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with or without a history of seizures or epilepsy, antiepileptic drugs, including TROKENDI XR®, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency [*see Clinical Studies (14)*].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.

The incidence of hyperammonemia in pediatric patients 12 to 17 years of age in migraine prophylaxis trials was 26% in patients taking topiramate monotherapy at 100 mg/day, and 14% in patients taking topiramate at 50 mg/day, compared to 9% in patients taking placebo. There was also an increased incidence of markedly increased hyperammonemia at the 100 mg dose.

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 < 35ºC (95ºF), 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.

6 ADVERSE REACTIONS

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

- Acute Myopia and Secondary Angle Closure Glaucoma [*see Warnings and Precautions (5.1)*]
- Visual Field Defects [*see Warnings and Precautions 5.2]*
- Oligohydrosis and Hyperthermia [*see Warnings and Precautions (5.3)*]
- Metabolic Acidosis [*see Warnings and Precautions (5.4)*]
- Suicidal Behavior and Ideation [*see Warnings and Precautions (5.6)*]
- Cognitive/Neuropsychiatric Adverse Reactions [*see Warnings and Precautions (5.7)*]
- Withdrawal of Antiepileptic Drugs [*see Warnings and Precautions (5.9)*]
- 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)*]

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

6.1 Clinical Trials Experience

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

Monotherapy Epilepsy

Adults 16 Years of Age and Older

The most common adverse reactions in the controlled trial (Study 1) that occurred in adults in the 400 mg/day topiramate group and at an incidence higher (≥ 10%) than in the 50 mg per day group were: paresthesia, weight loss, and anorexia (see Table 3).

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

Pediatric Patients 6 Years to 15 Years of Age
The most common adverse reactions in the controlled trial (Study 1) that occurred in pediatric patients in the 400 mg/day topiramate group and at an incidence higher (≥ 10%) than in the 50 mg/day group were fever and weight loss (see Table 4).

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

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

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

Body System/ Adverse Reaction	**Immediate-release topiramate (mg/day)**	
	50 (N=160)	**400 (N=159)**
Body as a Whole-General Disorders		
Asthenia	4	6
Leg pain	2	3
Central & Peripheral Nervous System Disorders		
Paresthesia	21	40
Dizziness	13	14
Hypoesthesia	4	5
Ataxia	3	4
Hypertonia	0	3
Gastro-intestinal System Disorders		
Constipation	1	4
Gastritis	0	3
Dry mouth	1	3
Liver and Biliary System Disorders		
Gamma-GT increased	1	3
Metabolic and Nutritional Disorders		

Weight Loss	6	17
Psychiatric Disorders		
Somnolence	10	15
Anorexia	4	14
Difficulty with Memory NOS	6	11
Insomnia	8	9
Depression	7	9
Difficulty with concentration/attention	7	8
Anxiety	4	6
Psychomotor slowing	3	5
Mood problems	2	5
Cognitive problem NOS	1	4
Decrease in libido	0	3
Reproductive Disorders, Female		
Vaginal hemorrhage	0	3
Resistance Mechanism Disorders		
Viral infection	6	8
Infection	2	3
Respiratory System Disorders		
Bronchitis	3	4
Rhinitis	2	4
Skin and Appendages Disorders		
Alopecia	3	4
Rash	1	4
Pruritus	1	4
Acne	2	3
Special Senses Other, Disorders		
Taste perversion	3	5
Urinary System Disorders		
Cystitis	1	3
Renal calculus	0	3

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

Table 4: Incidence (%) of Adverse Reactions in the Monotherapy Epilepsy Trial in Pediatric Patients (Ages 6 to 15 Years)[a] Where Incidence Was at Least 3% in the 400 mg/day Immediate-Release Topiramate Group and Greater than the Rate in the 50 mg/day Immediate-Release Topiramate Group

Body System/ Adverse Reaction	**Immediate-release topiramate (mg/day)**	
	50 (N=74)	**400 (N=77)**
Body as a Whole-General Disorders		
Fever	1	12
Asthenia	0	3
Central & Peripheral Nervous System Disorders		
Paresthesia	3	12

