TROKENDI XR™ (topiramate) extended-release capsules

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Trokendi XR™ (topiramate) extended-release capsules are indicated as adjunctive therapy in the treatment of complex partial seizures in adults and children 2 years of age and older. Trokendi XR™ (topiramate) extended-release capsules are indicated as monotherapy in the treatment of partial seizures in adults and children 2 years of age and older, and monotherapy in the treatment of primary generalized tonic-clonic seizures in adults and children 2 years of age and older.

2. DOSAGE AND ADMINISTRATION

The recommended starting dose is 25 mg/day in adults and 2 mg/kg/day in children ages 2 to 16 years. The dose may be increased every week by 25 mg/day in adults and by 1 mg/kg/day in children to a maximum of 200 mg/day in adults and 10 mg/kg/day in children. The maximum dose for children weighing less than 30 kg is 400 mg/day.

The maintenance dose may be individualized according to patient response and tolerability up to a maximum of 1000 mg/day.

3. CONTRAINDICATIONS

Trokendi XR™ (topiramate) extended-release capsules are contraindicated in patients with a hypersensitivity reaction to topiramate or any of its ingredients.

4. WARNINGS AND PRECAUTIONS

Hypothermia

Hypothermia is typically associated with a reduction in body temperature of 3 to 4°C. Patients treated with Trokendi XR™ (topiramate) extended-release capsules may present with signs of hypothermia, including signs of metabolic acidosis (7.5). Hypothermia most frequently occurs in patients with normal renal function. Accordingly, a prolonged period of dialysis may cause topiramate levels to rise above normal levels, which may result in hypothermia. Therefore, dialysis should be performed as needed and the dose of Trokendi XR™ (topiramate) extended-release capsules should be reduced or discontinued as necessary.

5. ADVERSE REACTIONS

In clinical trials, the most frequently reported adverse reactions included somnolence, fatigue, dyspepsia, vomiting, weight loss, insomnia, tremor, anorexia, and headache. Some adverse reactions, especially those associated with metabolic acidosis, occurred at a rate of 5% or less in the controlled and uncontrolled clinical trials. The incidence of adverse reactions was increased in the uncontrolled studies.

6. DRUG INTERACTIONS

Trokendi XR™ (topiramate) extended-release capsules have the potential to interact with other medications. Therefore, the use of Trokendi XR™ (topiramate) extended-release capsules in combination with other medications should be carefully considered.

7. USE IN SPECIFIC POPULATIONS

Pediatric Patients

Trokendi XR™ (topiramate) extended-release capsules are indicated for use in children 2 years of age and older. The safety and effectiveness of Trokendi XR™ (topiramate) extended-release capsules have been established in children ages 2 to 16 years in the treatment of partial seizures and primary generalized tonic-clonic seizures.

8. CLINICAL Trials

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

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Risk by Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>1.00</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1.00</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>1.00</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1.00</td>
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<tr>
<td>Oxytocin</td>
<td>1.00</td>
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<tr>
<td>Levetiracetam</td>
<td>1.00</td>
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<tr>
<td>Primidone</td>
<td>1.00</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>1.00</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>1.00</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The data in Table 1 were derived from a pooled analysis of 14 randomized, controlled clinical trials that compared the safety and effectiveness of topiramate with placebo in the treatment of partial seizures and primary generalized tonic-clonic seizures in adults and children 2 to 16 years of age. The incidence of adverse reactions was increased in the uncontrolled studies.

9. PATIENT FOCUS

The following information is provided to help patients understand the treatment of partial seizures and primary generalized tonic-clonic seizures with Trokendi XR™ (topiramate) extended-release capsules.

10. HOW SUPPLIED/STORAGE AND HANDLING

Trokendi XR™ (topiramate) extended-release capsules are supplied in bottles of 30, 90, and 180 capsules. The capsules are light-resistant white, oblong capsules containing topiramate, USP. Trokendi XR™ (topiramate) extended-release capsules are stored at controlled room temperature (15° to 30°C).
TROKENDI™ (topiramate) extended-release capsules

INDICATIONS AND USAGE

Trokendi™ (topiramate) extended-release capsules are indicated as initial monotherapy in adults and pediatric patients 10 years and older with partial onset or primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome that were seen at greater frequency in topiramate-monotherapy trials compared to placebo. 

Adjunctive Therapy Use

Trokendi™ (topiramate) extended-release capsules are indicated as adjunctive therapy in adults and pediatric patients 10 years and older with partial onset or primary generalized tonic-clonic seizures, and in patients 6 years of age and older with Lennox-Gastaut syndrome in whom monotherapy with a single AED has failed.

Pediatric Patients:

Trokendi™ (topiramate) extended-release capsules are indicated as adjunctive therapy in pediatric patients 2 years of age and older with partial onset or primary generalized tonic-clonic seizures, and in patients 6 years of age and older with Lennox-Gastaut syndrome in whom monotherapy with a single AED has failed.

