6	0	0	0
Mood altered	1.0	0	5.1	3.6	0
Mood swings	0	2.6	2.6	1.2	0
Sleep disorder	1.0	2.6	0	0	0
Suicidal ideation	0	2.6	0	0	0
Suicide attempt	0	2.6	0	0	0
Nervous system disorders	11.8	21.1	35.9	20.5	28.6
Psychomotor hyperactivity	0	2.6	0	0	21.4
Paresthesia	4.9	5.3	12.8	12.0	7.1
Poor quality sleep	0	0	0	1.2	7.1
Circadian rhythm sleep disorder	0	2.6	2.6	0	0
Disturbance in attention	3.9	2.6	15.4	9.6	0

Dysarthria	0	2.6	2.6	0	0
Hypoaesthesia	0	2.6	0	0	0
Lethargy	2.9	5.3	0	3.6	0
Nystagmus	0	2.6	2.6	0	0
Parosmia	0	0	2.6	0	0
Psychomotor skills impaired	1.0	0	2.6	0	0
Ear and labyrinth disorders	0	2.6	5.1	2.4	0
Ear pain	0	2.6	0	0	0
Vertigo	0	0	5.1	2.4	0
Cardiac disorders	0	2.6	0	0	0
Palpitations	0	2.6	0	0	0
Vascular disorders	0	0	2.6	0	0
Orthostatic hypotension	0	0	2.6	0	0
Respiratory, thoracic and mediastinal disorders	2.0	7.9	7.7	6.0	28.6
Nasal congestion	2.0	0	2.6	1.2	21.4
Epistaxis	0	5.3	5.1	3.6	14.3
Rhinorrhoea	0	2.6	0	1.2	0
Gastrointestinal disorders	10.8	23.7	10.3	14.5	28.6
Vomiting	5.9	10.5	5.1	6.0	14.3
Abdominal discomfort	0	0	0	1.2	7.1
Diarrhea	6.9	10.5	0	8.4	7.1
Stomach discomfort	0	0	2.6	0	7.1
Dry mouth	0	0	2.6	0	0
Gastritis	0	2.6	2.6	1.2	0
Gingival bleeding	0	2.6	0	0	0
Paraesthesia oral	0	2.6	0	0	0
Skin and subcutaneous tissue disorders	1.0	7.9	2.6	10.8	14.3
Rash	1.0	5.3	0	3.6	14.3
Alopecia	0	0	0	4.8	0
Pruritus	0	0	2.6	1.2	0
Urticaria	0	2.6	0	1.2	0
Musculoskeletal and connective tissue disorders	0	0	5.1	1.2	7.1
Arthralgia	0	0	5.1	1.2	7.1
Musculoskeletal stiffness	0	0	0	0	7.1
Myalgia	0	0	2.6	0	0
General disorders and administration site conditions	1.0	7.9	12.8	16.9	14.3
Asthenia	0	0	2.6	4.8	7.1
Pyrexia	1.0	5.3	7.7	7.2	7.1
Hyperthermia	0	0	0	3.6	0
Malaise	0	2.6	0	0	0
Sluggishness	0	0	2.6	0	0
Investigations	6.9	5.3	7.7	16.9	0
Weight decreased	6.9	5.3	7.7	16.9	0
Social circumstances	1.0	0	0	3.6	7.1
Learning disability	1.0	0	0	3.6	7.1

[a] Immediate Release Topiramate Dose 50 mg/day and 500 mg/day groups also include subjects from Study TOPMAT-EPMN-104 whose baseline weight were no more than 50 kg and were randomized to receive Immediate Release Topiramate Dose 25 mg/day and 200 mg/day, respectively.

Adjunctive Therapy Epilepsy

Adults

Adverse reactions reported in ≥1% of immediate-release topiramate-treated adult patients in double-blind, placebo-controlled adjunctive epilepsy trials are shown in Table 4. Adverse reactions that had an incidence >5% in the recommended dose range (200 to 400 mg/day) in adults in double-blind, placebo-controlled adjunctive epilepsy studies in descending order of frequency included somnolence, dizziness, fatigue, irritability, weight decreased, bradyphrenia, paresthesias, diplopia, coordination abnormal, nausea, nystagmus, lethargy, anorexia, dysarthria, vision blurred, decreased appetite, memory impairment and diarrhea.