Body System/ Adverse Reaction	**Immediate-release topiramate (mg/day)** **50 (N=74)**	**400 (N=77)**
Involuntary muscle contractions	0	3
Vertigo	0	3
Gastro-Intestinal System Disorders		
Diarrhea	8	9
Metabolic and Nutritional Disorders		
Weight decrease	7	17
Platelet, Bleeding & Clotting Disorders		
Epistaxis	0	4
Psychiatric Disorders		
Difficulty with concentration/attention	7	10
Mood problems	1	8
Cognitive problems	1	6
Difficulty with memory	1	3
Confusion	0	3
Depression	0	3
Personality disorder (behavior problems)	0	3
Red Blood Cell Disorders		
Anemia	1	3
Reproductive Disorders, Female[b]		
Intermenstrual bleeding	0	3
Resistance Mechanism Disorders		
Infection	3	8
Viral infection	3	6
Respiratory System Disorders		
Upper Respiratory Tract Infection	16	18
Rhinitis	5	6
Bronchitis	1	5
Sinusitis	1	4
Skin and Appendages Disorders		
Rash	3	4
Alopecia	1	4
Urinary System Disorders		
Urinary Incontinence	1	3
Micturition Frequency	0	3
Vascular (Extracardiac) Disorders		
Flushing	0	5

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

[b] N with Reproductive Disorders, Female-Incidence calculated relative to the number of females; Pediatric TPM 50 mg n=40; Pediatric TPM 400 mg n=33

Adjunctive Therapy Epilepsy

Adults 16 Years of Age and Older

In pooled controlled clinical trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, 183 patients received adjunctive therapy with immediate-release topiramate at dosages of 200 to 400 mg/day (recommended dosage range), and 291 patients received placebo. Patients in these trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to immediate-release topiramate or placebo.

The most common adverse reactions in the controlled clinical trial that occurred in adult patients in the 200-400 mg/day topiramate group with an incidence higher (≥10%) than in the placebo group were: dizziness, speech disorders/ related speech problems, somnolence, nervousness, psychomotor slowing, and vision abnormal (see Table 5) [*see Clinical Studies (14.3)*].

Table 5 presents the incidence of adverse reactions occurring in at least 3% of adult patients treated with 200 to 400 mg/day topiramate and was greater than placebo incidence. The incidence of some adverse reactions (e.g., fatigue, dizziness, paresthesia, language problems, psychomotor slowing, depression, difficulty with concentration/attention, mood problems) was dose-related and much greater at higher than recommended topiramate dosing (i.e., 600 to 1000 mg/day) compared to the incidence of these adverse reactions at the recommended dosing (200 to 400 mg/day) range.

Table 5: Most Common Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Epilepsy Trials in Adults [a,b]

Body System/Adverse Reaction	**Placebo (N=291) %**	**Topiramate 200-400 mg/day (N=183) %**
Body as a Whole-General Disorders		
Fatigue	13	15
Asthenia	1	6
Back pain	4	5
Chest pain	3	4
Influenza-like symptoms	2	3
Central & Peripheral Nervous System Disorders		
Dizziness	15	25
Ataxia	7	16
Speech disorders/Related speech problems	2	13
Paresthesia	4	11
Nystagmus	7	10
Tremor	6	9
Language problems	1	6
Coordination abnormal	2	4
Gait abnormal	1	3
Gastro-Intestinal System Disorders		
Nausea	8	10
Dyspepsia	6	7
Abdominal pain	4	6
Constipation	2	4
Metabolic and Nutritional Disorders		
Weight loss	3	9
Psychiatric Disorders		