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

The recommended total daily dose of Trokendi™ (topiramate) extended-release capsules in adults and pediatric patients 10 years and older for partial-onset seizures is 100 mg to 400 mg per day with a 50 mg increase at 1-week intervals to a maximum of 400 mg per day.

Adjunctive Therapy in Patients with Lennox-Gastaut Syndrome

The recommended total daily dose of Trokendi™ (topiramate) extended-release capsules in Lennox-Gastaut syndrome is 500 mg to 2,000 mg per day with a 250 mg increase at 2-week intervals to a maximum of 2,000 mg per day.

1.2 Lennox-Gastaut Syndrome

In Study 2 evaluating topiramate monotherapy in Lennox-Gastaut Syndrome, 84% of patients reached a 50% reduction in seizure frequency compared to 22% in placebo. Topiramate also resulted in a median 51% reduction in seizure frequency compared to 12% in placebo. At 12 months, 77% of patients were seizure-free or had a 90% reduction in seizure frequency. 

1.3 Partial Onset Seizures

Trokendi™ (topiramate) extended-release capsules are indicated for the adjunctive treatment of partial onset seizures in adults and children 2 years of age and older with partial onset or primary generalized tonic-clonic seizures, and in patients 6 years of age and older with Lennox-Gastaut syndrome in whom monotherapy with a single AED has failed.

Trokendi™ (topiramate) extended-release capsules are indicated for the treatment of partial onset seizures in adults and children 2 years of age and older with partial onset or primary generalized tonic-clonic seizures.

2.1 Dose Modifications in Patients with Renal Impairment

The recommended total daily dose of Trokendi™ (topiramate) extended-release capsules in patients with renal impairment is 100 mg to 200 mg per day. The maximum daily dose of Trokendi™ (topiramate) extended-release capsules in these patients is 400 mg per day.

2.2 Adjunctive Therapy Use

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Trokendi™ (topiramate) extended-release capsules are indicated for the treatment of partial onset seizures in adults and children 2 years of age and older with partial onset or primary generalized tonic-clonic seizures.

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TROKENDI XR™ (topiramate) extended-release capsules

INDICATIONS AND USAGE

TROKENDI XR™ is indicated in the treatment of partial-onset seizures, as well as primary generalized tonic-clonic seizures. It is also indicated for adjunctive therapy in the treatment of pediatric patients aged 2 years and older with focal seizures and in the treatment of pediatric patients aged 12 years and older with primary generalized tonic-clonic seizures.

TROKENDI XR™ is contraindicated in patients with a prior history of or allergy to topiramate or any of its components.

ADVERSE REACTIONS

The most common adverse reactions associated with the use of topiramate in adults include dizziness, somnolence, fatigue, and nausea.

The incidence of metabolic acidosis was 5.9 mEq/L for bicarbonate. The incidence of cognitive/psychiatric adverse reactions was 6.1% in the controlled trial (Study 1) that occurred most commonly in children aged 2 to 16 years.

LABORATORY STUDIES

In pediatric patients, the most common laboratory abnormalities were decreases in serum sodium, potassium, chloride, bicarbonate, and increases in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and creatinine. In adults, the most common laboratory abnormalities were decreases in serum sodium, potassium, chloride, bicarbonate, and increases in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and creatinine.

No allowance should be made for the use of the following procedures in patients on topiramate:

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Potassium rectal suppositories, potassium tablets, and potassium salt tablets should be avoided.

Concomitant Use of Topiramate with Other Drugs

The adverse reactions in the controlled trial (Study 1) that occurred most commonly in children aged 2 to 16 years were:

- Fatigue
- Somnolence
- Dizziness
- Nausea
- Headache

These adverse reactions were generally mild to moderate and occurred at incidences similar to those observed in the placebo group.

CONTRAINDICATIONS

TROKENDI XR™ is contraindicated in patients with a prior history of or allergy to topiramate or any of its components. Topiramate is also contraindicated in patients with a history of or a known propensity to develop hepatitis or jaundice.

WARNINGS AND PRECAUTIONS

- Renal Impairment: Topiramate is cleared primarily through the kidneys. In patients with renal impairment (creatinine clearance less than 70 mL/min/1.73 m2), one-half of the dose should be administered to avoid rapid drops in topiramate plasma concentration during hemodialysis.

- Metabolic Acidosis: The hyperammonemia associated with topiramate treatment appears to be more common when topiramate is used in combination with other medications that are associated with a risk of hyperammonemia, such as ketogenic diets, certain anticonvulsants, and other AEDs.

- Hemodialysis: Hemodialysis of patients treated with Trokendi XR™ is recommended to remove topiramate and prevent accumulation of the drug in the body.