Table 4: **Adverse Reactions Reported by ≥1% of Immediate-Release Topiramate-Treated Adult Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials**

	Immediate-Release Topiramate Dose		
	200-400 mg/day	**600-1000 mg/day**	**PLACEBO**
System/Organ Class Adverse Reaction	**(N=354)** **%**	**(N=437)** **%**	**(N=382)** **%**
Metabolism and Nutrition Disorders			
Anorexia	5.4	6.2	1.8
Decreased appetite	5.1	8.7	3.7
Psychiatric Disorders			
Bradyphrenia	8.2	19.5	3.1
Expressive language disorder	4.5	9.4	1.6
Confusional state	3.1	5.0	0.8
Depression	3.1	11.7	3.4
Insomnia	3.1	6.4	4.5
Aggression	2.8	3.2	1.8
Agitation	1.7	2.3	1.3
Anger	1.7	2.1	0.5
Anxiety	1.7	6.6	2.9
Disorientation	1.7	3.2	1.0
Mood altered	1.7	4.6	1.0
Nervous System Disorders			
Somnolence	17.8	17.4	8.4
Dizziness	16.4	34.1	13.6
Paresthesia	8.2	17.2	3.7
Coordination abnormal	7.1	11.4	4.2
Nystagmus	6.2	11.7	6.8
Lethargy	5.6	8.0	2.1
Dysarthria	5.4	6.2	1.0
Memory impairment	5.1	10.8	1.8
Disturbance in attention	4.5	11.9	1.8
Tremor	4.0	9.4	5.0
Amnesia	3.4	5.3	1.0
Balance disorder	3.4	3.9	2.4
Hypoesthesia	3.1	5.9	1.0
Intention tremor	3.1	4.8	2.9
Dysgeusia	1.4	4.3	0.8
Mental impairment	1.4	5.0	1.3
Speech disorder	1.1	2.7	0.5
Eye Disorders			

Diplopia	7.3	12.1	5.0
Vision blurred	5.4	8.9	2.4
Visual disturbance	2.0	1.4	0.3
Gastrointestinal Disorders			
Nausea	6.8	15.1	8.4
Diarrhea	5.1	14.0	5.2
Abdominal pain upper	3.7	3.9	2.1
Constipation	3.7	3.2	1.8
Stomach discomfort	3.1	3.2	1.3
Dyspepsia	2.3	3.0	2.1
Dry mouth	1.7	3.7	0.3
Abdominal pain	1.1	2.7	0.8
Musculoskeletal and Connective Tissue Disorders			
Myalgia	2.0	2.5	1.3
Muscle spasms	1.7	2.1	0.8
Musculoskeletal chest pain	1.1	1.8	0.3
General Disorders and Administration Site Conditions			
Fatigue	13.0	30.7	11.8
Irritability	9.3	14.6	3.7
Asthenia	3.4	3.0	1.8
Gait disturbance	1.4	2.5	1.3
Investigations			
Weight decreased	9.0	11.9	4.2

The recommended dose for adjunctive epilepsy therapy in adults is 200-400 mg/day.

Pediatric Patients

Adverse reactions reported in >2% of immediate-release topiramate-treated pediatric patients (2 to 16 years of age) in double-blind, placebo-controlled adjunctive epilepsy trials are shown in Table 5. Adverse reactions that had an incidence >5% in the recommended dose range (5 to 9 mg/kg/day) in descending order of frequency included decreased appetite, fatigue, somnolence, lethargy, irritability, disturbance in attention, weight decreased, aggression, rash, abnormal behavior, anorexia, balance disorder, and constipation.