Body System/Adverse Reaction	**Placebo (N=291) %**	**Topiramate 200-400 mg/day (N=183) %**
Somnolence	12	29
Nervousness	6	16
Psychomotor slowing	2	13
Difficulty with memory	3	12
Confusion	5	11
Anorexia	4	10
Difficulty with concentration/attention	2	6
Mood problems	2	4
Agitation	2	3
Aggressive reaction	2	3
Emotional liability	1	3
Cognitive problems	1	3
Reproductive Disorders, Female		
Breast pain	2	4
Respiratory System Disorders		
Pharyngitis	2	6
Rhinitis	6	7
Sinusitis	4	5
Vision Disorders		
Vision abnormal	2	13
Diplopia	5	10

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

In controlled clinical trials in adults, 11% of patients receiving immediate-release topiramate 200 to 400 mg per day as adjunctive therapy discontinued due to adverse reactions. This rate appeared to increase at dosages above 400 mg per day. Adverse reactions associated with discontinuing therapy included somnolence, dizziness, anxiety, difficulty with concentration or attention, fatigue, and paresthesia and increased at dosages above 400 mg per day.

Pediatric Patients 2 to 15 Years of Age

In pooled, controlled clinical trials in pediatric patients (2 to 15 years of age) with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, 98 patients received adjunctive therapy with immediate-release topiramate at dosages of 5 mg to 9 mg/kg/day (recommended dosage range) and 101 patients received placebo.

The most common adverse reactions in the controlled clinical trial that occurred in pediatric patients in the 5 mg to 9 mg/kg/day immediate-release topiramate group with an incidence higher (≥10%) than in the placebo group were: fatigue and somnolence (see Table 6).

Table 6 presents the incidence of adverse reactions that occurred in at least 3% of pediatric patients 2 to 15 years of age receiving 5 mg to 9 mg/kg/day (recommended dosage range) of immediate-release topiramate and was greater than placebo incidence.

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

Body System/ Adverse Reaction	**Placebo (N=101) %**	**Topiramate (N=98) %**
Body as a Whole-General Disorders		
Fatigue	5	16
Injury	13	14
Central & Peripheral Nervous System Disorders		
Gait abnormal	5	8
Ataxia	2	6
Hyperkinesia	4	5
Dizziness	2	4
Speech disorders/Related speech problems	2	4
Gastro-Intestinal System Disorders		
Nausea	5	6
Saliva increased	4	6
Constipation	4	5
Gastroenteritis	2	3
Metabolic and Nutritional Disorders		
Weight loss	1	9
Platelet, Bleeding & Clotting Disorders		
Purpura	4	8
Epistaxis	1	4
Psychiatric Disorders		
Somnolence	16	26
Anorexia	15	24
Nervousness	7	14
Personality disorder (Behavior Problems)	9	11
Difficulty with concentration/attention	2	10
Aggressive reaction	4	9
Insomnia	7	8
Difficulty with memory	0	5
Confusion	3	4
Psychomotor slowing	2	3
Resistance Mechanism Disorders		
Infection viral	3	7
Respiratory System Disorders		
Pneumonia	1	5
Skin and Appendages Disorders		
Skin Disorder	2	3
Urinary System Disorders		
Urinary incontinence	2	4

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

None of the pediatric patients who received topiramate adjunctive therapy at 5 mg/kg/day to 9 mg/kg/day in controlled clinical trials discontinued due to adverse reactions.

Migraine

Adults

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

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

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

Table 7: Adverse Reactions in Pooled, Placebo-Controlled, Migraine Trials in Adults[a,b,c]

Body System/ Adverse Reaction	**Placebo (N=445) %**	**Topiramate (mg/day) 50 (N=235) %**	**100 (N=386) %**
Body as a Whole-General Disorders			
Fatigue	11	14	15
Injury	7	9	6
Central & Peripheral Nervous System Disorders			
Paresthesia	6	35	51
Dizziness	10	8	9
Hypoaesthesia	2	6	7
Language problems	2	7	6
Gastro-Intestinal System Disorders			
Nausea	8	9	13
Diarrhea	4	9	11
Abdominal pain	5	6	6
Dyspepsia	3	4	5
Dry mouth	2	2	3
Gastroenteritis	1	3	3
Metabolic and Nutritional Disorders			
Weight loss	1	6	9
Musculoskeletal System Disorders			
Arthralgia	2	7	3
Psychiatric Disorders			
Anorexia	6	9	15
Somnolence	5	8	7