- Congenital Disorders: Topiramate is embryofetal toxic in animals, and there are no adequate and well-controlled studies in pregnant women. Trokendi XR™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- Breastfeeding: It is not known whether topiramate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Trokendi XR™ is administered to a nursing woman.

- Pediatric Use: The safety and effectiveness of Trokendi XR™ in children and adolescents have been established in pediatric clinical trials for the treatment of partial-onset seizures and primary generalized tonic-clonic seizures.

- Extrapyramidal Symptoms: In patients with a history of or a known propensity to develop extrapyramidal symptoms, such as Parkinson's disease, the adverse reactions associated with the use of topiramate should be monitored closely.

- Other Conditions: The use of Trokendi XR™ in patients with other conditions, such as those with a history of or a known propensity to develop hepatic or renal disease, should be monitored closely.

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Table 1 shows adverse events and relevant risk indicators for all marketed BCS.

Clinical Studies: The most commonly observed adverse reactions associated with the use of topiramate in patients aged 2 years and older with focal seizures or primary generalized tonic-clonic seizures were:

- Fatigue
- Somnolence
- Dizziness
- Nausea
- Headache

In double-blind adjunctive therapy and monotherapy epilepsy clinical studies conducted with Trokendi XR™, the most common adverse reactions associated with the use of topiramate in patients aged 12 years and older with primary generalized tonic-clonic seizures were:

- Fatigue
- Somnolence
- Dizziness
- Nausea
- Headache

In double-blind adjunctive therapy and monotherapy epilepsy clinical studies conducted with Trokendi XR™, the most common adverse reactions associated with the use of topiramate in patients aged 2 to 11 years with focal seizures were:

- Fatigue
- Somnolence
- Dizziness
- Nausea
- Headache

In double-blind adjunctive therapy and monotherapy epilepsy clinical studies conducted with Trokendi XR™, the most common adverse reactions associated with the use of topiramate in patients aged 12 years and older with primary generalized tonic-clonic seizures were:

- Fatigue
- Somnolence
- Dizziness
- Nausea
- Headache

Table 2 shows adverse events and relevant risk indicators for all marketed BCS.

Other Conditions: The use of Trokendi XR™ in patients with other conditions, such as those with a history of or a known propensity to develop hepatic or renal disease, should be monitored closely.

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- Somnolence
- Dizziness
- Nausea
- Headache

Table 2 shows adverse events and relevant risk indicators for all marketed BCS.
TROKENDI XR™ (topiramate) extended-release capsules

FULL PRECISE INFORMATION

1. DESCRIPTION

Trokendi XR™ (topiramate) extended-release capsules are indicated as adjunctive therapy in adults with Lennox-Gastaut Syndrome (LGS) for the treatment of drug-resistant partial seizures. Trokendi XR™ is not approved for pediatric patients less than 12 years of age.

2. PRECAUTIONS

2.1 General Information

Inform patients receiving Trokendi XR™ to take the capsules whole, without crushing, chewing, or splitting. If a capsule is accidentally crushed, chewed, or split, instruct patients to continue to take the dose as usual. If patients experience severe or persistent vomiting, instruct patients to contact their healthcare provider to determine if continuation of therapy is appropriate.

2.2 Safety and Effectiveness

Trokendi XR™ (topiramate) extended-release capsules are indicated as adjunctive therapy in patients with Lennox-Gastaut Syndrome for the treatment of drug-resistant partial seizures. Trokendi XR™ is not approved for pediatric patients less than 12 years of age. The safety and effectiveness of Trokendi XR™ for other uses have not been established.

3. CLINICAL STUDIES

3.1 Lennox-Gastaut Syndrome

Trokendi XR™ (topiramate) extended-release capsules are indicated as adjunctive therapy in adults with Lennox-Gastaut Syndrome for the treatment of drug-resistant partial seizures. Trokendi XR™ is not approved for pediatric patients less than 12 years of age. The safety and effectiveness of Trokendi XR™ for other uses have not been established.

3.2 Adjunctive Therapy

Trokendi XR™ (topiramate) extended-release capsules are indicated as adjunctive therapy in adults with Lennox-Gastaut Syndrome for the treatment of drug-resistant partial seizures. Trokendi XR™ is not approved for pediatric patients less than 12 years of age. The safety and effectiveness of Trokendi XR™ for other uses have not been established.

3.3 Adjunctive Therapy in Lennox-Gastaut Syndrome

Trokendi XR™ (topiramate) extended-release capsules are indicated as adjunctive therapy in adults with Lennox-Gastaut Syndrome for the treatment of drug-resistant partial seizures. Trokendi XR™ is not approved for pediatric patients less than 12 years of age. The safety and effectiveness of Trokendi XR™ for other uses have not been established.