Table 5: Adverse Reactions Reported by ≥2% of Immediate-Release Topiramate-Treated Pediatric Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

	Immediate-Release Topiramate Dose (N=104) %	**PLACEBO (N=102) %**
Metabolism and Nutrition Disorders		
Decreased appetite	19.2	12.7
Anorexia	5.8	1.0
Psychiatric Disorders		
Aggression	8.7	6.9
Abnormal behavior	5.8	3.9
Confusional state	2.9	2.0
Mood altered	2.9	2.0
Nervous System Disorders		
Somnolence	15.4	6.9
Lethargy	13.5	8.8
Disturbance in attention	10.6	2.0
Balance disorder	5.8	2.0
Dizziness	4.8	2.9

Memory impairment	3.8	1.0
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	4.8	1.0
Gastrointestinal Disorders		
Constipation	5.8	4.9
Skin and Subcutaneous Tissue Disorders		
Rash	6.7	5.9
General Disorders and Administration Site Conditions		
Fatigue	16.3	4.9
Irritability	11.5	8.8
Gait disturbance	4.8	2.0
Investigations		
Weight decreased	9.6	1.0

The recommended dose for adjunctive epilepsy therapy in children (2-16 years of age) is 5 to 9 mg/kg/day.

Migraine

Adults

Adverse reactions reported in ≥1% of immediate-release topiramate-treated adult patients in double-blind, placebo-controlled migraine prophylaxis trials are shown in Table 6. Adverse reactions that had an incidence >5% at the recommended dose (100 mg/day) in descending order of frequency included paresthesia, fatigue, nausea, diarrhea, weight decreased, dysguesia, anorexia, decreased appetite, insomnia, hypoesthesia, disturbance in attention, anxiety, somnolence, and expressive language disorder.

Table 6: Adverse Reactions Reported by ≥1% of Immediate-Release Topiramate-Treated Adult Patients in Double-Blind, Placebo-Controlled Migraine Prophylaxis Trials

	Immediate-Release Topiramate Dose			
	50 mg/day	**100 mg/day**	**200 mg/day**	**PLACEBO**
System/Organ Class Adverse Reaction	**(N=227) %**	**(N=374) %**	**(N=501) %**	**(N=436) %**
Metabolism and Nutrition Disorders				
Anorexia	3.5	7.5	7.2	3.0
Decreased appetite	5.7	7.0	6.8	3.0
Psychiatric Disorders				
Insomnia	4.8	7.0	5.6	3.9
Anxiety	4.0	5.3	5.0	1.8
Expressive language disorder	6.6	5.1	5.2	1.4
Depression	3.5	4.8	7.4	4.1
Depressed mood	0.4	2.9	2.0	0.9
Confusional state	0.4	1.6	2.0	1.1
Mood swings	1.8	1.3	1.0	0.2
Affect lability	0.4	1.1	0.2	0.2
Bradyphrenia	1.8	1.1	3.4	1.4
Nervous System Disorders				
Paresthesia	35.7	50.0	48.5	5.0
Dysgeusia	15.4	8.0	12.6	0.9
Hypoesthesia	5.3	6.7	7.4	1.4
Disturbance in attention	2.6	6.4	9.2	2.3

Somnolence	6.2	5.1	6.8	3.0
Memory impairment	4.0	4.5	6.2	1.6
Amnesia	3.5	2.9	5.2	0.5
Tremor	1.3	1.9	2.4	1.4
Balance disorder	0.4	1.3	0.4	0
Mental impairment	0.4	1.1	1.8	0.9
Eye Disorders				
Vision blurred	4.0	2.4	4.4	2.5
Ear and Labyrinth Disorders				
Tinnitus	0.4	1.3	1.6	0.7
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	1.3	2.7	1.6	1.4
Epistaxis	0.4	1.1	0.6	0.5
Gastrointestinal Disorders				
Nausea	9.3	13.6	14.6	8.3
Diarrhea	9.3	11.2	10.0	4.4
Dry mouth	1.8	3.2	5.0	2.5
Paresthesia oral	1.3	2.9	1.6	0.5
Constipation	1.8	2.1	1.8	1.4
Abdominal distension	0	1.3	0.2	0.2
Stomach discomfort	2.2	1.3	1.0	0.2
Gastroesophageal reflux disease	0.4	1.1	1.2	0.5
Musculoskeletal and Connective Tissue Disorders				
Muscle twitching	1.8	1.3	1.8	0.7
General Disorders and Administration Site Conditions				
Fatigue	15.0	15.2	19.2	11.2
Asthenia	0.9	2.1	2.6	0.5
Irritability	3.1	1.9	2.4	0.9
Thirst	1.3	1.6	1.0	0.5
Investigations				
Weight decreased	5.3	9.1	10.8	1.4

The recommended dose for migraine prophylaxis is 100 mg/day.