Body System/ Adverse Reaction	**Placebo (N=445) %**	**Topiramate (mg/day) 50 (N=235) %**	**100 (N=386) %**
Difficulty with memory	2	7	7
Insomnia	5	6	7
Difficulty with concentration/attention	2	3	6
Mood problems	2	3	6
Anxiety	3	4	5
Depression	4	3	4
Nervousness	2	4	4
Confusion	2	2	3
Psychomotor slowing	1	3	2
Reproductive Disorders, Female			
Menstrual disorder	2	3	2
Reproductive Disorders, Male			
Ejaculation premature	0	3	0
Resistance Mechanism Disorders			
Viral Infection	3	4	4
Respiratory System Disorders			
Upper respiratory tract infection	12	13	14
Sinusitis	6	10	6
Pharyngitis	4	5	6
Coughing	2	2	4
Bronchitis	2	3	3
Dyspnea	2	1	3
Skin and Appendages Disorders			
Pruritis	2	4	2
Special Sense Other, Disorders			
Taste perversion	1	15	8
Urinary System Disorders			
Urinary tract infection	2	4	2
Vision Disorders			
Blurred vision	2	4	2

[a]Includes 35 adolescent patients age 12 to 15 years

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

[c] Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for more than 50% of reactions coded as vision abnormal, a preferred term

Of the 1135 patients exposed to immediate-release topiramate in the adult placebo-controlled studies, 25% discontinued due to adverse reactions, compared to 10% of the 445 placebo patients. The adverse reactions associated with discontinuing therapy in the immediate-release topiramate-treated patients in these studies

included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%).

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

Pediatric Patients 12 to 17 Years of Age

In five randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials, most of the adverse reactions occurred more frequently during the titration period than during the maintenance period. Among adverse reactions with onset during titration, approximately half persisted into the maintenance period.

In four, fixed-dose, double-blind migraine prophylaxis clinical trials in immediate-release topiramate treated pediatric patients 12 to 17 years of age, the most common adverse reactions with immediate-release topiramate 100mg that were seen at an incidence higher (≥5%) than in the placebo group were: paresthesia, upper respiratory tract infection, anorexia, and abdominal pain (see Table 8). Table 8 shows adverse reactions from the pediatric trial (Study 3 *[see Clinical Studies (14.4)]*) in which 103 pediatric patients were treated with placebo or 50 mg or 100 mg of immediate-release topiramate, and three predominantly adult trials in which 49 pediatric patients (12 to 17 years) were treated with placebo or 50 mg, 100 mg or 200 mg of immediate-release topiramate *[see Clinical Studies (14.4)]*. Table 8 also shows adverse reactions in pediatric patients in controlled migraine trials when the incidence in an immediate-release topiramate dose group was at least 5% or higher and greater than the incidence of placebo. Many adverse reactions shown in Table 8 indicate a dose-dependent relationship. The incidence of some adverse reactions (e.g., allergy, fatigue, headache, anorexia, insomnia, somnolence, and viral infection) was dose-related and greater at higher than recommended immediate-release topiramate dosing (200 mg daily) compared to the incidence of these adverse reactions at the recommended dosing (100 mg daily).