4. ADVERSE REACTIONS

4.1 Adverse Events

Adverse reactions may occur during treatment with Trokendi XR™ (topiramate) extended-release capsules. The most frequently reported adverse events (incidence at least 1% higher in patients receiving Trokendi XR™ than in placebo) were somnolence, fatigue, dizziness, and headache. Other adverse events may include gastrointestinal disorders (nausea, vomiting, diarrhea), neurosensory disorders (visual disturbances, paresthesia), somnolence, and headache.

5. DRUG INTERACTIONS

5.1 General Information

The use of Trokendi XR™ (topiramate) extended-release capsules may result in significant alterations of drug levels and interactions. Patients receiving Trokendi XR™ should be monitored for adverse effects, as well as for changes in the effectiveness of other medications.

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

Trokendi XR™ (topiramate) extended-release capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There is no adequate and well-controlled study in pregnant women. Trokendi XR™ is not approved for use during pregnancy.

6.2 Nursing Mothers

Trokendi XR™ (topiramate) extended-release capsules should not be used during breastfeeding. There is no adequate and well-controlled study in breastfeeding women. Trokendi XR™ is not approved for use during breastfeeding.

6.3 Pediatric Use

Trokendi XR™ (topiramate) extended-release capsules are indicated as adjunctive therapy in adults with Lennox-Gastaut Syndrome for the treatment of drug-resistant partial seizures. Trokendi XR™ is not approved for pediatric patients less than 12 years of age. The safety and effectiveness of Trokendi XR™ in pediatric populations have not been established.

7. PATIENT COUNSELING INFORMATION

Inform patients that Trokendi XR™ (topiramate) extended-release capsules should be taken whole, without crushing, chewing, or splitting. If a capsule is accidentally crushed, chewed, or split, instruct patients to continue to take the dose as usual. If patients experience severe or persistent vomiting, instruct patients to contact their healthcare provider to determine if continuation of therapy is appropriate.

8. LABORATORY TESTS

Labs tests should be monitored during treatment with Trokendi XR™ (topiramate) extended-release capsules. Serum bicarbonate and blood pH should be monitored for changes in acid-base balance. Other labs tests may include liver function tests, complete blood count, and electrolytes.

9. NON-MEDICAL THERAPIES

Non-medical therapies may be used in conjunction with Trokendi XR™ (topiramate) extended-release capsules. These therapies may include dietary modifications, behavioral therapies, and case management.

10. ADVERSE REACTIONS

10.1 Adverse Events

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11. DESCRIPTION

Trokendi XR™ (topiramate) extended-release capsules are indicated as adjunctive therapy in adults with Lennox-Gastaut Syndrome for the treatment of drug-resistant partial seizures. Trokendi XR™ is not approved for pediatric patients less than 12 years of age. The safety and effectiveness of Trokendi XR™ for other uses have not been established.

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12.1 Lennox-Gastaut Syndrome

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14. USE IN SPECIFIC POPULATIONS

14.1 Pregnancy

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18. ADVERSE REACTIONS

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19. DESCRIPTION

Trokendi XR™ (topiramate) extended-release capsules are indicated as adjunctive therapy in adults with Lennox-Gastaut Syndrome for the treatment of drug-resistant partial seizures. Trokendi XR™ is not approved for pediatric patients less than 12 years of age. The safety and effectiveness of Trokendi XR™ for other uses have not been established.

20. CLINICAL STUDIES

20.1 Lennox-Gastaut Syndrome

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21. DRUG INTERACTIONS

21.1 General Information

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22. USE IN SPECIFIC POPULATIONS

22.1 Pregnancy

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24. LABORATORY TESTS

Labs tests should be monitored during treatment with Trokendi XR™ (topiramate) extended-release capsules. Serum bicarbonate and blood pH should be monitored for changes in acid-base balance. Other labs tests may include liver function tests, complete blood count, and electrolytes.

25. NON-MEDICAL THERAPIES

Non-medical therapies may be used in conjunction with Trokendi XR™ (topiramate) extended-release capsules. These therapies may include dietary modifications, behavioral therapies, and case management.

26. ADVERSE REACTIONS

26.1 Adverse Events

Adverse events may occur during treatment with Trokendi XR™ (topiramate) extended-release capsules. The most frequently reported adverse events (incidence at least 1% higher in patients receiving Trokendi XR™ than in placebo) were somnolence, fatigue, dizziness, and headache. Other adverse events may include gastrointestinal disorders (nausea, vomiting, diarrhea), neurosensory disorders (visual disturbances, paresthesia), somnolence, and headache.
TROKENDI XR™ (topiramate) extended-release capsules are available in the following strengths:

- 50 mg
- 100 mg
- 200 mg

Full prescribing information is available at www.TrokendiXR.com.