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

Other Adverse Reactions Observed During Clinical Trials

Other adverse reactions seen during clinical trials were: abnormal coordination, eosinophilia, gingival bleeding, hematuria, 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.

6.2 Postmarketing Experience

Adverse events first identified as adverse reactions during postmarketing experience with Immediate-Release Topiramate are included in Tables 8. In each table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports

In Table 7, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 7: Adverse Reactions Identified During Postmarketing Experience with Immediate-Release Topiramate by Frequency Category Estimated from Spontaneous Reporting Rates

Infections and Infestations	
Very rare	Nasopharyngitis
Blood and Lymphatic System Disorders	
Very rare	Neutropenia
Immune System Disorders	
Very rare	Allergic edema
Metabolism and Nutrition Disorders	
Very rare	Hyperammonemia
Very rare	Hyperammonemic encephalopathy

Psychiatric Disorders	
Very rare	Feeling of despair
Eye Disorders	
Very rare	Abnormal sensation in eye
Very rare	Angle closure glaucoma
Very rare	Conjunctival edema
Very rare	Eye movement disorder
Very rare	Eyelid edema
Very rare	Maculopathy
Very rare	Myopia
Very rare	Uveitis
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Cough
Skin and Subcutaneous Tissue Disorders	
Very rare	Erythema multiforme
Very rare	Periorbital edema
Very rare	Stevens-Johnson syndrome
Very rare	Toxic epidermal necrolysis
Musculoskeletal and Connective Tissue Disorders	
Very rare	Joint swelling
Very rare	Limb discomfort
Renal and Urinary Disorders	
Very rare	Renal tubular acidosis
Very rare	Nephrocalcinosis
General Disorders and Administration Site Reactions	
Very rare	Generalized edema
Very rare	Influenza like illness
Investigations	
Very rare	Weight increased

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 phenytoin or carbamazepine with topiramate resulted in a clinically significant decrease in plasma concentrations of topiramate when compared to topiramate given alone. A dosage adjustment may be needed [*see Dosage and Administration (2.1), Clinical Pharmacology (12.3)*].

Concomitant administration of valproic acid and topiramate has been associated with hypothermia and hyperammonemia with and without encephalopathy. Examine blood ammonia levels in patients in whom the onset of hypothermia has been reported [*see Warnings and Precautions (5.10, 5.12) and Clinical Pharmacology (12.3)*].

7.3 Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. 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, as well as other cognitive and/or neuropsychiatric adverse reactions, TROKENDI XR® should be used with extreme caution if used in combination with alcohol and other CNS depressants [*see Warnings and Precautions (5.7)*].

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 Clinical Pharmacology (12.3)*].

7.6 Hydrochlorothiazide (HCTZ)

Topiramate C_{max} 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 these observations 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)*].

7.9 Amitriptyline

Some patients may experience a large increase in amitriptyline concentration in the presence of TROKENDI XR® and any adjustments in amitriptyline dose should be made according to the patients' clinical response and not on the basis of plasma levels *[see Clinical Pharmacology (12.3)]*.

7.10 Digoxin

In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased 12% due to concomitant administration of immediate-release topiramate. The clinical relevance of this observation has not been established. When immediate-release topiramate is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

7.11 Risperidone

Drug-drug interaction studies conducted under single and multiple dose conditions in healthy volunteers and patients with bipolar disorder yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses,

respectively). Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no clinically significant changes in the systemic exposure of the risperidone total active moiety or of topiramate, therefore this interaction is not likely to be of clinical significance.

7.12 Metformin

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean C_{max} and mean AUC_{0-12h} increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When immediate-release topiramate is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

7.13 Glyburide

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady- state pharmacokinetics of glyburide (5mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glyburide AUC_{24} during topiramate administration. Systemic exposure of the active metabolites, 4-trans-hydroxy-glyburide (M1) and 3-cis- hydroxyglyburide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide. When topiramate is added to glyburide therapy or glyburide is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

7.14 Vitamin K-antagonist anticoagulant medications

Decreased Prothrombin Time/International Normalized Ratio (PT/INR) responses have been reported following concomitant administration of topiramate with vitamin K-antagonist anticoagulant medications. Closely monitor INR during concomitant administration of topiramate therapy with vitamin K-antagonist anticoagulant medications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse reactions

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

Labor or Delivery

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

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.