Table 8: Adverse Reactions in Pooled Double-Blind Migraine Prophylaxis Studies in Pediatric Patients 12 to 17 Years of Age)[ab]

Body System/ Adverse Reaction	**Placebo (N=45) %**	**Topiramate (mg/day) 50 (N=46) %**	**100 (N=48) %**
Body as a Whole – General Disorders			
Fatigue	7	7	8
Fever	2	4	6
Central & Peripheral Nervous System Disorders			
Paresthesia	7	20	19
Dizziness	4	4	6
Gastrointestinal System Disorders			
Abdominal pain	9	7	15
Nausea	4	4	8
Metabolic and Nutritional Disorders			
Weight loss	2	7	4
Psychiatric Disorders			

Body System/ Adverse Reaction	**Placebo (N=45) %**	**Topiramate (mg/day) 50 (N=46) %**	**100 (N=48) %**
Anorexia	4	9	10
Somnolence	2	2	6
Insomnia	2	9	2
Resistance Mechanism Disorders			
Infection viral	4	4	8
Respiratory System Disorders			
Upper respiratory tract infection	11	26	23
Rhinitis	2	7	6
Sinusitis	2	9	4
Coughing	0	7	2
Special Senses Other, Disorders			
Taste perversion	2	2	6
Vision Disorders			
Conjunctivitis	4	7	4

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

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

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.

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of immediate-release topiramate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

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

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

Urinary System Disorders: kidney stones *[see Warnings and Precautions (5.11)]*

Vision disorders: acute myopia, secondary angle closure glaucoma *[see Warnings and Precautions (5.1)]*, maculopathy

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)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

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

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)*].

Migraine Prophylaxis in Pediatric Patients 12 to 17 Years of Age

Safety and effectiveness of topiramate in the prophylaxis of migraine was studied in 5 double-blind, randomized, placebo-controlled, parallel-group trials in a total of 219 pediatric patients, at doses of 50 mg/day to 200 mg/day, or 2 to 3 mg/kg/day. These comprised a fixed dose study in 103 pediatric patients 12 to 17 years of age *[see Clinical Studies (14.4)]*, a flexible dose (2 to 3 mg/kg/day), placebo-controlled study in 157 pediatric patients 6 to 16 years of age (including 67 pediatric patients 12 to 16 years of age), and a total of 49 pediatric patients 12 to 17 years of age in 3 studies of migraine prophylaxis primarily in adults. Open-label extension phases of 3 studies enabled evaluation of long-term safety for up to 6 months after the end of the double-blind phase.

Efficacy of topiramate for migraine prophylaxis in pediatric patients 12 to 17 years of age is demonstrated for a 100 mg daily dose in Study 3 *[see Clinical Studies (14.4)]*. Efficacy of topiramate (2 to 3 mg/kg/day) for migraine prophylaxis was not demonstrated in a placebo-controlled trial of 157 pediatric patients (6 to 16 years of age) that included treatment of 67 pediatric patients 12 to 16 years of age) for 20 weeks.

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

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

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

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

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

Migraine Prophylaxis in Pediatric Patients 6 to11 Years of Age

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

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

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

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)*].

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)*].

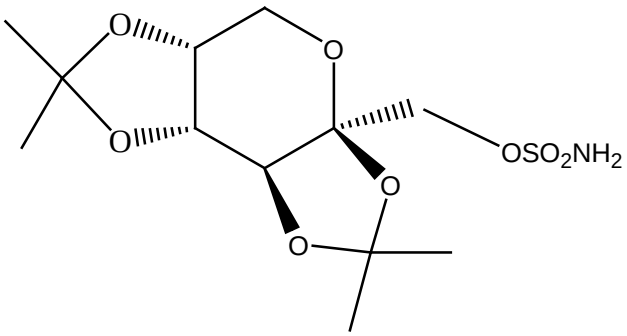
A patient who ingested a dose of immediate-release topiramate between 96 g and 110 g was admitted to hospital with coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.

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

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

The colorants are:

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

Riboflavin, USP (25 mg capsules)

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

Changes (increases and decreases) from baseline in vital signs (systolic blood pressure-SBP, diastolic blood pressure-DBP, pulse) occurred more frequently in pediatric patients (6 to 17 years) treated with various daily doses of topiramate (50 mg, 100 mg, 200 mg, 2 to 3 mg/kg) than in patients treated with placebo in controlled trials for migraine prophylaxis. The most notable changes were SBP < 90 mm Hg, DBP < 50 mm Hg, SBP or DBP increases or decreases ≥ 20 mm Hg, and pulse increases or decreases ≥ 30 beats per minute. These changes were often dose-related, and were most frequently associated with the greatest treatment difference at the 200 mg dose level. 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. The elderly subject population had reduced renal function (creatinine clearance [-20%]) compared to young adults. Following a single oral 100 mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1 to 2 hours. Reflecting the primary renal elimination of topiramate, topiramate plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced.