TROKENDI XR™ is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include diuretics or other drugs that increase body fluid loss, antipsychotics or other drugs that interfere with the central mechanism regulating temperature, or calcium channel blockers and/or nitrates that increase vasodilation.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting treatment, with a peak incidence at 2-4 weeks.

TROKENDI XR™ is not approved for use in patients below the age of 6.

Full prescribing information is available at www.TrokendiXR.com.
The most common dose-related adverse reactions at dosages of 200 mg to 1,000 mg per day were:

- Nervous system disorders: Somnolence (2%), anorexia (2%), headache (2%), fatigue (2%), speech disorder (1%), dysphasia (1%), and paresthesia (1%).
- Gastrointestinal disorders: Nausea (3%), diarrhea (3%), constipation (2%), vomiting (2%), and dyspepsia (2%).
- Special senses disorders: Diplopia (1%), hearing impairment (1%), and visual disturbance (1%).
- General disorders and administration site conditions: Fatigue (2%), weight decreased (2%), anorexia (2%), and taste perversion (1%).
- Musculoskeletal and connective tissue disorders: Arthralgia (1%), myalgia (1%), and muscle spasm (1%).
- Skin and subcutaneous tissue disorders: Rash (3%), urticaria (1%), pruritus (1%), and dermatitis (1%).
- Hypersensitivity: Rash (1%), Stevens-Johnson syndrome (1%), and toxic epidermal necrolysis (1%).
- Laboratory test abnormalities: Agranulocytosis (1%), anemia (1%), and leukopenia (1%).


drug-related adverse reactions, but not necessarily drug-related, were reported in less than 1% of patients.

- Nervous system disorders: Somnolence (1%), anorexia (1%), headache (1%), fatigue (1%), speech disorder (1%), dysphasia (1%), and paresthesia (1%).
- Gastrointestinal disorders: Nausea (2%), diarrhea (2%), constipation (1%), vomiting (1%), and dyspepsia (1%).
- Special senses disorders: Diplopia (1%), hearing impairment (1%), and visual disturbance (1%).
- General disorders and administration site conditions: Fatigue (1%), weight decreased (1%), anorexia (1%), and taste perversion (1%).
- Musculoskeletal and connective tissue disorders: Arthralgia (1%), myalgia (1%), and muscle spasm (1%).
- Skin and subcutaneous tissue disorders: Rash (1%), urticaria (1%), pruritus (1%), and dermatitis (1%).
- Hypersensitivity: Rash (1%), Stevens-Johnson syndrome (1%), and toxic epidermal necrolysis (1%).
- Laboratory test abnormalities: Agranulocytosis (1%), anemia (1%), and leukopenia (1%).

Patients treated with topiramate for partial onset seizures (Studies 2 through 7) had a lower incidence of treatment-emergent adverse reactions compared to placebo and low-dose topiramate. The most common adverse reactions observed in adult patients treated with topiramate were:

- Nervous system disorders: Somnolence (2%), anorexia (2%), headache (2%), fatigue (2%), speech disorder (1%), dysphasia (1%), and paresthesia (1%).
- Gastrointestinal disorders: Nausea (3%), diarrhea (3%), constipation (2%), vomiting (2%), and dyspepsia (2%).
- Special senses disorders: Diplopia (1%), hearing impairment (1%), and visual disturbance (1%).
- General disorders and administration site conditions: Fatigue (2%), weight decreased (2%), anorexia (2%), and taste perversion (1%).
- Musculoskeletal and connective tissue disorders: Arthralgia (1%), myalgia (1%), and muscle spasm (1%).
- Skin and subcutaneous tissue disorders: Rash (3%), urticaria (1%), pruritus (1%), and dermatitis (1%).
- Hypersensitivity: Rash (1%), Stevens-Johnson syndrome (1%), and toxic epidermal necrolysis (1%).
- Laboratory test abnormalities: Agranulocytosis (1%), anemia (1%), and leukopenia (1%).

In the study of primary generalized tonic-clonic seizures, the assigned dose of 6 mg/kg once daily (range of 1 mg/kg/day to 3 mg/kg/day) given nightly for the first 4 weeks and then every other night for an additional 4 weeks was associated with a mean decrease of 7.9 mEq/L for serum bicarbonate. The incidence of metabolic acidosis (defined by a serum bicarbonate less than 20 mEq/L) was 0% for placebo, 30% for 5 mg/kg/day, 39% for 7.5 mg/kg/day, and 42% for 10 mg/kg/day. Upper urinary tract stones occurred in 0% of patients in the placebo group, 2% of patients in the 5 mg/kg/day group, 3% of patients in the 7.5 mg/kg/day group, and 0% of patients in the 10 mg/kg/day group. The most common treatment-emergent adverse reactions observed in the 10 mg/kg/day group (incidence greater than 5% more frequent than placebo or low-dose topiramate) were:

- Nervous system disorders: Somnolence (2%), anorexia (2%), headache (2%), fatigue (1%), speech disorder (1%), dysphasia (1%), and paresthesia (1%).
- Gastrointestinal disorders: Nausea (3%), diarrhea (3%), constipation (2%), vomiting (2%), and dyspepsia (2%).
- Special senses disorders: Diplopia (1%), hearing impairment (1%), and visual disturbance (1%).
- General disorders and administration site conditions: Fatigue (2%), weight decreased (2%), anorexia (2%), and taste perversion (1%).
- Musculoskeletal and connective tissue disorders: Arthralgia (1%), myalgia (1%), and muscle spasm (1%).
- Skin and subcutaneous tissue disorders: Rash (3%), urticaria (1%), pruritus (1%), and dermatitis (1%).
- Hypersensitivity: Rash (1%), Stevens-Johnson syndrome (1%), and toxic epidermal necrolysis (1%).
- Laboratory test abnormalities: Agranulocytosis (1%), anemia (1%), and leukopenia (1%).

In the study of adult patients with primary generalized tonic-clonic seizures, the assigned dose of 6 mg/kg once daily (range of 1 mg/kg/day to 3 mg/kg/day) given nightly for the first 4 weeks and then every other night for an additional 4 weeks was associated with a mean decrease of 7.9 mEq/L for serum bicarbonate. The incidence of metabolic acidosis (defined by a serum bicarbonate less than 20 mEq/L) was 0% for placebo, 30% for 5 mg/kg/day, 39% for 7.5 mg/kg/day, and 42% for 10 mg/kg/day. Upper urinary tract stones occurred in 0% of patients in the placebo group, 2% of patients in the 5 mg/kg/day group, 3% of patients in the 7.5 mg/kg/day group, and 0% of patients in the 10 mg/kg/day group. The most common treatment-emergent adverse reactions observed in the 10 mg/kg/day group (incidence greater than 5% more frequent than placebo or low-dose topiramate) were:

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- Gastrointestinal disorders: Nausea (3%), diarrhea (3%), constipation (2%), vomiting (2%), and dyspepsia (2%).
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- Nervous system disorders: Somnolence (2%), anorexia (2%), headache (2%), fatigue (1%), speech disorder (1%), dysphasia (1%), and paresthesia (1%).
- Gastrointestinal disorders: Nausea (3%), diarrhea (3%), constipation (2%), vomiting (2%), and dyspepsia (2%).
- Special senses disorders: Diplopia (1%), hearing impairment (1%), and visual disturbance (1%).
- General disorders and administration site conditions: Fatigue (2%), weight decreased (2%), anorexia (2%), and taste perversion (1%).
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- Skin and subcutaneous tissue disorders: Rash (3%), urticaria (1%), pruritus (1%), and dermatitis (1%).
- Hypersensitivity: Rash (1%), Stevens-Johnson syndrome (1%), and toxic epidermal necrolysis (1%).
- Laboratory test abnormalities: Agranulocytosis (1%), anemia (1%), and leukopenia (1%).
Topiramate is a derivative of the succinimide group that is structurally related to ethotoin ( Dilantin). Topiramate is a CNS depressant. Concomitant administration of topiramate with other CNS depressants (for example, barbiturates) is not recommended.
For topiramate, all strengths are scored. A capsule contains topiramate USP, an inactive ingredient, and a white to off-white powder. Each capsule contains topiramate USP in an extended-release formulation.

**Pharmacology**

Topiramate is a sulfamate-substituted monosaccharide. It is a competitive inhibitor of the sodium channel, which is involved in the generation and propagation of action potentials in neurons of the central nervous system. Topiramate is an effective means of removing topiramate from the body. The following pharmacokinetic parameters were determined in patients with normal renal function: Topiramate is eliminated primarily by the kidneys. The volume of distribution of topiramate is approximately 15 liters per kilogram of body weight. The clearance of topiramate is reduced by 42% in moderately renally impaired (creatinine clearance 30 to 69 mL/min/1.73m²) patients and by 54% in severely renally impaired (creatinine clearance less than 30 ml/min/1.73m²) patients. Topiramate exposure is not significantly affected by concomitant ingestion of food. Topiramate is not metabolized in the liver and is primarily excreted unchanged in the urine. Overdoses of topiramate resulted in signs and symptoms which included convulsions, coma, respiratory depression, and hemodynamic instability. 

**Overdosage**

Topiramate is a competitive inhibitor of the sodium channel. Overdosage may lead to central nervous system depression and decreased excitability. Topiramate is metabolized in the liver and is primarily excreted unchanged in the urine. Overdoses of topiramate resulted in signs and symptoms which included convulsions, coma, respiratory depression, and hemodynamic instability. Topiramate exposure is not significantly affected by concomitant ingestion of food. Topiramate is not metabolized in the liver and is primarily excreted unchanged in the urine. Overdoses of topiramate resulted in signs and symptoms which included convulsions, coma, respiratory depression, and hemodynamic instability. Topiramate is metabolized in the liver and is primarily excreted unchanged in the urine. 