Data

Human Data

Data from pregnancy registries indicate an increased risk of oral clefts in infants exposed to topiramate during the first trimester of pregnancy. In the NAAED pregnancy registry, the prevalence of oral clefts among topiramate-exposed infants (1.1%) was higher than the prevalence of infants exposed to reference AEDs (0.36%) , or the prevalence in infants of mothers without epilepsy and without exposure to AEDs (0.12%). It was also higher than the background prevalence in United States (0.17%) as estimated by the Centers for Disease Control and Prevention (CDC). The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 9.6 (95% Confidence Interval=[CI] 4.0-23.0) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a prevalence of oral clefts among infants exposed to topiramate monotherapy (3.2%) that was 16 times higher than the background rate in the UK (0.2%).

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

Animal Data

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

recommended human dose (MRHD) for epilepsy (400 mg/day) or migraine (100 mg/day) on a body surface area (mg/m^2) basis.

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

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

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

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

8.2 Lactation

Risk Summary

Topiramate is excreted in human milk *[see Data]*. The effects of topiramate exposure in breastfed infants 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 milk similar to those in maternal plasma.

8.3 Females and Males of Reproductive Potential

Contraception

Women of childbearing potential who are not planning a pregnancy should use effective contraception because of the risks to the fetus of oral clefts and of being small for gestational age [*see Drug Interactions (7.5) and Use in Specific Populations (8.1)*].

8.4 Pediatric Use

Seizures in Pediatric Patients 6 Years of Age and Older

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

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

These include, but are not limited to:

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

Not Recommended for Pediatric Patients Younger than 6 Years of Age

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

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

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

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

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

These very young pediatric patients appeared to experience an increased risk for infections (any topiramate dose 12%, placebo 0%) and of respiratory disorders (any topiramate dose 40%, placebo 16%). The following adverse

reactions were observed in at least 3% of patients on immediate-release topiramate and were 3% to 7% more frequent than in patients on placebo: viral infection, bronchitis, pharyngitis, rhinitis, otitis media, upper respiratory infection, cough, and bronchospasm. A generally similar profile was observed in older pediatric patients [*see Adverse Reactions (6)*].

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

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

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

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

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

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

Other Pediatric Studies

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

Juvenile Animal Studies

When topiramate (30, 90, and 300 mg/kg/day) was administered orally to rats during the juvenile period of development (postnatal days 12 to 50), bone growth plate thickness was reduced in males at the highest dose, which is approximately 5-8 times the maximum recommended pediatric dose (9 mg/kg/day) on a body surface area (mg/m^2) basis.

8.5 Geriatric Use

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

8.6 Renal Impairment

The clearance of topiramate is reduced in patients with moderate (creatinine clearance 30 to 69 mL/min/1.73m^2) and severe (creatinine clearance less than 30 mL/min/1.73m^2) renal impairment. A dosage adjustment is recommended in patients with moderate or severe renal impairment [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)*].

8.7 Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than in a normal individual. A dosage adjustment may be required [*see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)*].

9 Effects on Ability to Drive and Use Machines

Topiramate acts on the central nervous system and may produce drowsiness, dizziness or other related symptoms. It may also cause visual disturbances and/or blurred vision. These adverse events could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the drug is established.

10 OVERDOSAGE

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

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

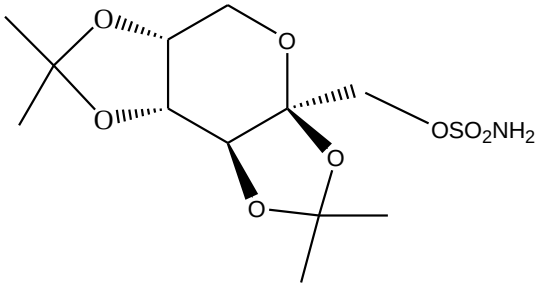
A patient who ingested a dose of immediate-release topiramate between 96 g and 110 g was admitted to hospital with coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.