In a study of 13 healthy elderly subjects and 18 healthy young adults who received TROKENDI XR®, 30% higher mean C_{max} and 44% higher AUC values were observed in elderly compared to young subjects. Elderly subjects exhibited shorter median T_{max} at 16 hours versus 24 hours in young subjects. The apparent elimination

half-life was similar across age groups. As recommended for all patients, dosage adjustment is indicated in elderly patients with a creatinine clearance rate less than 70 mL/min/1.73 m^2) [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 9. Interaction of TROKENDI XR® and standard AEDs is not expected to differ from the experience with immediate-release topiramate products.

In Table 9, 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 9: 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_{0-12h} increased by 17% and 25%, respectively, when topiramate was added. Topiramate did not affect metformin T_{max}. The clinical significance of the effect of

dosage of 6 mg/kg/day was reached, unless intolerance prevented increases. After titration, patients entered a 12-week stabilization period.

Patients With Lennox-Gastaut Syndrome

The effectiveness of topiramate as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in patients 6 years of age and older was established in a multicenter, randomized, double-blind, placebo-controlled trial (Study 10), comparing a single dosage of topiramate with placebo (see Table 11).

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

Table 10: Immediate Release Topiramate Dose Summary During the Stabilization Periods of Each of Six Double-Blind, Placebo-Controlled, Adjunctive Trials in Adults with Partial Onset Seizures[a]

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

[a] Dose-response studies were not conducted for other indications or pediatric partial-onset seizures

[b] Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Study 4 (4 tablets/day); Studies 2 and 5 (6 tablets/day); Studies 6 and 7 (8 tablets/day); Study 3 (10 tablets/day)

In all adjunctive topiramate trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reductions in seizure rates and the responder rates (fraction of patients with at least a 50% reduction) by treatment group for each study are shown below in Table 11. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

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

Target Topiramate Dosage (mg per day)								
Study #	**#**	**Placebo**	**200**	**400**	**600**	**800**	**1,000**	**≈6mg/ kg/day***
Partial Onset Seizures Studies in Adults								
2	N	45	45	45	46	--	--	--
	Median % Reduction	12	27[a]	48[b]	45[c]	--	--	--
	% Responders	18	24	44[d]	46[d]	--	--	--
3	N	47	--	--	48	48	47	--
	Median % Reduction	2	--	--	41[c]	41[c]	36[c]	
	% Responders	9	--	--	40[c]	41[c]	36[d]	
4	N	24	--	23	--	--	--	--
	Median % Reduction	1	--	41[e]	--	--	--	--
	% Responders	8	--	35[d]	--	--	--	--
5	N	30	--	--	30	--	--	--
	Median % Reduction	-12	--	--	46[f]	--	--	--
	% Responders	10	--	--	47[c]	--	--	--
6	N	28	--	--	--	28	--	--
	Median % Reduction	-21	--	--	--	24[c]	--	--
	% Responders	0	--	--	--	43[c]	--	--
7	N	91	168	--	--	--	--	--
	Median % Reduction	20	44[c]	--	--	--	--	--
	% Responders	24	45[c]					
Partial Onset Seizures Studies in Pediatric Patients[k]								
8	N	45	--	--	--	--	--	41
	Median % Reduction	11	--	--	--	--	--	33[d]
	% Responders	20	--	--	--	--	--	39
Primary Generalized Tonic-Clonic[h, k]								
9	N	40	--	--	--	--	--	39
	Median % Reduction	9	--	--	--	--	--	57[d]
	% Responders	20	--	--	--	--	--	56[c]
Lennox-Gastaut Syndrome[i, k]								
10	N	49	--	--	--	--	--	46
	Median % Reduction	-5	--	--	--	--	--	15[d]
	% Responders	14						28[g]
	Improvement in Seizure Severity[j]	28						52d