**Mechanism of Action**

The mechanism of action of topiramate is not fully understood. Topiramate is a competitive inhibitor of the sodium channel. It is metabolized in the liver and is primarily excreted unchanged in the urine. Overdoses of topiramate resulted in signs and symptoms which included convulsions, coma, respiratory depression, and hemodynamic instability. Topiramate exposure is not significantly affected by concomitant ingestion of food. Topiramate is not metabolized in the liver and is primarily excreted unchanged in the urine. Overdoses of topiramate resulted in signs and symptoms which included convulsions, coma, respiratory depression, and hemodynamic instability. Topiramate is metabolized in the liver and is primarily excreted unchanged in the urine. 

**Dosage and Administration**

Topiramate is available as immediate-release capsules and an extended-release product. The immediate-release capsules are available in strengths of 25 mg, 50 mg, 100 mg, and 200 mg. The extended-release capsules are available in strengths of 100 mg, 200 mg, and 300 mg. The extended-release capsules contain topiramate USP and an inactive ingredient. The extended-release capsules also contain an extended-release formulation of topiramate USP. The extended-release capsules are scored. A capsule contains topiramate USP, an inactive ingredient, and a white to off-white powder. Each capsule contains topiramate USP in an extended-release formulation.
2.3 Pharmacokinetics

Clearance in adults was not affected by gender or race. Elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly (25% less than young adults). Topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects compared to young adults. The peak plasma concentrations (Cmax) of topiramate occurred at approximately 24 hours following single administration. For trokendi XR, the Cmax and Tmax after oral dosing were 18.0 µg/mL and 12.3 hours, respectively, for immediate-release topiramate.

2.3.1 Age, Gender and Race

Topiramate is cleared by hemodialysis. Using a high-efficiency, counterflow, single pass-dialysate system, plasma concentrations were decreased by 70% in adults following a single oral dose of topiramate 50 mg to 200 mg. Renal function was inferred by creatinine clearance (CLcr) and was normal (<80 mL/min) in 20 patients. A higher than expected concentration of topiramate was achieved in a single subject with creatinine clearance of 15 mL/min. The peak plasma concentrations (Cmax) of topiramate occurred at approximately 24 hours following single administration. For trokendi XR, the Cmax and Tmax after oral dosing were 18.0 µg/mL and 12.3 hours, respectively, for immediate-release topiramate.

2.3.2 Hepatic Impairment

Topiramate is metabolized by the liver. Approximately 1% to 10% of topiramate undergoes metabolism by CYP2C9. Topiramate is also metabolized by CYP3A4 and CYP2C19, but the contribution of these pathways to the overall metabolism of topiramate is unknown. Topiramate is not extensively metabolized by CYP2C19. Topiramate is excreted primarily in the urine as glucuronide conjugates, with a small fraction of the unchanged drug also excreted in the urine. The mean elimination half-life of topiramate in healthy adults is 30 h. The apparent elimination half-life was similar across age groups. As recommended for the elderly, dosage adjustment is indicated in elderly patients with a creatinine clearance rate less than 70 mL/min/1.73 m².

2.3.3 Renal Impairment

As in adults, hepatic enzyme-inducing antiepileptic drugs decrease the steady state plasma concentrations of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate treatment. The maximum plasma concentrations of topiramate were decreased by 30%, respectively, for immediate-release topiramate. The AUC and Cmax of topiramate were increased by 20%, respectively, for trokendi XR. The concentration of topiramate in experimental settings when topiramate was given alone. In addition to the pharmacokinetic interaction described in the above table, concomitant administration of topiramate with valproic acid and phenobarbital has been associated with hyperammonemia with or without encephalopathy.

2.3.4 Specific Populations

Pediatric patients on adjunctive treatment exhibited a higher oral clearance (L/h) of topiramate in adults was not affected by gender or race. Elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly (25% less than young adults). Topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects compared to young adults. The peak plasma concentrations (Cmax) of topiramate occurred at approximately 24 hours following single administration. For trokendi XR, the Cmax and Tmax after oral dosing were 18.0 µg/mL and 12.3 hours, respectively, for immediate-release topiramate.

2.4.1 Induction Products

Topiramate is a substrate for CYP2C9, CYP3A4, and CYP2C19. Topiramate is also a substrate for UGT1A1. The effects of concomitant administration of topiramate with other CYP2C9, CYP3A4, and CYP2C19 substrates or inhibitors have not been evaluated. The effects of concomitant administration of topiramate with other UGT1A1 substrates or inhibitors have not been evaluated.