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

11 DESCRIPTION

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

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



TROKENDI XR® (topiramate) is an extended-release capsule. TROKENDI XR® capsules contain the following inactive ingredients: Sugar Spheres, Hypromellose, Mannitol, Docusate Sodium 85% / Sodium Benzoate 15%, Surelease Clear E-7-19040 (ethylcellulose, purified water, oleic acid, ammonium hydroxide, and medium chain triglycerides/Caprylin and Caprin GB), Opadry Clear YS-1-7006 (hypromellose (Type 2910), polyethylene glycol) and Opadry AMB White 80W68912 (polyvinyl alcohol, titanium dioxide, talc, lecithin, and xanthan gum).

The capsule shells contain:

- 25 mg: Hard Gelatin Capsules, Size 2, Light Green/Yellow : FD&C Blue #1, FDA/E172 Yellow Iron Oxide, Riboflavin, Titanium Dioxide and Gelatin.
- 50 mg: Hard Gelatin Capsules, Size 0, Light Green/Orange : FD&C Blue #1, FD&C Red #3, FD&C Yellow #6, FDA/E172 Yellow Iron Oxide, Titanium Dioxide and Gelatin.
- 100 mg: Hard Gelatin Capsules, Size 00, Green/Blue : FD&C Blue #1, FD&C Red #3, FD&C Yellow #6, Titanium Dioxide and Gelatin.
- 200 mg: Hard Gelatin Capsules, Size 00, Pink /Blue : FD&C Blue #1, FD&C Red #3, FD&C Yellow #6, Titanium Dioxide and Gelatin.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

Changes (increases and decreases) from baseline in vital signs (systolic blood pressure-SBP, diastolic blood pressure-DBP, pulse) occurred more frequently in pediatric patients (6 to 17 years) treated with various daily doses of topiramate (50 mg, 100 mg, 200 mg, 2 to 3 mg/kg) than in patients treated with placebo in controlled trials for migraine prophylaxis. The most notable changes were SBP < 90 mm Hg, DBP < 50 mm Hg, SBP or

DBP increases or decreases ≥ 20 mm Hg, and pulse increases or decreases ≥ 30 beats per minute. These changes were often dose-related, and were most frequently associated with the greatest treatment difference at the 200 mg dose level. Systematic collection of orthostatic vital signs has not been conducted. The clinical significance of these various changes in vital signs has not been clearly established.

12.3 Pharmacokinetics

Absorption and Distribution

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

The peak plasma concentrations (C_{max}) of topiramate occurred at approximately 24 hours following a single 200 mg oral dose of TROKENDI XR®. At steady-state, the (AUC_{0-24}, C_{max}, and C_{min}) of topiramate from TROKENDI XR® administered once-daily and the immediate-release tablet administered twice-daily were shown to be bioequivalent. Fluctuation of topiramate plasma concentrations at steady-state for TROKENDI XR® administered once-daily was approximately 26% and 42% in healthy subjects and in epileptic patients, respectively, compared to approximately 40% and 51%, respectively, for immediate-release topiramate [see *Clinical Pharmacology (12.6)*].

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

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

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

Metabolism and Excretion

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

Specific Populations

Renal Impairment

The clearance of topiramate was reduced by 42% in subjects with moderate renal impairment (creatinine clearance 30 to 69 mL/min/1.73m^2) and by 54% in subjects with severe renal impairment (creatinine clearance less than 30 mL/min/1.73m^2) compared to subjects with normal renal function (creatinine clearance greater than 70 mL/min/1.73m^2) [*see Dosage and Administration (2.5)*].

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

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

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

In a study of 13 healthy elderly subjects and 18 healthy young adults who received TROKENDI XR®, 30% higher mean C_{max} and 44% higher AUC values were observed in elderly compared to young subjects. Elderly subjects exhibited shorter median T_{max} at 16 hours versus 24 hours in young subjects. The apparent elimination half-life was similar across age groups. As recommended for all patients, dosage adjustment is indicated in elderly patients with a creatinine clearance rate less than 70 mL/min/1.73 m^2) [s*ee Dosage and Administration (2.5) and Use in Specific Populations (8.5)*].