Comparisons with placebo: [a]p=0.080; [b]p ≤ 0.010; [c]p ≤ 0.001; [d]p ≤ 0.050; [e]p=0.065; [f]p ≤0.005; [g]p=0.071;
[h]Median % reduction and % responders are reported for PGTC seizures;
[i]Median % reduction and % responders for drop attacks, i.e., tonic or atonic seizures
[j]Percentage of subjects who were minimally, much, or very much improved from baseline.
[K] Studies included pediatric patients 2 years of age and older, an age group for which TROKENDI XR is not indicated *[see Indications and Usage (1.2) and Use in Specific Populations (8.4)]*

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

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

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

14.4 Migraine Prophylaxis

Adult Patients

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

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

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

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

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

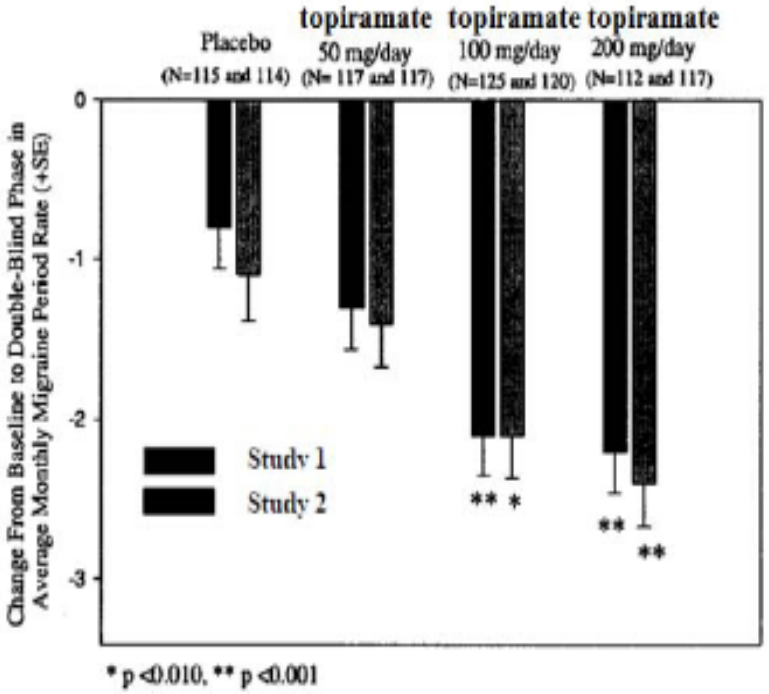
In Study 2, a total of 468 patients (406 females, 62 males) ranging in age from 12 to 65 years, were randomized and provided efficacy data. Two hundred fifty-five patients completed the entire 26-week double-blind phase. The median average daily dosages were 47 mg/day, 86 mg/day, and 150 mg/day in the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

The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches per 28 days and was similar across treatment groups. The change in the mean 4-week migraine headache period frequency from baseline to the double-blind phase was -1.4, -2.1, and -2.4 in the immediate-release topiramate 50, 100, and 200 mg/day groups, respectively, versus -1.1 in the placebo group (see Figure 2). The differences between the immediate-release topiramate 100 and 200 mg per day groups versus placebo were similar and statistically significant (p equals 0.008 and p less than 0.001, respectively).