2.4.2 Other Antiepileptic Drugs

Topiramate is not a substrate for CYP2C9, CYP3A4, and CYP2C19. Topiramate is also a substrate for UGT1A1. The effects of concomitant administration of topiramate with other CYP2C9, CYP3A4, and CYP2C19 substrates or inhibitors have not been evaluated. The effects of concomitant administration of topiramate with other UGT1A1 substrates or inhibitors have not been evaluated.

2.4.3 Orally Administered Contraceptives

Concomitant administration of Trokendi XR and other OTC medications or alcohol has not been evaluated. Concomitant administration of Trokendi XR and other anticonvulsants has not been evaluated. Concomitant administration of Trokendi XR and other antipsychotics has not been evaluated. Concomitant administration of Trokendi XR and other antidepressants has not been evaluated. Concomitant administration of Trokendi XR and other mood stabilizers has not been evaluated. Concomitant administration of Trokendi XR and other antihypertensives has not been evaluated.

2.4.4 Hepatic Enzyme Inductors

The effects of concomitant administration of topiramate with other hepatic enzyme inducers have not been evaluated. The effects of concomitant administration of topiramate with other hepatic enzyme inducers have not been evaluated. The effects of concomitant administration of topiramate with other hepatic enzyme inducers have not been evaluated.

2.4.5 Hepatic Enzyme Inhibitors

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2.5.1 OTC Medications

Concomitant administration of Trokendi XR and other OTC medications or alcohol has not been evaluated. Concomitant administration of Trokendi XR and other anticonvulsants has not been evaluated. Concomitant administration of Trokendi XR and other antipsychotics has not been evaluated. Concomitant administration of Trokendi XR and other antidepressants has not been evaluated. Concomitant administration of Trokendi XR and other mood stabilizers has not been evaluated. Concomitant administration of Trokendi XR and other antihypertensives has not been evaluated.

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A single-dose, open-label, randomized dose escalation study in healthy volunteers evaluated the steady-state pharmacokinetics and bioavailability of topiramate 200 mg extended-release tablets and topiramate 100 mg immediate-release capsules. The study was conducted in 2 parts: Part 1 enrolled 10 healthy volunteers (5 males, 5 females) and Part 2 enrolled 9 healthy volunteers (3 males, 6 females), each of whom received a single 200 mg topiramate extended-release tablet and a single 100 mg topiramate immediate-release capsule at the same time. The median area under the concentration-time curve (AUC) and median maximum concentration (C_max) were comparable between the two formulations. In addition, the 90% confidence interval (CI) for the ratios of topiramate plasma concentration at steady state (C_{ss}) at the 4 highest dose levels was within the bioequivalence limits, except for the initial time points before 1.5 hour post-dose.

Therefore, if Trokendi XR is given concomitantly with a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor, or with a nonsteroidal anti-inflammatory drug, the risk of elevated intracranial pressure or new-onset increased intracranial pressure may be increased.

An increase in urinary bladder tumors was observed in mice given topiramate (20 mg/kg, 60 mg/kg, and 180 mg/kg) in the diet for 2 years. Topiramate increased the number of hamsters surviving 2 years in a dietary carcinogenicity study and increased the number of hamsters dying in a study of the effects of topiramate on lifespan. The relevance of this finding to human carcinogenic risk is not known.

No evidence of carcinogenicity was seen in mice following topiramate administration for 2 years at doses up to 150 mg/kg (equivalent to 5 mg/kg in a human).

The mean change from baseline in QT interval in the electrocardiogram was a small increase in patients treated with topiramate compared to a small decrease in patients treated with placebo. Topiramate was not associated with a clinically significant increase in the incidence of ventricular arrhythmias detected by signal-averaged electrocardiography.

No evidence of increased liver enzyme activity was observed in rats. The rats treated with topiramate for 2 years in the diet study had a higher incidence of histologically confirmed liver tumors than control rats. In the 2-year carcinogenicity study, an increase in hepatic tumors due to chronic inflammation was observed in mice given topiramate at the highest dose level tested (20 mg/kg, 60 mg/kg, and 180 mg/kg) in the diet for 2 years. The relevance of this finding to human carcinogenic risk is not known.

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### Table 1: Mean and Median Doses in the Stabilization Period

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### Table 2: Summary of Studies

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### Table 3: Placebo Dosages

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### Table 4: Median Dose and D12
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### Table 5: Median % Reduction

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### Table 6: Mean and Median Doses

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### Table 7: Summary of Studies

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### Table 8: Placebo Dosages

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### Table 9: Median Dose and D12
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### Table 10: Median % Reduction

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### Table 11: Mean and Median Doses

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### Table 12: Summary of Studies

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### Table 13: Placebo Dosages

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### Table 14: Median Dose and D12
d

| Median Dose | D12 | D12%
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### Table 15: Median % Reduction

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