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

Pediatric Pharmacokinetics
Pharmacokinetics of immediate-release topiramate were evaluated in patients ages 2 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 relevant topiramate 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 from concomitant enzyme-inducing antiepileptic drugs. In comparison, topiramate clearance per kg is greater in pediatric patients than in adults and in young pediatric patients (down to 2 years 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 younger pediatric patients compared to older pediatric patients. Clearance was independent of dose.

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

Drug-Drug Interaction Studies

In vitro studies indicate that topiramate does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5 isozymes. *In vitro* studies indicate that immediate-release topiramate is a mild

inhibitor of CYP2C19 and a mild inducer of CYP3A4. The same drug interactions can be expected with the use of TROKENDI XR® .

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 8. Interaction of TROKENDI XR® and standard AEDs is not expected to differ from the experience with immediate-release topiramate products.

In Table 8, the second column (AED concentration) describes what happens to the concentration of the co-administered AED listed in the first column when topiramate was added. The third column (topiramate concentration) describes how the co-administration of a drug listed in the first column modifies the concentration of topiramate when compared to topiramate given alone.

Table 8: **Summary of AED Interactions with topiramate**

AED Coadministered	**AED Concentration**	**Topiramate Concentration**
Phenytoin	NC or 25% increase*	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide†	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400mg per day	13% decrease
* =Plasma concentration increased 25% in some patients, generally those on a twice a day dosing regimen of phenytoin † =Is not administered but is an active metabolite of carbamazepine NC=Less than 10% change in plasma concentration AED=Antiepileptic drug NE=Not evaluated TPM=topiramate		

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 (7.5)*].

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

Hydrochlorothiazide

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 12 hours) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination *[see Drug Interactions (7.6)]*.

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

Pioglitazone
A drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the $AUC_{\tau,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known *[see Drug Interactions (7.7)]*.

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

Lithium
In patients, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg per day; however, there was an observed increase in systemic exposure of lithium (27% for C_{max} and 26% for AUC) following topiramate doses up to 600 mg per day[*see Drug Interactions (7.8)*].

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

Amitriptyline
There was a 12% increase in AUC and C_{max} for amitriptyline (25 mg per day) in 18 healthy subjects (9 males, 9 females) receiving 200 mg per day of immediate-release topiramate *[see Drug Interactions (7.9)]*.

Sumatriptan

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

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

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

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

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

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

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

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

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

Study in Patients with Epilepsy

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

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg/day) in the diet for 21 months. An increase in the incidence of bladder tumors in males and females receiving 300 mg/kg was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. The higher of the doses not associated with an increase in tumors (75 mg/kg/day) is equivalent to the maximum recommended human dose (MRHD) for epilepsy and approximately 4 times the MRHD for migraine (100 mg) on a mg/m^2 basis. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg/day (approximately 3 times the MRHD for epilepsy and 12 times the MRHD for migraine on a mg/m^2 basis).

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

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

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

15 HOW SUPPLIED/STORAGE AND HANDLING

15.1 How Supplied

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

25 mg	light green opaque body with black ink “25”/ yellow opaque cap with black print “SPN” • HDPE bottles of 30-count and 100-count • PVC-Alu blister packages of 28-count
50 mg	light green opaque body with black ink “50”/ orange opaque cap with black print “SPN” • HDPE bottles of 30-count and 100-count • PVC-Alu blister packages of 28-count
100 mg	green opaque body with black ink “100”/ blue opaque cap with black print “SPN” • HDPE bottles of 30-count and 100-count • PVC-Alu blister packages of 28-count
200 mg	pink opaque body with black ink “200”/ blue opaque cap with black print “SPN” • HDPE bottles of 30-count and 100-count • PVC-Alu blister packages of 28-count

15.2 Storage and Handling

Protect from moisture and light. Store at temperatures not exceeding 30˚C.
Keep out of reach of children.
When pack type of bottle was used, discard unused capsules 1 month after first opening.

Manufactured by: Orient Pharma Co., Ltd.
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Product Registration Holder Orient Europharma Pte., Ltd.
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