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

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

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



Pediatric Patients 12 to 17 Years of Age

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

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

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

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

25 mg (light green opaque body/yellow opaque cap with black print "SPN" and "25"):
- bottles of 30 count (NDC-17772-101-30) and 100 count (NDC-17772-101-01)
- blister packages of 30-count (NDC-17772-101-15)

50 mg (light green opaque body/orange opaque cap with black print "SPN" and "50"):
- bottles of 30 count (NDC-17772-102-30) and 100 count (NDC-17772-102-01)
- blister packages of 30-count (NDC-17772-102-15)

100 mg (green opaque body/blue opaque cap with black print "SPN" and "100"):
- bottles of 30 count (NDC-17772-103-30) and 100 count (NDC-17772-103-01)
- blister packages of 30-count (NDC-17772-103-15)

200 mg (pink opaque body/blue opaque cap with black print "SPN" and "200"):
- bottles of 30 count (NDC-17772-104-30) and 100 count (NDC-17772-104-01)

- blister packages of 30-count (NDC-17772-104-15)

16.2 Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

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

Administration Instructions

Counsel patients to swallow TROKENDI XR® capsules whole and intact. TROKENDI XR® should not be sprinkled on food, chewed or crushed [*See Dosage and Administration (2.7)*].

Consumption of Alcohol

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

Eye Disorders

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

Oligohydrosis and Hyperthermia

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

Metabolic Acidosis

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

Suicidal Behavior and Ideation

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

Interference with Cognitive and Motor Performance

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

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

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

Fetal Toxicity

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

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

Encourage pregnant women using topiramate to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The registry is collecting information about the safety of antiepileptic drugs during pregnancy [*see Use in Specific Populations (8.1)*].

Hyperammonemia and Encephalopathy

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

Kidney Stones

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

Hypothermia

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

Paresthesia

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

Manufactured by: Catalent Pharma Solutions, Winchester, Kentucky 40391

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

RA-TRO-Vx

MEDICATION GUIDE

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

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

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

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

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

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

Trokendi XR may cause decreased sweating and increased body temperature (fever). People, especially children, should be watched for signs of decreased sweating and fever, especially in hot temperatures. Some people may need to be hospitalized for this condition. If a high fever, a fever that does not go away, or decreased sweating develops, call your healthcare provider right away.

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

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

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

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

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

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

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

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

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

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

Trokendi XR can harm your unborn baby.

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

provider should decide if you will continue to take Trokendi XR while you are pregnant.

- If you take Trokendi XR during pregnancy, your baby may be smaller than expected at birth. The long-term effects of this are not known. Talk to your healthcare provider if you have questions about this risk during pregnancy.
- Metabolic acidosis may have harmful effects on your baby. Talk to your healthcare provider if Trokendi XR has caused metabolic acidosis during your pregnancy.
- Pregnancy Registry: If you become pregnant while taking Trokendi XR, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of Trokendi XR and other antiepileptic drugs during pregnancy.

What is Trokendi XR?

Trokendi XR is a prescription medicine used:

- to treat certain types of seizures (partial onset seizures and primary generalized tonic-clonic seizures) in people 6 years and older,
- with other medicines to treat certain types of seizures (partial onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children 6 years and older
- to prevent migraine headaches in adults and adolescents 12 years of age and older.

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

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

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

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

Ask your healthcare provider if you are not sure if your medicine is listed above.

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

How should I take Trokendi XR?

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

What should I avoid while taking Trokendi XR?

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

your thinking and motor skills, and may affect vision.

What are the possible side effects of Trokendi XR?

Trokendi XR may cause serious side effects, including:

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

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

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

The most common side effects of Trokendi XR include:

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

Tell your healthcare provider about any side effect that bothers you or that does not go away.
These are not all the possible side effects of Trokendi XR.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Supernus Pharmaceuticals, Inc. at 1-866-398-0833.

How should I store Trokendi XR?

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

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

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

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

What are the ingredients in Trokendi XR?

Active ingredient: topiramate

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

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

Colorants:

FD&C Blue #1 (all strength capsules)

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

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

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

Riboflavin, USP (25 mg capsules)

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

Manufactured by: Catalent Pharma Solutions, Winchester, KY USA 40391
Manufactured for: Supernus Pharmaceuticals, Inc. Rockville, MD USA 20850

RA-TRO-MGVX
For more information, go to www.trokendixr.com or call 1-866-398-0833.
This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 01/2018